April 2019

Evaluation of Ventilation Assistance for Improving Respiratory Reproducibility in Radiation Therapy

Cameron J. Sprowls
Louisiana State University and Agricultural and Mechanical College, camsprowls@gmail.com

EVALUATION OF VENTILATION ASSISTANCE FOR IMPROVING RESPIRATORY REPRODUCIBILITY IN RADIATION THERAPY

A Thesis

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Master of Science

in

The Department of Physics and Astronomy

By
Cameron Jay Sprowls
B.S., West Chester University of Pennsylvania, 2015
May 2019

Acknowledgement

I thank my supervisory committee members, Connel Chu, Dr. Jonas Fontenot, Dr. Kenneth Matthews II, and Dr. Thomas Corbitt. I thank Connel for his constant support and mentorship throughout this project, Dr. Fontenot for his invaluable expertise and clear vision, Dr. Matthews for his advice and commitment to seeing students succeed, and Dr. Corbitt for his time and supervision of this project.

I express my sincerest thanks and appreciation for the entire Mary Bird Perkins Cancer Center staff; this project would not have been possible without their assistance. I thank Roxanne Kenny for notifying me of patient arrivals; Mary Broussard, Jovanda Julian, and Morgan Wiley for their help with the testing of equipment; the therapists for their help with coordinating patient data collection; and the CT technologists for their help during patient enrollment. I thank Katelynn Fontenot, Megan Jarrell, and Katherine Pevey for their help with the clinical logistics of this project. I also thank Susan Hammond and Yao Zeng for their administrative assistance in navigating the deadlines and requirements of completing my degree.

I thank Addie Barron and Elizabeth Hilliard for volunteering for preliminary data collection and John Doiron for the use of his projector during this project. I thank Phillip Wall for his discussions and support throughout this project. Additional thanks go to my fellow classmates and peers at LSU for aiding in my academic success.

I thank my family and friends for their unconditional love and support not only during this project, but throughout my life. Finally, I thank Dani whose understanding and encouragement kept me going when I needed it most.

Table of Contents

List of Tables

List of Figures

Abstract

Background: Respiratory motion affects all tumor sites in the thorax and abdomen. Variations of the respiratory pattern cause variations of the tumor motion which can result in differences between the planned and delivered dose distributions. Previous breathing guidance techniques have been investigated to improve respiratory reproducibility; however, ventilation assistance has not been investigated. We evaluated using bi-level positive airway pressure (BIPAP) ventilation assistance for improving respiratory reproducibility in patients with tumor sites impacted by respiratory motion.

Methods: Written informed consent was obtained for 10 patients currently undergoing radiation therapy treatment. Patients participated in sessions over their course of treatment, which occurred either before or after their radiation treatments. We collected and analyzed unassisted free-breathing (FB) and BIPAP ventilation-assisted respiratory volume data using spirometry. Patients used two BIPAP ventilators which both aimed to deliver the same volume of air each breath (i.e. tidal volume); however, one permitted patient triggering (i.e. permitted patients to initiate each breath) and the other did not. Intra-session and inter-session variation metrics were calculated for each patient using the platform-specific (i.e. FB or BIPAP) tidal volumes. We compared variation metrics between the platforms using the Wilcoxon signed-rank test, with a level of significance of 0.05.

Results: The BIPAP ventilator which permitted patient triggering was well tolerated; however, the other was not as well tolerated. Both BIPAP ventilators significantly reduced the intra-session tidal volume variation ($p = 0.022$ and $p = 0.007$) compared to FB. Neither of the BIPAP ventilators significantly reduced the inter-session tidal volume variation compared to FB ($p = 0.203$ and $p = 0.074$).

Conclusions: Based on the high correlation of tidal volume to tumor motion, any reduction of the tidal volume variation could result in a reduction of the tumor motion variation. Future work will include an investigation into the possible clinical benefits of using BIPAP ventilation assistance to reduce tumor motion variations.

1. Introduction

1.1. Background and Motivation

1.1.1. Cancers Affected by Respiratory Motion

Respiratory motion affects all organs in the thorax and abdomen. Consequently, cancers located in these organs are affected by respiratory motion. Lung cancer is the second most diagnosed cancer and the leading cause of cancer deaths, accounting for 25% of all cancer deaths in the U.S. in 2018. An estimated 234,030 new cases were diagnosed in 2018, with an estimated 154,050 deaths. The five-year survival rate for all stages combined is only 18%.[1] Depending on the stage of disease, treatment options include surgery, chemotherapy, or radiation therapy. When patients are not suitable candidates for surgery due to existing health complications, radiation therapy, either alone or in combination with chemotherapy, is the preferred treatment option for lung cancer.[2]

Treatment options for other cancers located in the thorax and abdomen, such as esophageal cancer or stomach cancer, also include radiation therapy. External beam radiation therapy, where ionizing radiation is delivered from a linear accelerator to the patient, is the primary method for the treatment of these cancers. The goal of external beam radiation therapy is to deliver radiation to cancerous tissues while minimizing radiation to surrounding healthy tissues and critical structures; however, achieving this goal can be difficult due to the influence of respiratory motion.

1.1.2. The Mechanics of Breathing

The lungs are paired, cone-shaped organs located in the thoracic cavity and are separated from each other by the heart and other structures of the mediastinum. The primary function of the lung is to facilitate respiration or the exchange of gases (O_2 and CO_2) between the atmosphere and blood, thus maintaining normal levels of O_2 and CO_2 in the blood. Respiration is an involuntary

action and takes place in three basic steps: pulmonary ventilation (exchange of gas between atmosphere and lungs), external respiration (exchange of gas between lungs and blood), and internal respiration (exchange of gas between blood and tissue cells). Breathing is an important process of pulmonary ventilation and consists of the inhalation (breathing in) and exhalation (breathing out) of gas. The nervous system, specifically the respiratory center located in the medulla oblongata and pons of the brain stem, usually controls breathing automatically to meet the body's demand without conscious effort. Because the cerebral cortex also has connections with the respiratory center, breathing can be controlled voluntarily for short periods of time.[3]

Quiet or relaxed breathing requires the participation of respiratory muscles. During inhalation, the diaphragm, which is a dome-shaped skeletal muscle that separates the thoracic and abdominal cavities, contracts and descends inferiorly. The abdomen is forced inferiorly and anteriorly by the diaphragm, increasing the superior-inferior dimension of the thoracic cavity. The external intercostal muscles, which connect adjacent ribs, also contract during inhalation. This pulls the ribs superiorly and anteriorly, increasing both the anterior-posterior and lateral diameters of the thoracic cavity. The lungs expand, increasing the lung volume, thus decreasing the pressure in the lungs below atmospheric pressure. This pressure gradient between the atmosphere and lungs results in the flow of gas from the atmosphere to the lungs. Exhalation is passive for quiet breathing. The muscles of inhalation relax and the elastic lungs and thoracic walls return passively to their pre-inhalation positions, decreasing the lung volume, thus increasing the pressure in the lungs above atmospheric pressure. This opposite pressure gradient results in the flow of gas from the lungs to the atmosphere. Other respiratory muscles are involved only during labored exhalation.[3]

1.1.3. Problems of Respiratory Motion During Radiation Therapy

Respiratory motion, which is a consequence of the mechanics of breathing, affects all tumor sites in thorax and abdomen. Not accounting for respiratory motion can introduce problems or uncertainties during image acquisition, treatment planning, and radiation delivery. It is important to note that respiratory motion is just one potential source of uncertainty in radiation therapy. Other sources of uncertainty include patient setup variations (inter-fraction motion) and inter-observer variations in gross target volume (GTV) delineation.[4]

Conventional image acquisition techniques used for tumor sites in the thorax and abdomen affected by respiratory motion can result in image artifacts. Scalloping artifacts are commonly seen with helical computed tomography (CT) scans of the thorax (Figure 1.1.). These artifacts manifest themselves as tumor/normal tissue delineation errors and can adversely affect dose-calculation accuracy.[4]

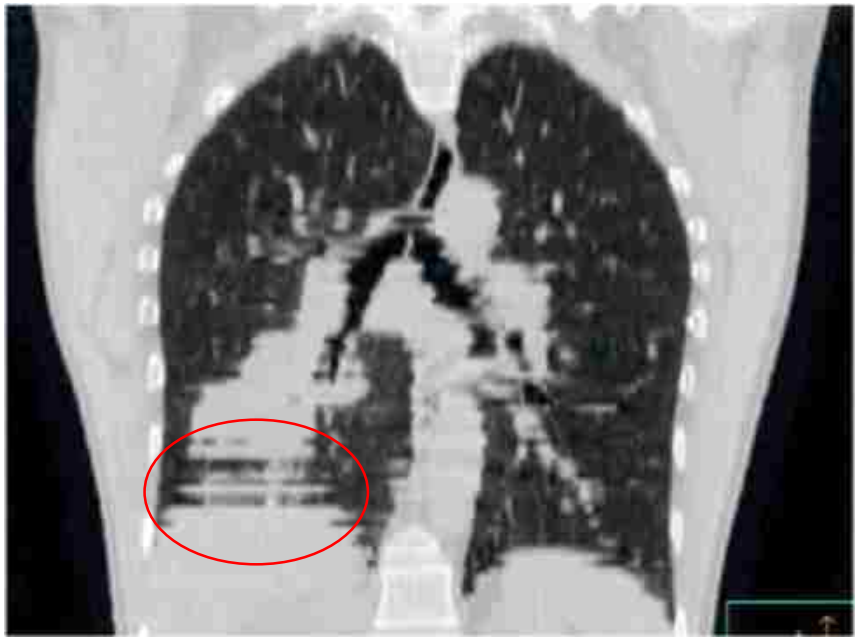

Figure 1.1. Coronal view of a conventional CT scan of the thorax. Note the scalloping artifacts at the right lung/diaphragm interface, circled in red.[4]

During treatment planning, different margins are added to the GTV to account for different uncertainties, ensuring coverage of the tumor during radiation delivery. Using the International Commission on Radiation Units and Measurements (ICRU) 62 nomenclature, adding a margin to the GTV to include suspected microscopic spread creates the clinical target volume (CTV).[5] The internal target volume (ITV) is obtained by adding additional margins to the CTV to account for intra-fraction tumor motion. Additional margins to include setup uncertainties are added to the ITV to create the planning target volume (PTV). Scalloping artifacts observed in conventional CT images of the thorax and abdomen, when respiratory motion is not accounted for, can make quantifying adequate margins difficult.

Radiation delivery for tumor sites impacted by respiratory motion can result in deviations between the planned and delivered dose distributions. Intra-fraction tumor motion induced by respiratory motion causes an average or blurring of the dose distribution over the path of tumor motion while inter-fraction changes in respiratory motion cause a shift of the dose distribution.[4] These radiation delivery limitations can be exacerbated when respiratory motion is not accounted for during image acquisition and treatment planning.

1.1.4. Respiratory Motion Management Strategies

To reduce the impact of respiratory induced tumor motion, respiratory motion management strategies have been developed. The American Association of Physicists in Medicine (AAPM) Task Group (TG) 76 report includes respiratory motion management strategies that can be applied during image acquisition, treatment planning, and radiation delivery. A few strategies that are often utilized clinically are respiratory gating techniques, breath-hold techniques, and motion-encompassing methods.

Respiratory gating techniques involve administering radiation (during both image acquisition and radiation delivery) within a particular portion of the patient's breathing cycle. This portion or

window is often referred to as the "gate." The gate is usually chosen to extend over a region of the patient's breathing cycle where the motion of the tumor is estimated to be less, which is generally end exhalation. Tumor motion is typically monitored using a respiration surrogate signal such as an infrared reflector marker placed on the anterior abdominal surface or spirometry (i.e. air flow) measurements of the respiratory volume. Vedam *et al.* reported a strong correlation (R^2 = 0.85) between the anterior abdominal surface position, midway between the xiphoid process and umbilicus, and the diaphragm position which is typically used as a surrogate for tumor postion.[6] In reality, there is the possibility that the surrogate for tumor motion does not accurately correspond to the time-dependent tumor position (Figure 1.2.). This can result in radiation being delivered when the tumor is not within the gate. The correlation between the tumor position and surrogate signal should always be verified prior to radiation delivery.[7]

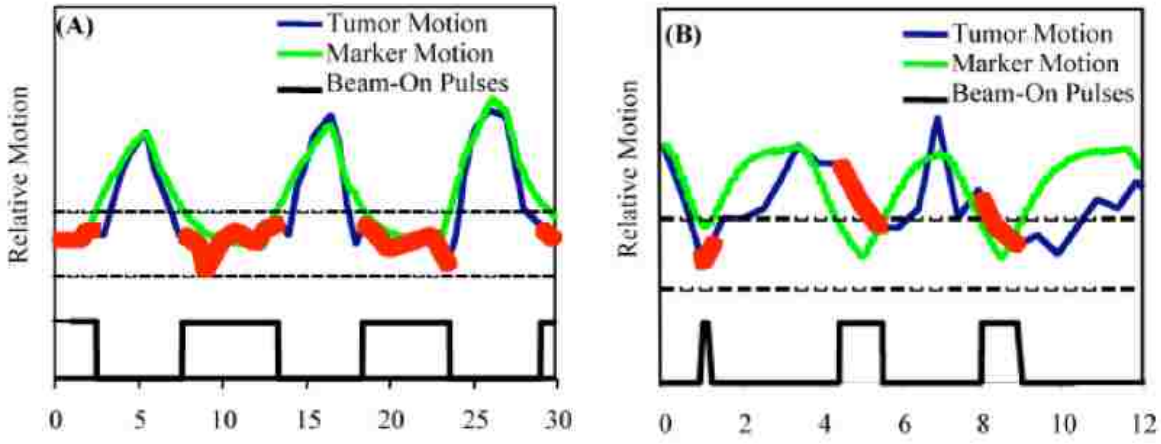

Figure 1.2. Comparison of tumor position and an external respiration signal (anterior abdominal surface marker) for a patient with (A) no phase shift and (B) a phase shift during respiratory gating. The dashed lines represent the gate and the orange lines represent the tumor's position during a beam-on pulse.[7]

Breath-hold techniques require that patients hold their breath during the administration of radiation (during both image acquisition and radiation delivery) and have predominately been

applied to breast cancer radiation therapy. An external respiration signal (e.g. infrared abdominal reflector) is often used to monitor patient respiration, as well as provide visual feedback to the patient. During image acquisition, patients receive verbal coaching and visual feedback of the external respiration signal to achieve and hold a reproducible inhalation state. Patients are provided visual feedback of the external respiration signal and asked to achieve the same inhalation state during radiation delivery. While breath-hold techniques aim to minimize respiratory motion during image acquisition and radiation delivery, they can be strenuous on patients, particularly in those with compromised respiratory function.

Motion-encompassing methods involve scanning a region that includes the entire range of tumor motion during image acquisition and developing treatment volumes to encompass that range during treatment planning. Treatment planning using motion-encompassing methods typically utilize a series of time-resolved three-dimensional CT images.[4] This image acquisition technique, referred to as four-dimensional CT (4D CT), provides information on the mean tumor position, tumor range of motion, and tumor shape throughout the respiratory cycle (Figure 1.3.). 4D CT is accomplished by acquiring CT data in axial cine mode throughout the respiratory cycle at each scan location. External respiration signals are simultaneously acquired during CT scanning using surrogate signals (e.g. infrared abdominal reflector). To create the 4D CT image set, reconstructed CT images are retrospectively sorted into different spatially and temporally coherent volumes based on respiratory phase (e.g. 0%, 25%, 50%, 75%), which is obtained from the surrogate signal.[8] A maximum intensity projection (MIP) image, or image displaying the maximum CT number found in a given voxel for all respiratory phases, can be created from the 4D CT image set.[9] Other images created from the 4D CT image set include the minimum intensity projection image and average intensity projection image. The MIP image is often used to obtain the

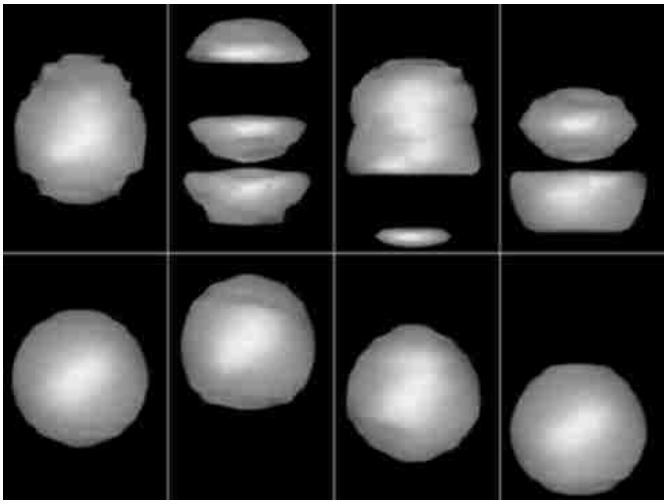

Figure 1.3. Isosurface renderings of CT data of a spherical object undergoing periodic motion during imaging. Top row: Examples of artifacts obtained by standard axial CT scanning, which depend on the interplay between CT data acquisition and object motion. Bottom row: Left image shows CT scan of the static spherical object. Other images show three positions (at different phases) of the moving object imaged with 4D CT.[8]

motion-encompassing ITV (Figure 1.4.). Any variations of the respiratory patterns can increase the ITV, thus increasing the PTV. Larger treatment volumes result in increased dose to surrounding normal tissues,[9] which increases the risk of post-radiation complications such as radiation pneumonitis.[10, 11]

1.1.5. Breathing Guidance Techniques

Motion management strategies, specifically motion-encompassing methods, assume that patients will be breathing the same way during subsequent radiation delivery treatments as they were during image acquisition. In reality, patients' natural or free-breathing patterns can vary from breath to breath and day to day (Figure 1.5.).[12-14] Both breath-to-breath and day-to-day breathing variations can cause tumor motion variations which can result in the tumor not being encompassed in the PTV during radiation delivery. Therefore, tumor motion variations can result in differences between the planned dose distributions and the delivered dose distributions.

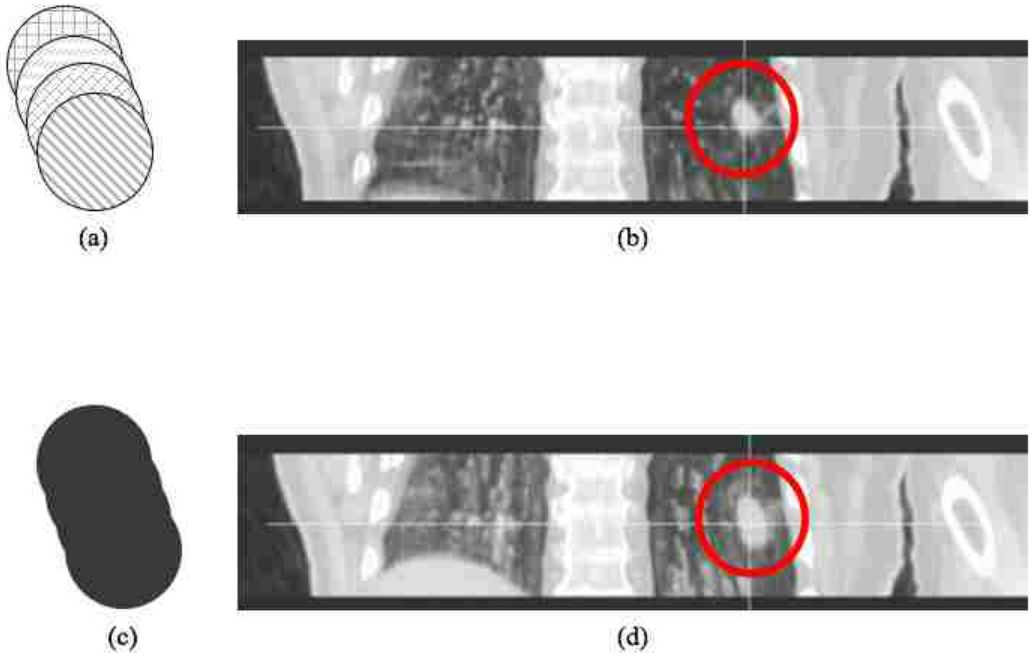

Figure 1.4. Generating the motion-encompassing ITV from the maximum intensity projection (MIP) image. (a) Schematic illustration of a mobile object imaged at four separate phases of motion. (b) Coronal CT slice from one phase of 4D CT image set (e.g. 25%). Lung tumor circled in red. (c) ITV of schematic mobile object. (d) Coronal CT slice of MIP image.

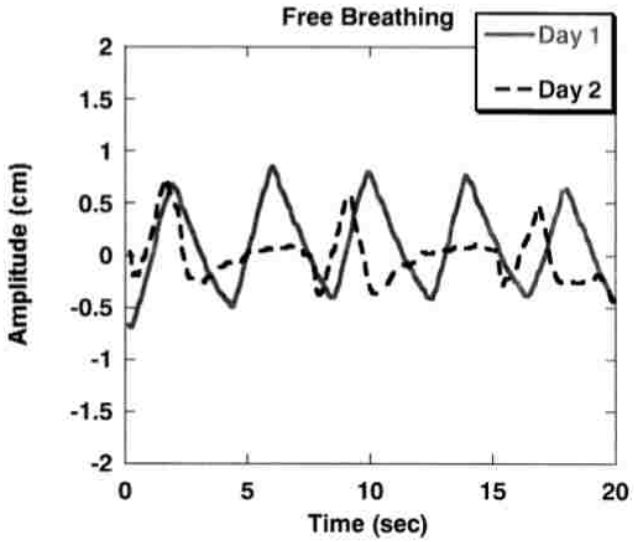

Figure 1.5. An example of free-breathing pattern variations for one patient recorded on two different days. Breathing was monitored using an infrared abdominal surface reflector. Note the variations in both the abdominal surface amplitude and period.[12]

Breathing guidance techniques, ranging from simple audio buzzers to providing visual feedback of the respiration signal, have been developed to reduce respiratory pattern variations, which in turn can improve image quality and radiation delivery accuracy.[15] Kini *et al.* investigated using audio prompting and visual feedback, separately, as breathing guidance techniques on five patients. Breathing was monitored and recorded using an infrared abdominal surface reflector. A free-breathing recording was used as each patient's control. Audio prompting methods used instructions to "breath in" or "breath out" at periodic intervals which closely matched patients' free-breathing patterns. Visual feedback methods consisted of providing patients with a real-time trace of the abdominal surface reflector position. The results of using audio prompting included a reproducible (i.e. less variation) period and a variable abdominal surface amplitude while the results of using visual feedback included a reproducible abdominal surface amplitude and a variable period (Figure 1.6.). Kini *et al.* concluded that using some form of breathing guidance, either audio or visual, can improve patients' respiratory reproducibility, compared to free-breathing.[12]

Most breathing guidance techniques use the anterior abdominal surface as a surrogate for the respiration signal; however, Lim *et al.* utilized respiratory volume, which has been shown to more highly correlate to tumor motion than the anterior abdominal surface.[16] Lim *et al.* provided the real-time breathing pattern, monitored using a previously developed thermocouple respiratory monitoring mask, in addition to a breathing guidance curve, to ten healthy volunteers. Their results included significant ($p < 0.05$) reductions in the standard deviations of the respiratory volume amplitudes and periods compared to free-breathing.[17]

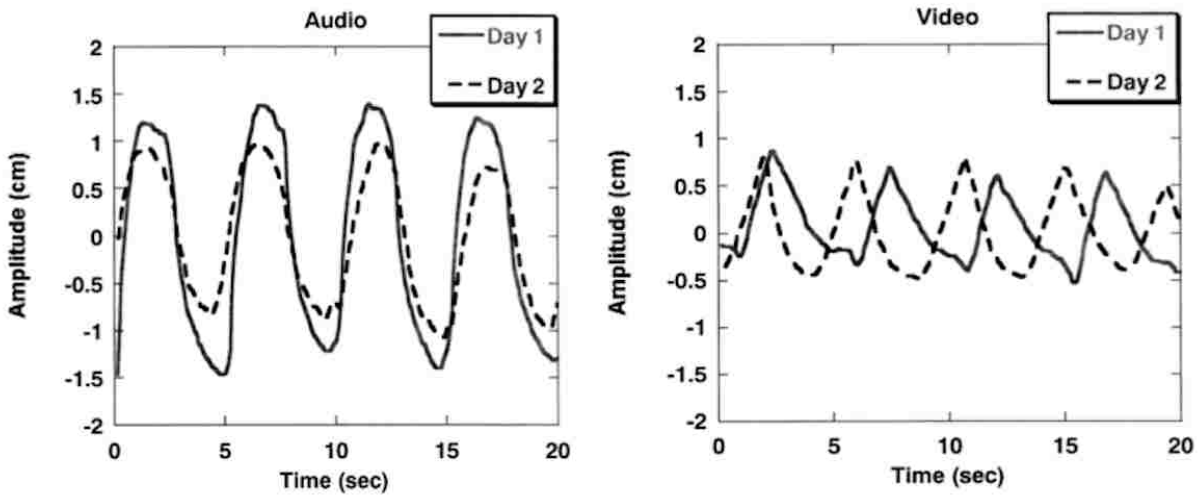

Figure 1.6. Breathing patterns using audio prompting and visual feedback as breathing guidance techniques on a single patient recorded on two different days. The corresponding free-breathing pattern for the same patient is shown in Figure 1.5.[12]

Interest in breathing guidance techniques has increased with time since the early investigations by Kini *et al.* and Lim *et al.* (Figure 1.7.), mainly due to the advancements of radiation delivery techniques which require accurate tumor localization during image acquisition and treatment planning.[15] Pollock *et al.* performed a systematic search of the current literature on breathing guidance techniques which yielded a total of 480 articles. Only 27 of the 480 articles met their eligibility criteria for review, which consisted of a quantitative evaluation of the breathing guidance technique and included a control group. In 21/27 studies, significant ($p < 0.05$) improvements using breathing guidance techniques were observed.[15] These largely positive results warrant further studies to investigate and assess the possible clinical impact of using breathing guidance techniques.

1.1.6. Continuous Positive Airway Pressure (CPAP) Ventilation

Continuous positive airway pressure (CPAP) ventilation is a form of non-invasive ventilation that delivers a constant stream of pressurized air to the upper airways and lungs throughout the respiratory cycle.[18] CPAP ventilation has safely been used for respiratory complications such as

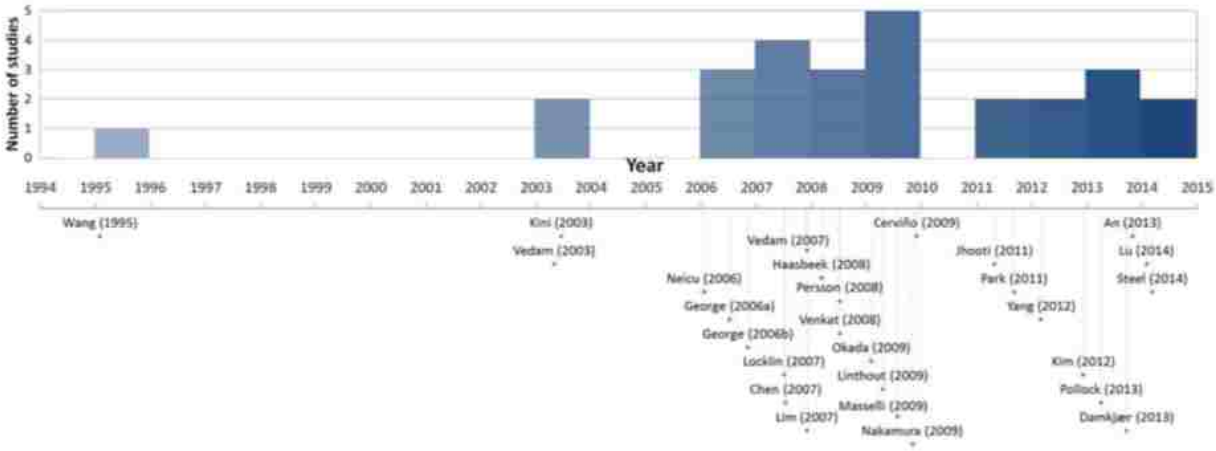

Figure 1.7. Breathing guidance studies published since 1994. Note the increase of studies with time indicating a growing clinical interest.[15]

obstructive sleep apnea, acute respiratory failure, and chronic obstructive pulmonary disease.[19] Functionally, CPAP ventilation increases the baseline lung volume (Figure 1.8.), compared to unassisted free breathing, which may improve lung compliance or the lung's ability to stretch and expand. This improvement in lung compliance decreases the work of breathing.[20]

Recently, there has been some interest in using CPAP ventilation as a respiratory motion management strategy in radiation therapy. Goldstein *et al.* investigated the effects of using CPAP ventilation on tumor motion, lung volume, and dose to critical organs in patients receiving stereotactic body radiation therapy for lung tumors. 10 patients underwent two 4D CT scans, one free-breathing and one using CPAP ventilation. Tumor motion, lung volumes, and dose to critical organs was compared between the two scans. Their results show that using CPAP ventilation significantly increased the total lung volume and reduced tumor motion, which contributed to reduced dose to the lungs and heart.[21] The initial results of using CPAP as a respiratory motion management strategy are encouraging; however, Goldstein *et al.* utilized CPAP ventilation to increase the total lung volume to minimize tumor motion. Improving patients' respiratory

reproducibility cannot be accomplished with CPAP ventilation alone because it only provides a constant pressure throughout the respiratory cycle.

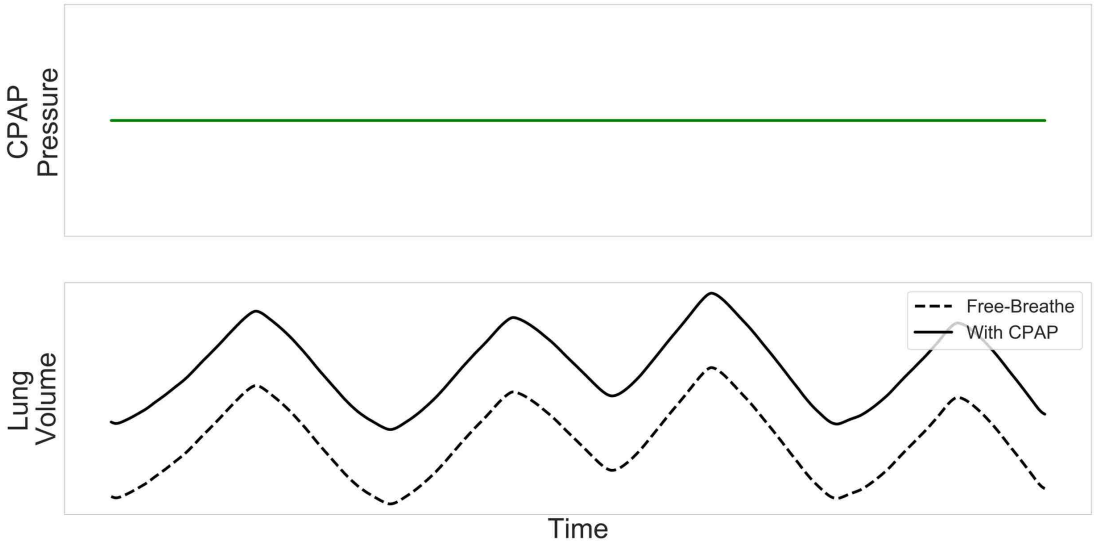

Figure 1.8. Example of CPAP ventilation. Top: A constant stream of pressurized air is delivered to the upper airways and lungs throughout the respiratory cycle. Bottom: Example of a free-breathe respiratory pattern (dashed line). With CPAP ventilation (solid line), the baseline lung volume is increased and the respiratory pattern is relatively unchanged.

1.1.7. Bi-Level Positive Airway Pressure (BIPAP) Ventilation

Bi-level positive airway pressure (BIPAP) ventilation is another form of non-invasive ventilation and has been used for similar respiratory complications as CPAP ventilation. BIPAP ventilation allows the independent adjustment of both the inhalation and exhalation pressures, as opposed to CPAP ventilation which only provides a constant pressure throughout the respiratory cycle. BIPAP ventilators deliver a higher pressure during inhalation and lower pressure during exhalation (Figure 1.9.). Functionally, BIPAP ventilation increases the baseline lung volume, compared to unassisted free breathing; however, the difference in positive pressures throughout the respiratory cycle provides greater assistance of patients' breathing efforts, compared to CPAP

ventilation.[22] Most commercially-available BIPAP ventilators offer volume-targeted modes, which aim to assist patients' breathing efforts.[22]

Volume-targeted modes deliver a preset volume of air each breath. This volume of air each breath is referred to as the tidal volume. Depending on the BIPAP ventilator, volume-targeted modes can be delivered using either a pneumatic blower ventilation system or a piston-driven ventilation system. Volume-targeted modes may or may not permit patient-triggering. Patient-triggering allows patients to initiate or trigger each breath as well as control their tidal volume each breath. Volume-targeted modes that do not permit patient-triggering offer the most control of the tidal volume and breathing period while still assisting patients' breathing efforts.[22] BIPAP ventilation assistance using a volume-targeted mode could improve patients' respiratory reproducibility.

1.1.8. Research Motivation

BIPAP ventilation assistance has not been investigated as a technique to improve patients' respiratory reproducibility in the radiation therapy setting. Volume-targeted BIPAP ventilation assistance has added advantages, compared to free-breathing and CPAP ventilation, of assisting patients' respiratory patterns and delivering a preset tidal volume each breath. Based on the high correlation of tidal volume to tumor motion,[16] improving patients' respiratory reproducibility could ultimately improve tumor motion reproducibility. We hypothesized that candidates for BIPAP ventilation assistance will show improved respiratory reproducibility both breath to breath and day to day. To test this hypothesis, we used two different BIPAP ventilators, both with volume-targeted modes. We collected breathing data on a sample of patients currently undergoing radiation therapy treatment during sessions throughout their course of treatment.

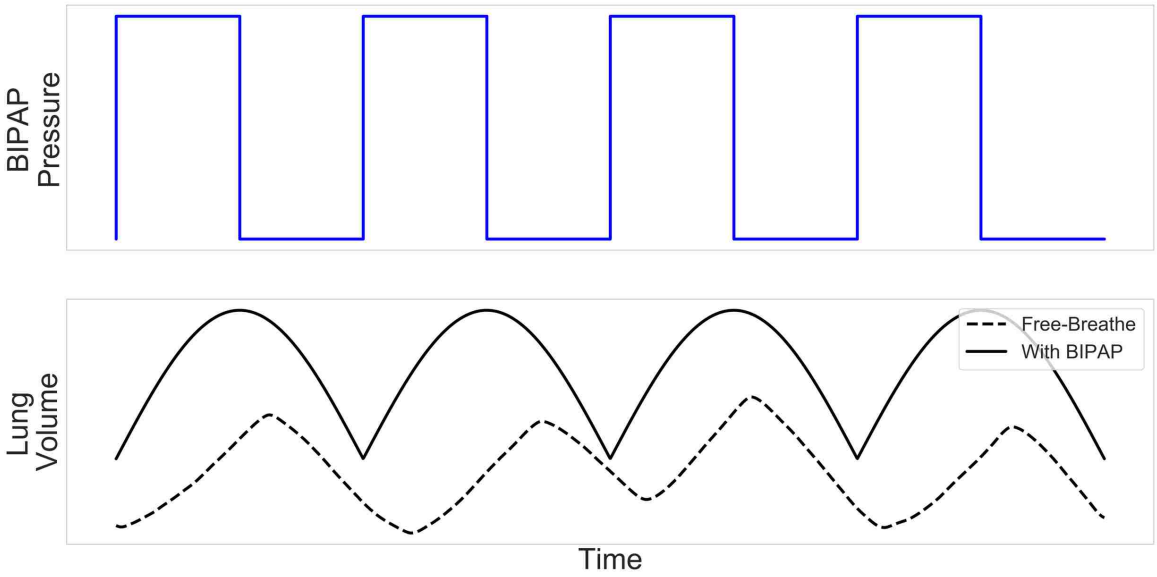

Figure 1.9. Example of BIPAP ventilation. Top: A higher pressure is delivered during inhalation and a lower pressure is delivered during exhalation. Bottom: Example of a free-breathe respiratory pattern (dashed line). With BIPAP ventilation (solid line), the baseline lung volume is slightly increased and the respiratory pattern is optimally assisted. An ideal, reproducible respiratory pattern would be consistent in both the tidal volume and period each breath.

1.2. Hypothesis and Specific Aims

We hypothesized that candidates for BIPAP ventilation assistance will show significantly reduced ($p < 0.05$) intra-session and inter-session tidal volume variation compared to unassisted free-breathing. To test our hypothesis, we developed the following aims:

Aim 1: Modifications of equipment needed for this study.

Aim 2: Collect and evaluate patients' free-breath data.

Aim 3: Collect and evaluate patients' BIPAP ventilation-assisted data.

2. Methods and Materials

2.1. Aim 1: Equipment Modifications

2.1.1. Aim 1 Overview

In this aim, we modified equipment needed for this study. Modifications included extracting data from one of the BIPAPs, adapting the other BIPAP for exhalation, and developing a method for the tracking of an abdominal surface marker.

2.1.2. BIPAP Ventilators Used in this Study

We utilized two different commercially-available BIPAP ventilators in this study; the Philips BIPAP and the Lifecare BIPAP. Both ventilators provided volume-targeted ventilation assistance; however, the Philips BIPAP permitted patient triggering while the Lifecare BIPAP did not.

The Philips Respironics V60 BIPAP ventilator is a microprocessor-controlled pneumatic blower ventilation-assistance system (Philips Respironics California, LLC., Carlsbad, CA). The Philips BIPAP (Figure 2.1.) offers a volume-targeted mode named the average volume-assured pressure support (AVAPS) mode. The AVAPS mode maintains a target tidal volume each breath by monitoring previous tidal volumes and continuously adjusting the delivered pressures. An important characteristic of the Philips BIPAP is the "Auto-Trak Sensitivity," which is its ability to recognize and compensate for unintentional leaks in the patient circuit system. The output air from the Philips BIPAP exits the ventilator through the patient air outlet and into the patient circuit, which consists of a six-foot-long, ¾" diameter, piece of flexible plastic tubing connected to the patient's ventilation mask. The user interface includes a color LCD touchscreen which displays monitored patient parameters, as well as the real-time pressure, flow, and volume waveforms (Figure 2.1.). The Philips BIPAP provides pure ventilation assistance, meaning that both the volume of air output by the ventilator and the initiation of each breath is determined by the patient (i.e. permits patient triggering).

Figure 2.1. Left: Philips Respironics V60 BIPAP ventilator. Right: Philips BIPAP LCD touchscreen which displays monitored patient parameters such as the tidal volume and breathing period as well as the real-time pressure, flow, and volume waveforms.

The Lifecare Personal Lightweight Ventilator (PLV) 100 is a microprocessor-controlled, piston-driven ventilation assistance system (Respironics, Inc., Murrysville, PA). Unlike the Philips BIPAP, the Lifecare BIPAP (Figure 2.2.) offers a Control mode which is a volume-targeted mode that does not permit patient triggering. The Control mode delivers all breaths at a preset tidal volume and breathing period. Similar to the Philips BIPAP, the output air from the Lifecare BIPAP exits the ventilator through the patient air outlet and into the patient circuit. The front panel includes digital displays of user-selected settings (e.g. tidal volume), which are controlled by associated knobs. The Lifecare BIPAP provides controlled ventilation assistance, meaning that both the volume of air output by the ventilator and the start of each breath is determined by the ventilator (i.e. does not permit patient triggering).

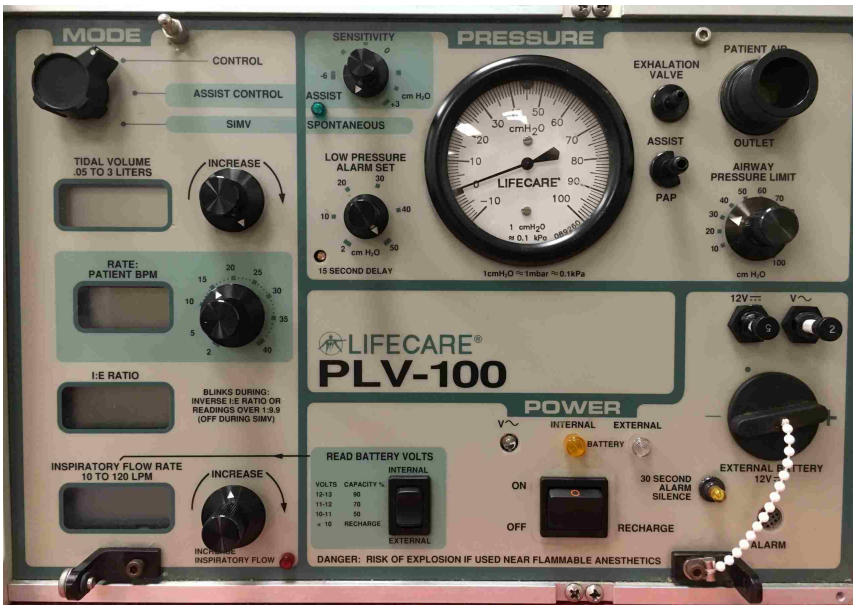

Figure 2.2. Lifecare PLV-100 BIPAP ventilator.

2.1.3. Extracting Philips BIPAP Volume Waveform Data

The Philips BIPAP ventilator provides a color LCD touchscreen that displays monitored patient parameters, in addition to the real-time volume waveforms (Figure 2.1.). The real-time volume waveform is continuously updated and resets to zero after 24 seconds has expired. Unfortunately, the volume waveform data displayed by the ventilator could not be easily retrieved due to manufacturer limitations. As a result, we extracted the Philips BIPAP volume waveforms by recording the real-time volume waveform and post-processing the video using in-house developed video analysis code.

We built a custom camera mount to record the real-time volume waveform. We used foam, an 1/8" acrylic sheet, and bar clamps to build the camera mount that clamped to the Philips BIPAP. An IPEVO® Ziggi-HD USB document camera (IPEVO, Sunnyvale, CA) was attached to the camera mount using mini bar clamps and a C-clamp (Figure 2.3.). The camera was connected to a dedicated computer which contained the camera's software, IPEVO Visualizer, and was used to record the Philips BIPAP volume waveforms.

Figure 2.3. Camera attached to the custom camera mount on the Philips BIPAP.

In-house MATLAB® (The MathWorks, Inc., Natick, Massachusetts, US) video analysis code, utilizing Canny edge detection, was written to extract the Philips BIPAP displayed volume waveforms from the recorded videos (Figure 2.4.). We validated our extracted volume values to the displayed Philips BIPAP volume values. The Philips BIPAP volume values were acquired by freezing the waveform and sliding a provided cursor along the waveform. Eight volume waveforms were recorded and analyzed. Each volume waveform was created manually using a silicone lung phantom connected to the Philips BIPAP. Statistically significant differences between the extracted volume values and Philips BIPAP displayed volume values were tested using the parametric Student's paired t-test, with a level of significance of 0.05.

2.1.4. Adapting Lifecare BIPAP to Permit Patient Exhalation

Unlike the Philips BIPAP, the Lifecare BIPAP contains multiple one-way airflow valves which do not permit patient exhalation through the patient circuit and back into the ventilator. To permit patient exhalation, we developed an in-house exhalation valve that we inserted into the patient circuit. We utilized a one-way Adafruit 12V plastic water solenoid valve to permit patient exhalation through the patient circuit and a plastic Y-valve to allow the valve to be inserted into

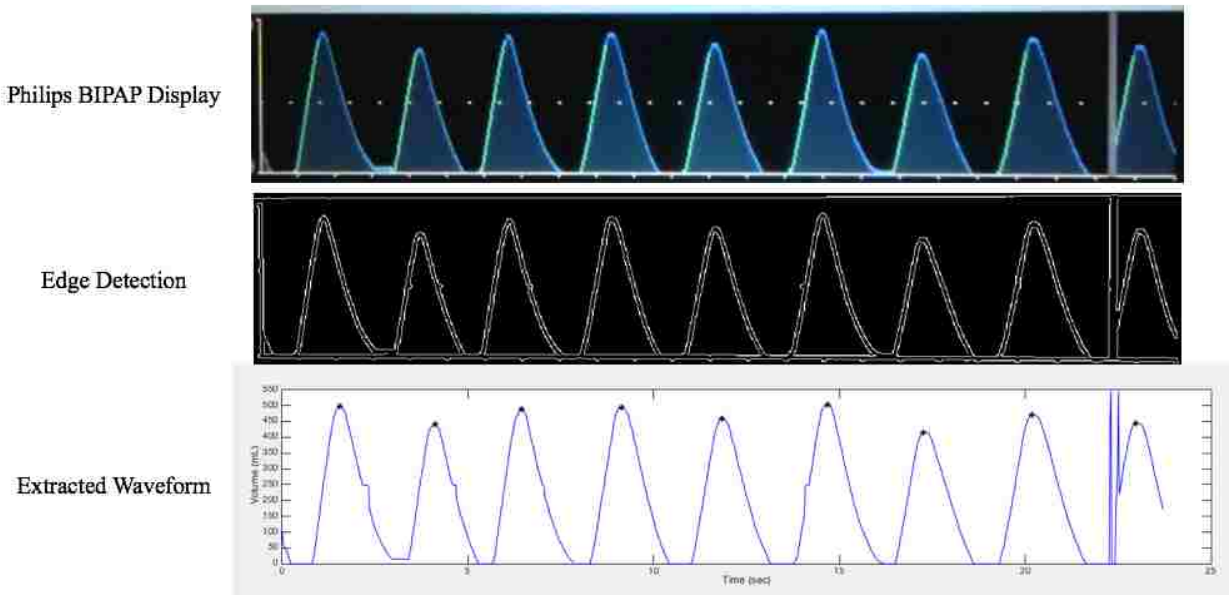

Figure 2.4. Screenshot of the real-time volume waveform displayed by the Philips BIPAP. The corresponding edge detection image and extracted waveform are also shown, which were produced from in-house MATLAB® video analysis code. Tidal volume peaks are shown in the extracted waveform as black stars.

the patient circuit (Adafruit Industries, New York City, NY). Both had ¾" (outer diameter) outlets, which allowed the valves to be inserted into the patient circuit without any modifications (Figure 2.5.). The water solenoid valve, which was normally closed, was opened by applying 12 volts (from an external battery), direct current, across two power terminals. Electronic timing was used from the Lifecare BIPAP to synchronize the open/closed states of the valve with the air volume output of the ventilator.

2.1.5. Developing a Method for Tracking an Abdominal Surface Marker

As previously mentioned, respiratory motion is often monitored using respiration surrogate signals such as spirometry measurements of the tidal volume or the tracking of an anterior abdominal surface marker. We wanted to use the tracking of an anterior abdominal surface marker to provide a monitoring system that was independent of the tidal volume measurements and consistent across both the free-breathing and BIPAP ventilation data collection platforms.

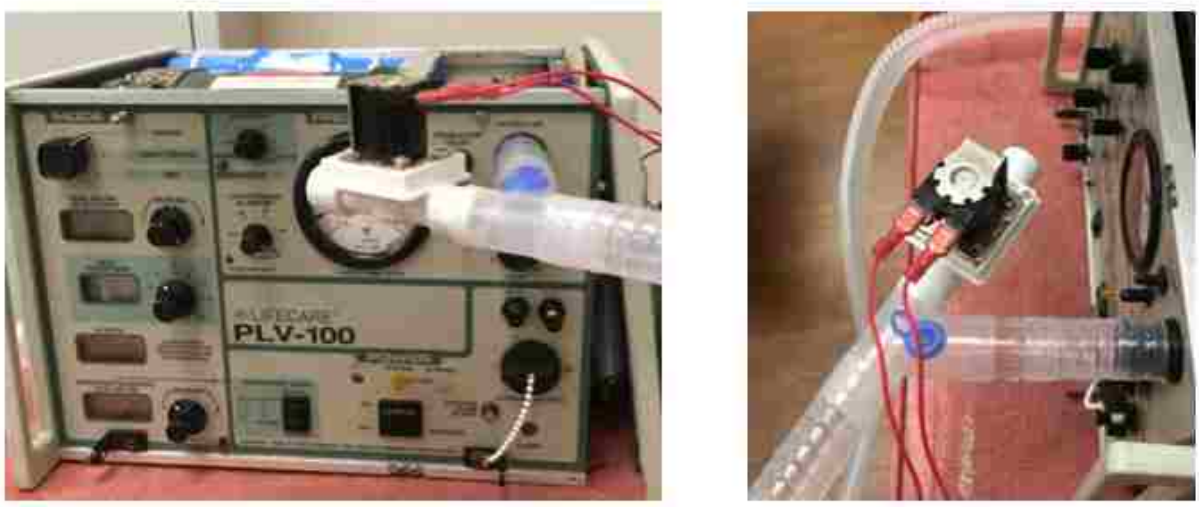

Figure 2.5. One-way water solenoid valve and Y-valve inserted into the Lifecare BIPAP patient circuit to permit patient exhalation.

We developed an in-house method for the tracking of an anterior abdominal surface marker. We used an abdominal compression frame, ½" acrylic sheet, foam, wood, hex bolts, and a heavy-duty plastic stick and associated track to build a custom abdominal surface marker system (Figure 2.6.). Circular reflectors (1 cm diameter) were glued along the plastic stick, which was used as the abdominal surface marker. A 12-megapixel iPhone 6s, positioned between the two blue foam pieces, was used to record the abdominal surface marker motion at 30 frames per second (Apple Inc., Cupertino, CA). In-house Python™ (Python Software Foundation, Beaverton, Oregon, US) video analysis code was written to track the circular reflectors on the abdominal surface marker. We validated the tracked positions of the circular reflectors using the Quality Assurance System for Advanced Radiotherapy (QUASAR) Respiratory Motion Phantom, which provided a stage that oscillated with a manufacturer stated 10 mm amplitude, at a user-selected rate (4-60 breaths per minute).

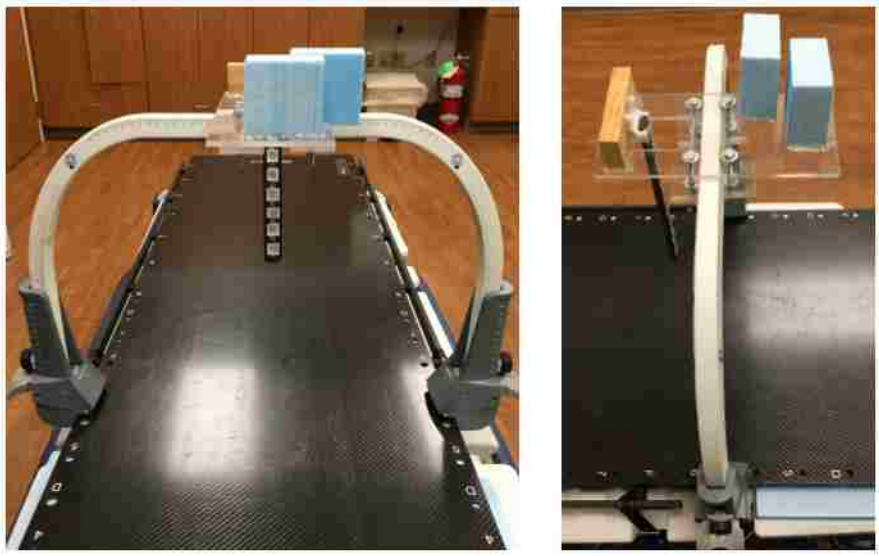

Figure 2.6. Custom built abdominal surface marker system. The abdominal surface marker (plastic stick) rested on the patient's anterior abdominal surface. The abdominal surface marker's motion was recorded with an iPhone, which was positioned between the two blue pieces of foam.

To verify reproducibility, we recorded eight 5-minute sessions, using different rates of the QUASAR phantom and different tracked circular reflectors. The abdominal surface marker rested on the oscillating stage of the QUASAR phantom. Reproducibility was quantified using the standard deviation of the abdominal surface marker amplitudes for all eight sessions.

2.2. Aims 2 & 3: Collect and Evaluate Patients' Free-Breathe (FB) & BIPAP Data

2.2.1. Institutional Review Board Approval and Patient Enrollment

We obtained institutional review board (IRB) approval from Our Lady of the Lake (OLOL) College in March of 2018 (OLOL IRB #2018-029). The IRB protocol (Appendix A. Institutional Review Board Protocol) consisted of collecting patients' breathing data with and without BIPAP ventilation assistance during daily sessions, either before or after their radiation treatments. Written informed consent was obtained for all patients on their initial imaging simulation day. Candidates for BIPAP ventilation assistance included patients that met the following criteria:

- Presented at Mary Bird Perkins Cancer Center's Essen Lane location for fractionated radiation therapy with disease sites impacted by respiratory motion (e.g. lung cancer and esophageal cancer);
- Were to be treated with normal breathing during treatment (i.e. non-breath-hold patients);
- Were able to tolerate wearing a nasal ventilation mask;
- Were able to breathe through their nose only for at least two-minute intervals; and
- Were amenable to coaching for their breathing.

Eleven patients were initially enrolled in this research study and were fitted with a nasal ventilation mask and bacteria filter (Figure 2.7.); however, one patient was excluded from this study because they could not breathe through their nose. We collected free-breathe and BIPAP data from the remaining 10 patients during sessions which occurred either before or after patients' radiation treatments and lasted 10-15 minutes.

Figure 2.7. Left: Bacteria filter. Right: Nasal ventilation mask with black Velcro® straps.

The patient characteristics (Table 2.1.) included a mean age of 58 years and range of 34-75 years. Three patients received 28 radiation treatment fractions for esophageal cancer. Five patients

received 30-33 radiation treatment fractions for lung cancer. The remaining two patients received four and seven stereotactic body radiation treatment fractions for lung cancer. All patients had a smoking history, which ranged from an unknown amount of pack-years to 90 pack-years (1 pack-year = 7300 cigarettes). All patients had sessions on more than 50% of their treatment days.

Table 2.1. Patient characteristics.

Patient	Age (years)	Gender	Treatment Site	Smoking History	Treatment Fractions	Sessions
1	57	M	Esophageal	‡	28	25
2	61	M	RLL	‡	30	21
3	75	M	RUL	†	33	17
4	57	M	Esophageal	†	28	16
5	59	F	RLL	‡	33	17
6	66	M	LL	U	30	18
7	43	F	RUL	†	33	17
8	71	M	Esophageal	†	28	15
9	34	M	LLL	†	4	4
10	52	F	LL	†	7	4

Abbreviations: RLL = right lower lung; RUL = right upper lung; LL = left lung; LLL = left lower lung
†: < 30 pack-years
‡: 31-90 pack-years
U: Unknown pack-years
1 pack-year = (1 pack/day)*(20 cigarettes/pack)*(365 days/year)*(1 year) = 7300 cigarettes

2.2.2. FB Data Collection

Free-breathe (FB) data, which included the FB tidal volume data and FB abdominal surface marker data, was recorded at the beginning of patients' sessions. Patients first put on their nasal ventilation mask and bacteria filter, and then were immobilized using the same devices created during their initial imaging simulation. Patients were not asked to remove any clothing. The abdominal surface marker system was positioned such that the marker, which rested on a 1" x 2" x 1/8" (width x length x thickness) acrylic sheet, was midway between the xiphoid process and the umbilicus. Indexing on the couch was used to ensure abdominal surface marker placement

reproducibility for each session. The seal of patients' ventilation masks was checked by having patients forcefully exhale through their nose and blocking the mask outlet. This process was repeated until the patient and investigator were satisfied that the mask was not leaking (i.e. no audible leak and patient could not feel any air leaking).

Components of the FB data that were analyzed included the tidal volumes, and the abdominal surface marker amplitudes, periods, and baselines (Figure 2.8.). FB tidal volume data was recorded using a mass flow meter, which uses complementary metal-oxide-semiconductor technology to measure air flow at rates up to 200 standard liters per minute (slm) and with an accuracy of ± 0.05 slm (Sensirion AG, Switzerland). The SFM 3000 flow meter (Figure 2.9.), with a vendor supplied adapter cable and USB stick, was connected to the same dedicated computer as the camera used to record the Philips BIPAP volume waveforms. The sensor's software sampled the air flow approximately every eight milliseconds and logged the flow signal in a comma separated variable file. The tidal volume data, which is simply the integrated flow signal, was calculated using in-house developed MATLAB® code (Appendix B. Calculating Volume from Flow Signal). The flow meter, which had ¾" outlets, was coupled to patients' bacteria filters. Patients were instructed to breathe through their nose only for two minutes, simulating a typical volumetric modulated arc therapy (VMAT) radiation treatment beam-on time,[23] and were notified when the FB data collection began.

2.2.3. BIPAP Ventilator Settings

The Philips BIPAP ventilator settings and Lifecare BIPAP ventilator settings were determined during patients' first sessions. Patient-specific ventilator settings were set to closely match patients' natural free-breathing patterns. Patients were asked to provide verbal feedback during this process to assist with any fine tuning of the ventilator settings.

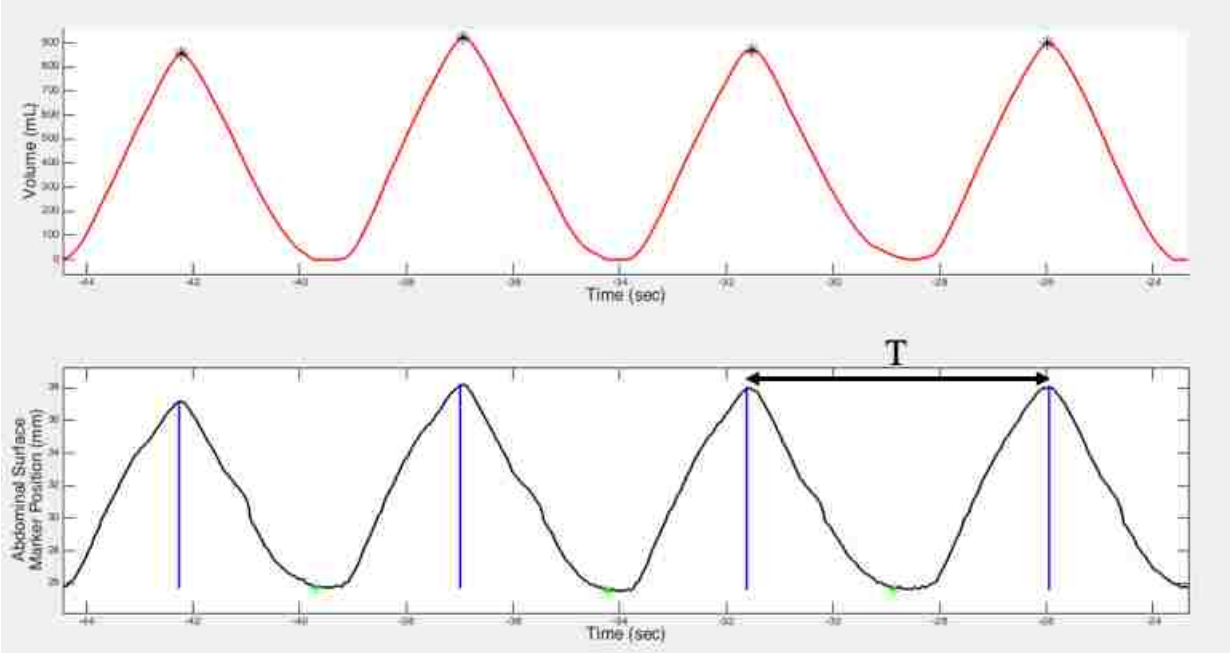

Figure 2.8. An example of collected free-breath data. Top: Plot of volume as a function of time with the tidal volume of each breath indicated by the black stars. Bottom: Plot of abdominal surface marker position as a function of time. The amplitude of each breath is indicated by the blue lines. The baseline, or starting position of each breath, is indicated by the green stars. The period, or time between adjacent peaks, is indicated by the T. Patients were instructed to take a large breath at the end of the data recording. We used this large breath to synchronize the volume plot and abdominal surface marker position plot (i.e. time = 0). Similar data was collected using the Philips BIPAP and Lifecare BIPAP.

Figure 2.9. Sensirion SFM 3000 mass flow meter.

The Philips BIPAP aimed to maintain a target tidal volume each breath by monitoring previous tidal volumes and continuously adjusting the delivered pressures. The tidal volume was the only ventilator setting that needed to be determined since the Philips BIPAP permitted patient triggering. During the first session, following the FB data collection, patients were connected to the Philips BIPAP to introduce them to BIPAP ventilation. Patients were asked to establish a natural breathing pattern. Inhalation and exhalation maximum pressures were limited to 8 cmH_20 and 4 cmH_20, respectively. After patients felt comfortable with BIPAP ventilation assistance (usually a few minutes) a target tidal volume was set, which was determined from the mean tidal volume from the FB data collection. Patient feedback was then used to adjust the tidal volume.

The Lifecare BIPAP delivered a preset tidal volume at a fixed breathing period. Both the tidal volume and breathing period ventilator settings needed to be determined since the Lifecare BIPAP did not permit patient triggering. During the first session, following the Philips BIPAP data collection, patients were connected to the Lifecare BIPAP. The same tidal volume was used as the Philips BIPAP. The breathing period was determined from the mean breathing period calculated from the FB data collection. The Lifecare BIPAP ventilator settings were fine-tuned using patient feedback.

2.2.4. Philips BIPAP Data Collection

The Philips BIPAP provided pure ventilation assistance (i.e. permitted patient triggering) which required patients to actively control their breathing to improve their respiratory reproducibility. We provided patients with visual feedback of their real-time volume waveform when using the Philips BIPAP. A projector was mounted to the patient couch and aimed at the ceiling directly above patients' heads (Figure 2.10.). The real-time volume waveform, captured by the camera mounted to the Philips BIPAP, was fed from the dedicated computer to the projector. A dotted line at the level of the target tidal volume was superimposed on the volume waveform

(Figure 2.4.). Patients were instructed to inhale to the dotted line and then exhale. The Philips BIPAP continuously adjusted the applied pressures to assist patients in achieving the target tidal volume each breath.

After the completion of the FB data collection, patients were connected to the Philips BIPAP using the appropriate patient-specific settings. The flow meter that was used during the FB data collection was removed from the patient circuit. It could not be used with the Philips BIPAP because the BIPAP continuously adjusted the delivered pressures to maintain the target tidal volume (i.e. the flow signal baseline was continuously changing). After a short warm-up period (10-90 seconds), patients were notified that the Philips BIPAP data collection would begin and last two minutes. Components of the Philips BIPAP data that were analyzed included tidal volumes, and abdominal surface marker amplitudes, periods, and baselines (Figure 2.8.).

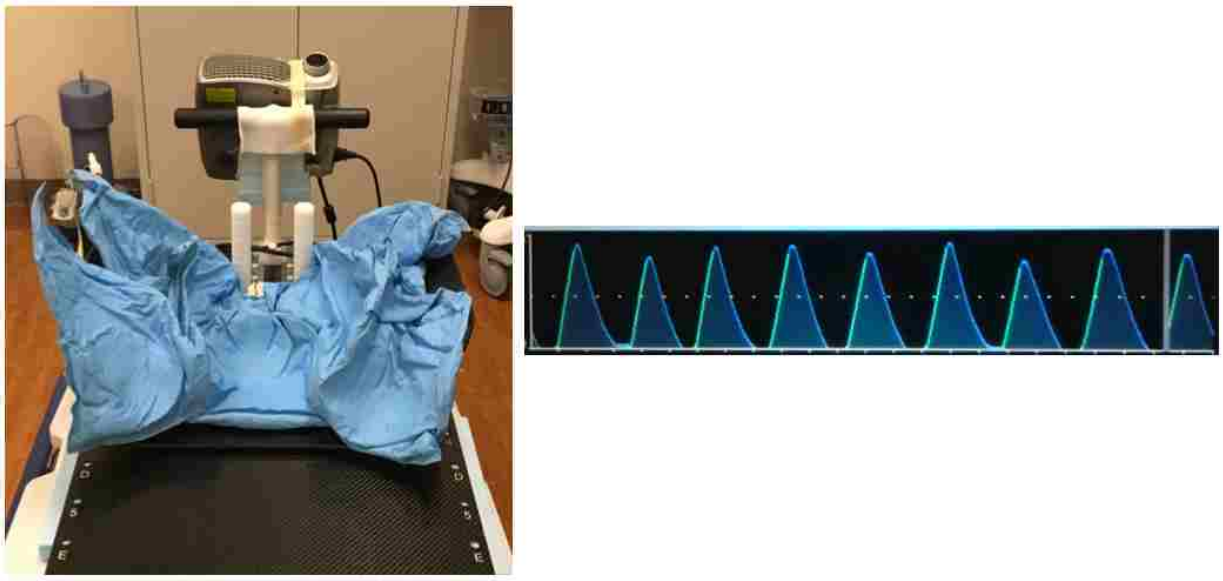

Figure 2.10. Left: Projector aimed at the ceiling directly above patients' heads. Right: Example of the real-time volume waveform that was provided to patients.

2.2.5. Lifecare BIPAP Data Collection

The Lifecare BIPAP provided controlled ventilation assistance (i.e. did not permit patient triggering) which required patients to synchronize their breathing with the air volume output of the Lifecare BIPAP to improve their respiratory reproducibility. We provided patients with inhalation and exhalation visual cues when using the Lifecare BIPAP. We built a visual cue stand that clamped to the couch and hung above patients' heads (Figure 2.11.). The visual cue stand contained a green "inhale" LED and a red "exhale" LED. The same electronic timing as the exhalation valve was used to synchronize the inhale and exhale LEDs with the air volume output of the Lifecare BIPAP. Patients were instructed to inhale when the green LED was illuminated and exhale when the red LED was illuminated.

The order of the Philips BIPAP and Lifecare BIPAP was switched daily to mitigate any potential bias of using the BIPAPs in the same order. After the completion of either the FB data collection or Philips BIPAP data collection, patients were connected to the Lifecare BIPAP, using the appropriate patient-specific ventilator settings. The flow meter that was used during the FB data collection was inserted into the patient circuit. After a short "warm-up" period (10-90 seconds), patients were notified that the Lifecare BIPAP data collection would begin and last two minutes. Components of the Lifecare BIPAP data that were analyzed included tidal volumes, and abdominal surface marker amplitudes, periods, and baselines (Figure 2.8.).

2.2.6. Data Analysis

After each session for a single patient, we calculated a mean and standard deviation for each component of the FB data, Philips BIPAP data, and Lifecare BIPAP data. Data components of each platform (i.e. FB, Philips BIPAP, and Lifecare BIPAP) included the tidal volumes, and abdominal surface marker amplitudes, periods, and baselines (Figure 2.8.). Variations of each platform-specific data component for each session were quantified using a variation metric, which

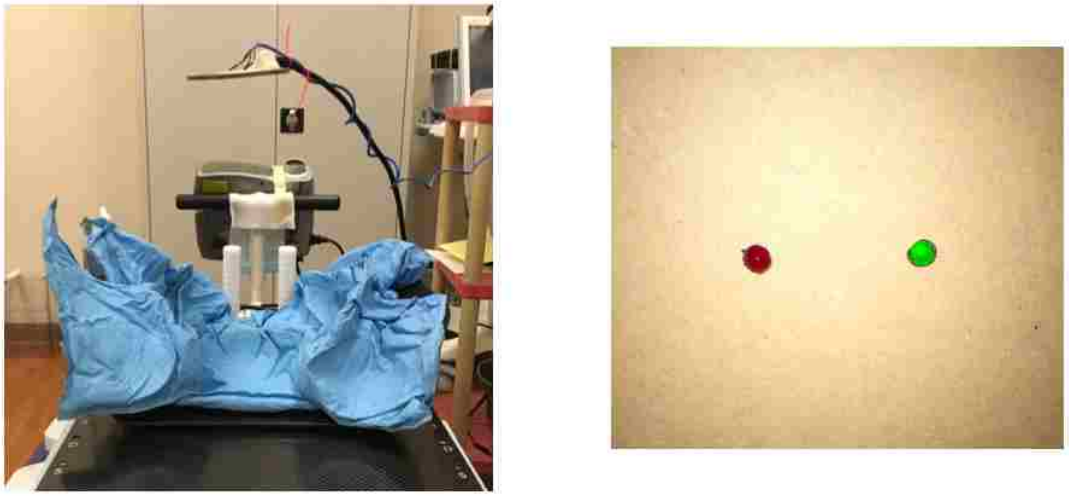

Figure 2.11. Left: Visual cue stand hanging above patient's head. Right: Visual cue stand which contained a green "inhale" LED and a red "exhale" LED.

was either the coefficient of variation (CV), which is simply the ratio of the standard deviation to the mean, or the standard deviation (SD).

We defined intra-session variation for each platform-specific data component as the mean variation metric for that platform-specific data component of all sessions. We defined inter-session variation for each platform-specific data component as the CV of the platform-specific data component session means. This intra-session and inter-session analysis process was repeated for all patients (Table 2.2.).

Table 2.2. Summary of variation metrics for each platform-specific (i.e. FB, Philips BIPAP, Lifecare BIPAP) data component. Variation metrics were calculated for each patient.

Platform-Specific Data Component	Intra-Session Variation Metric	Inter-Session Variation Metric
Tidal Volume	$\overline{CV}$	CV
ASM$^{\lozenge}$ Amplitude	$\overline{CV}$	CV
ASM$^{\lozenge}$ Period	$\overline{CV}$	CV
ASM$^{\lozenge}$ Baseline	$\overline{SD}$	

◊ Abdominal Surface Marker (ASM)
CV = Coefficient of Variation
SD = Standard Deviation

The intra-session variation metric for the abdominal surface marker baseline was defined differently than the other data components. The mean abdominal surface marker baseline position does not provide any useful information, meaning we were only interested in the variation of the baseline, not the location in space around which that baseline variation was averaged. As a result, we used the SD of the abdominal surface marker baselines, rather than the CV, as the intra-session variation metric. We also could not calculate an inter-session variation metric for the abdominal surface marker baselines because we did not have a reliable method for monitoring the baseline session to session. For example, if a patient wore a thick sweatshirt during one session and did not wear the same sweatshirt during another session, then the mean abdominal surface marker baseline would be different session to session because of patient clothing.

We compared the variation results of each data component for all patients between platforms (i.e. FB vs. Philips BIPAP, FB vs. Lifecare BIPAP, Philips BIPAP vs. Lifecare BIPAP). Statistical significance was determined for each comparison using the non-parametric Wilcoxon signed-rank test, with a significance level of 0.05, based on the small number of samples and a visual inspection of the data distributions.

3. Results

3.1. Aim 1 Results: Equipment Modifications

3.1.1. Extracting Philips BIPAP Volume Waveform Data

Eight volume waveform videos, each 24 seconds, were recorded and analyzed to validate the extracted volume values. 100 extracted volume values were compared to the displayed Philips BIPAP volume values. No significant difference (p = 0.533) was found between the extracted volume values and Philips BIPAP volume values. The mean relative percent difference ([extracted value – Philips value]/Philips value) was -1.46% (Figure 3.1.), which corresponded to a mean absolute percent difference of 3.80%.

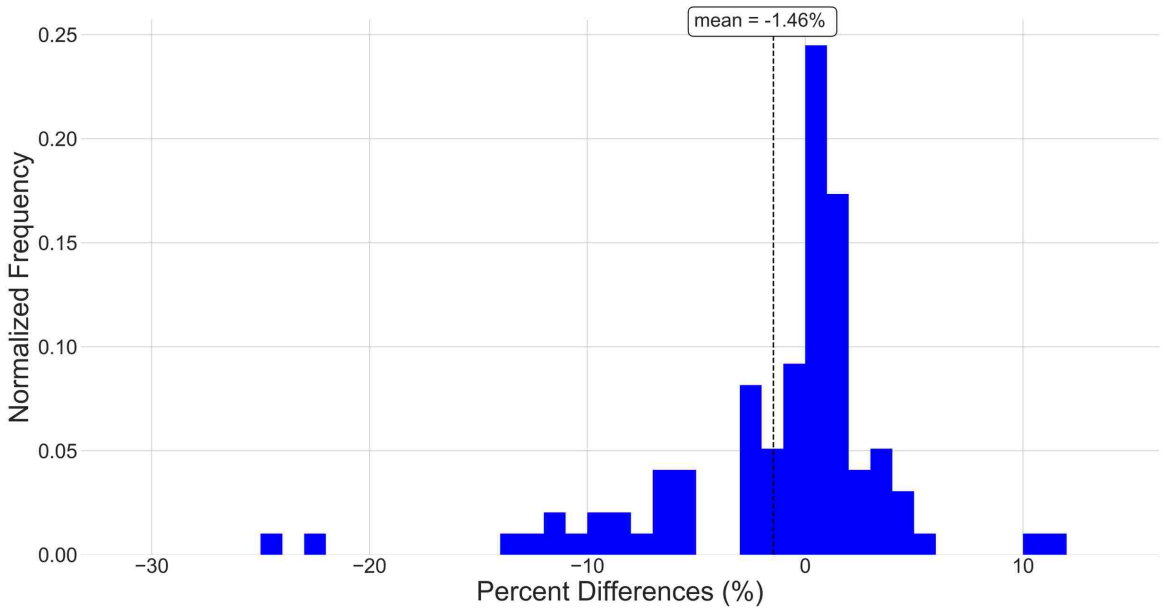

Figure 3.1. Histogram of the percent differences between the extracted volume values and Philips BIPAP displayed volume values. The two most negative bins correspond to small differences with small Philips BIPAP volume values (e.g. a difference of ~10 mL with a Philips BIPAP volume value of ~50 mL). Bin sizes are 1%.

3.1.2. Developing a Method for Tracking an Abdominal Surface Marker

Eight 5-minute videos were recorded to verify reproducibility of the tracked circular reflector positions. Each video used different QUASAR phantom oscillation rates and tracked circular reflectors. Reproducibility was quantified using the standard deviation of the abdominal surface marker amplitudes for all eight sessions. The mean abdominal surface marker amplitude, calculated by our in-house video analysis code, was 9.66 mm (Figure 3.2.), which was 0.34 mm different than the expected amplitude of 10 mm. The standard deviation of the abdominal surface marker amplitudes for all eight sessions was 0.1 mm.

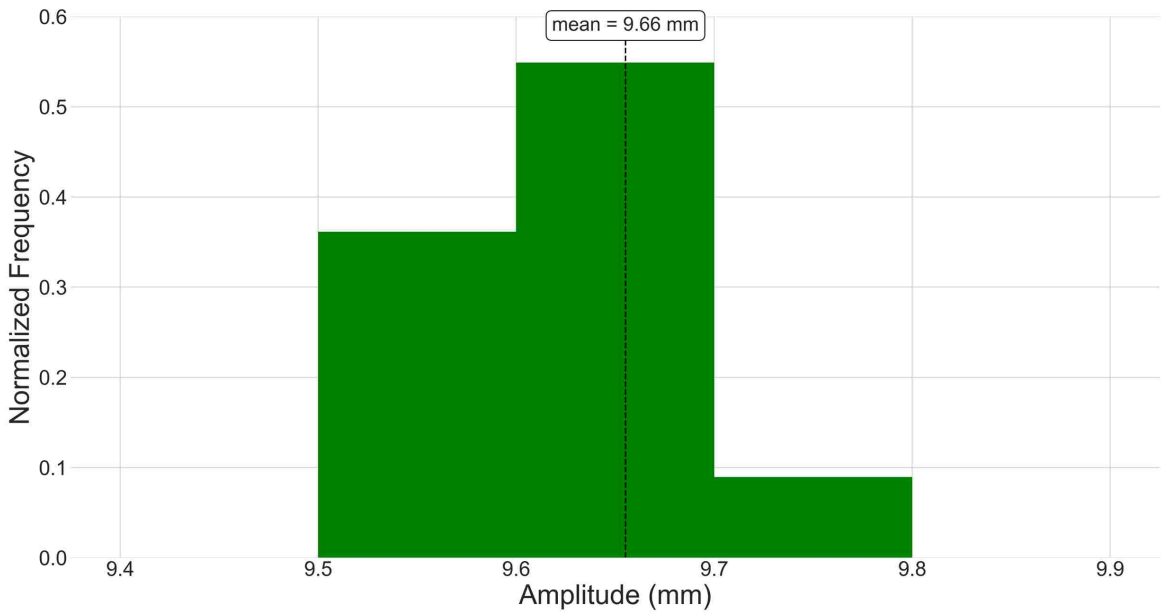

Figure 3.2. Histogram of the calculated abdominal surface marker amplitude values using the QUASAR phantom with stated amplitude of 10 mm. Bin sizes are 0.1 mm.

3.2. Aims 2 & 3 Results: Collect and Evaluate Patients' FB & BIPAP Data

3.2.1. Overview of Results

The results of aims 2 and 3, which involved collecting and evaluating patients' free-breath (FB) data and BIPAP ventilation assistance data (Philips BIPAP and Lifecare BIPAP), are presented simultaneously. We collected FB data and BIPAP data from 10 patients during sessions which occurred either before or after patients' radiation treatments. Not all patients had the same number of sessions because patients were prescribed different numbers of radiation treatment fractions (Table 2.1.). Patients were also permitted to skip sessions on treatment days when they were not feeling well, running late, or had other appointments (i.e. physician visits, chemotherapy, etc.). We calculated variation metrics for the platform-specific data components and compared the results between platforms (i.e. FB vs. Philips BIPAP, FB vs. Lifecare BIPAP, Philips BIPAP vs. Lifecare BIPAP). Statistical significance was determined for each comparison using the non-parametric Wilcoxon signed-rank test, with a significance level of 0.05. Patient 8's results are presented first as an example, followed by the results for all patients. The results are presented in the order of:

- Tidal Volume
- Abdominal Surface Marker Amplitude
- Abdominal Surface Marker Period
- Abdominal Surface Marker Baseline
- Compilation of Results

Coefficient of variation (CV) values are unitless quantities and can be thought of as a percent variation. Qualitatively, both intra-session variation figures and inter-session variation figures that show lower CV values indicate lower variation (i.e. more reproducible).

3.2.2. Tidal Volume

Intra-session tidal volume variation for each patient was quantified using the mean coefficient of variation (CV) of the CVs for all sessions. Patient 8's FB, Philips BIPAP, and Lifecare BIPAP intra-session tidal volume variation was 0.107, 0.069, and 0.078, respectively (Figure 3.3.). The mean intra-session tidal volume variation of all patients (Figure 3.4.) was 0.172, 0.118, and 0.096 for FB, Philips BIPAP, and Lifecare BIPAP, respectively. Both the Philips BIPAP and Lifecare BIPAP intra-session tidal volume variations were significantly lower ($p = 0.022$ and $p = 0.007$) than the FB intra-session tidal volume variation. The Philips BIPAP had a 0.055 mean variation reduction. The Lifecare BIPAP had the largest mean variation reduction of 0.077.

Inter-session tidal volume variation for each patient was quantified using the CV of the tidal volume session means. Patient 8's FB, Philips BIPAP, and Lifecare BIPAP inter-session tidal volume variation was 0.094, 0.053, and 0.095, respectively (Figure 3.5.). The mean inter-session tidal volume variation of all patients (Figure 3.6.) was 0.161, 0.106, and 0.113 for FB, Philips BIPAP, and Lifecare BIPAP, respectively. Neither the Philips BIPAP nor Lifecare BIPAP inter-session tidal volume variations were significantly lower ($p = 0.203$ and $p = 0.074$) than the FB inter-session tidal volume variation. The Philips BIPAP had the largest mean variation reduction of 0.054. The Lifecare BIPAP had a mean variation reduction of 0.048.

3.2.3. Abdominal Surface Marker Amplitude

Intra-session abdominal surface marker amplitude variation for each patient was quantified using the mean coefficient of variation (CV) of the CVs for all sessions. Patient 8's FB, Philips BIPAP, and Lifecare BIPAP intra-session abdominal surface marker amplitude variation was 0.087, 0.058, and 0.070, respectively (Figure 3.7.). The mean intra-session abdominal surface marker amplitude of all patients (Figure 3.8.) was 0.185, 0.134, and 0.139 for FB, Philips BIPAP, and Lifecare BIPAP, respectively. Neither the Philips BIPAP nor Lifecare BIPAP intra-session

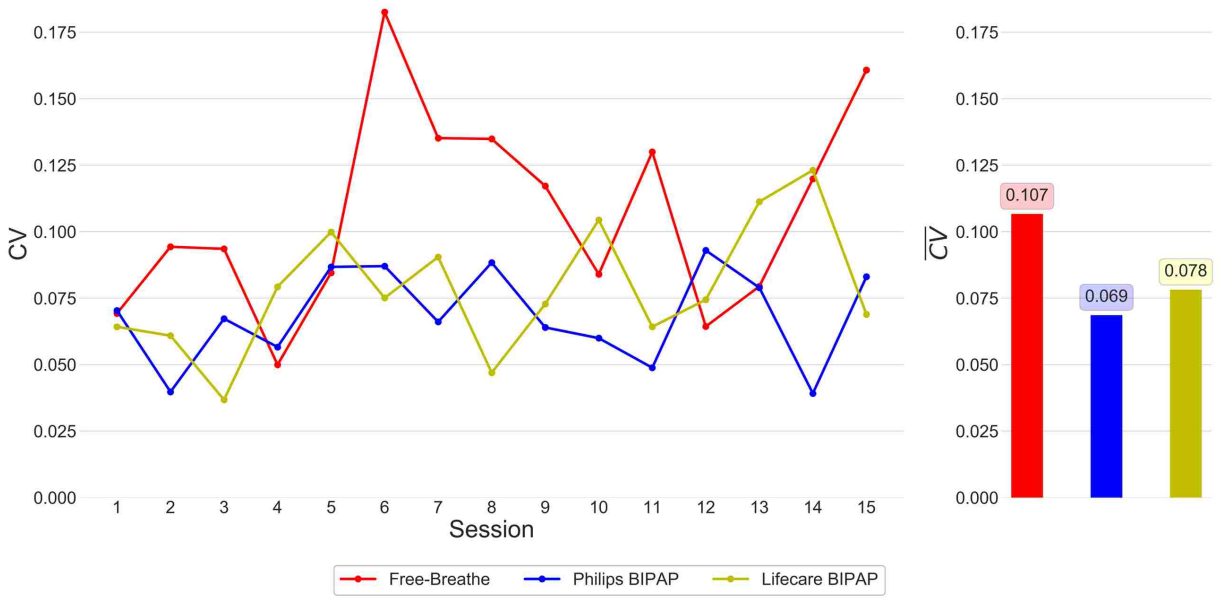

Figure 3.3. Intra-session tidal volume variation for patient 8. Left: CV of the tidal volume for each session. Right: Mean tidal volume CV of all sessions. This represents the intra-session tidal volume variation.

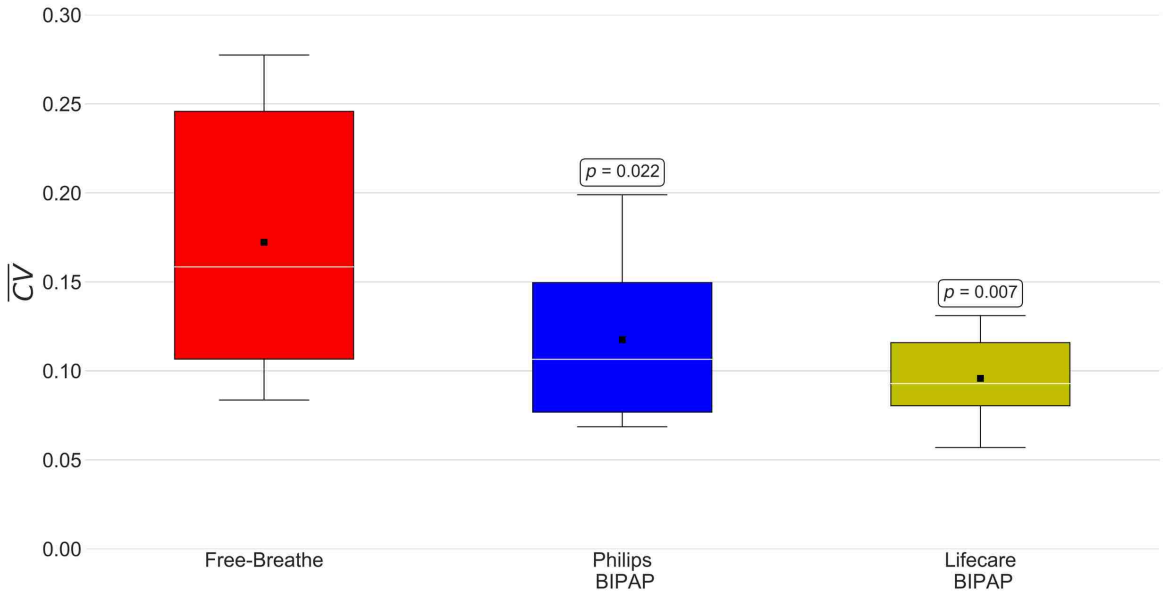

Figure 3.4. Intra-session tidal volume variation results for all patients. Black boxes indicate the means and white lines indicate the medians. *p*-values shown are compared to free-breathe.

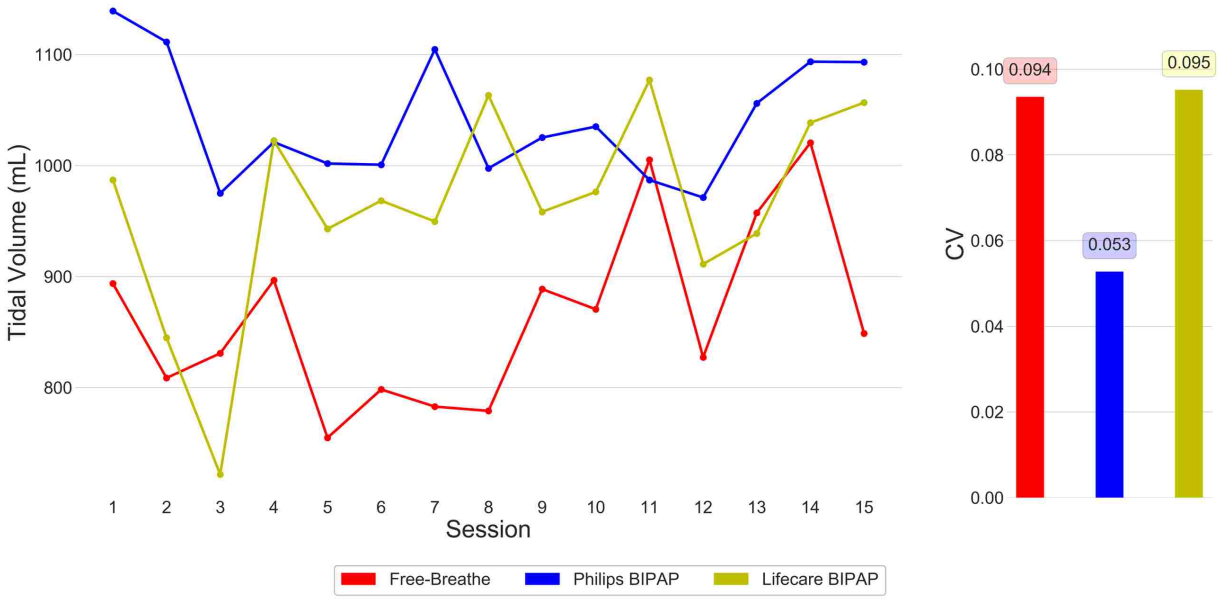

Figure 3.5. Inter-session tidal volume variation for patient 8. Left: Mean tidal volume of each session. Right: CV of the tidal volume session means. This represents the inter-session tidal volume variation.

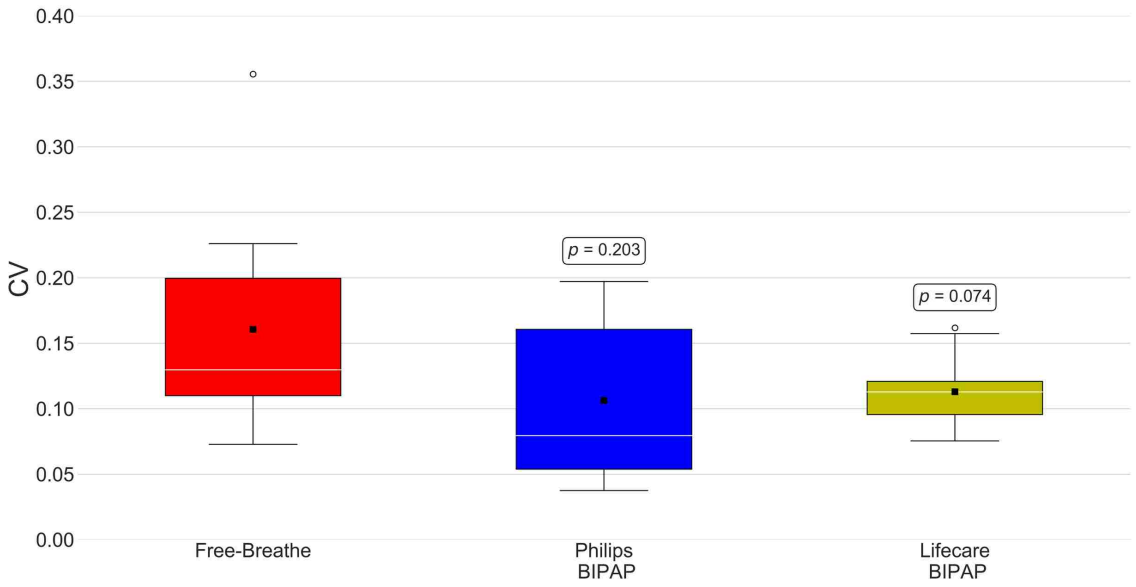

Figure 3.6. Inter-session tidal volume variation results for all patients. Black boxes indicate the means, white lines indicate the medians, and circles indicate outliers. *p*-values shown are compared to free-breathe.

abdominal surface marker amplitude variations were significantly lower ($p = 0.059$ and $p = 0.114$) than the FB intra-session abdominal surface marker amplitude variation. The Philips BIPAP had the largest mean variation reduction of 0.051. The Lifecare BIPAP had a mean variation reduction of 0.045.

Inter-session abdominal surface marker amplitude variation for each patient was quantified using the CV of the abdominal surface marker amplitude session means. Patient 8's FB, Philips BIPAP, and Lifecare BIPAP inter-session abdominal surface marker amplitude variation was 0.090, 0.087, and 0.094, respectively (Figure 3.9.). The mean inter-session abdominal surface marker amplitude variation of all patients (Figure 3.10.) was 0.254, 0.209, and 0.207 for FB, Philips BIPAP, and Lifecare BIPAP, respectively. Neither the Philips BIPAP nor Lifecare BIPAP inter-session abdominal surface marker amplitude variations were significantly lower ($p = 0.074$ and $p = 0.074$) than the FB inter-session abdominal surface marker amplitude variation. The Philips BIPAP had a mean variation reduction of 0.045. The Lifecare BIPAP had the largest mean variation reduction of 0.047.

3.2.4. Abdominal Surface Marker Period

Intra-session abdominal surface marker period variation for each patient was quantified using the mean coefficient of variation (CV) of the CVs for all sessions. Patient 8's FB, Philips BIPAP, and Lifecare BIPAP intra-session abdominal surface marker period variation was 0.083, 0.051, and 0.045, respectively (Figure 3.11.). The mean intra-session abdominal surface marker period variation of all patients (Figure 3.12.) was 0.140, 0.086, and 0.055 for FB, Philips BIPAP, and Lifecare BIPAP, respectively. Both the Philips BIPAP and Lifecare BIPAP intra-session abdominal surface marker period variations were significantly lower ($p = 0.022$ and $p = 0.005$) than the FB intra-session abdominal surface marker period variation. The Philips BIPAP had a

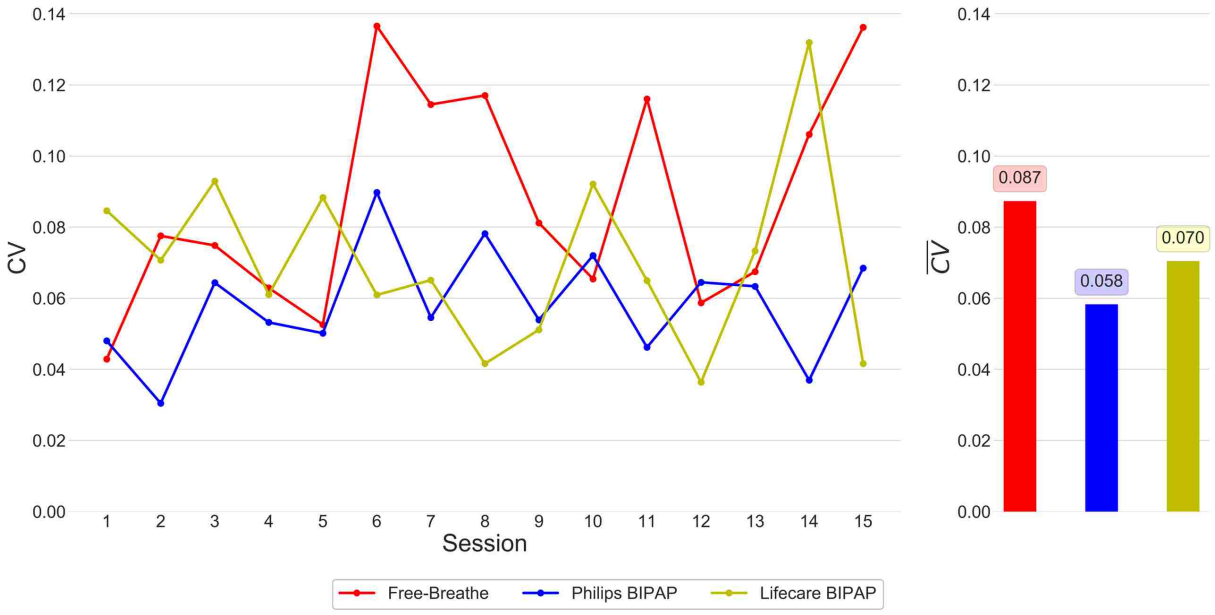

Figure 3.7. Intra-session abdominal surface marker amplitude variation for patient 8. Left: CV of the abdominal surface marker amplitude for each session. Right: Mean abdominal surface marker amplitude CV of all sessions. This represents the intra-session abdominal surface marker amplitude variation.

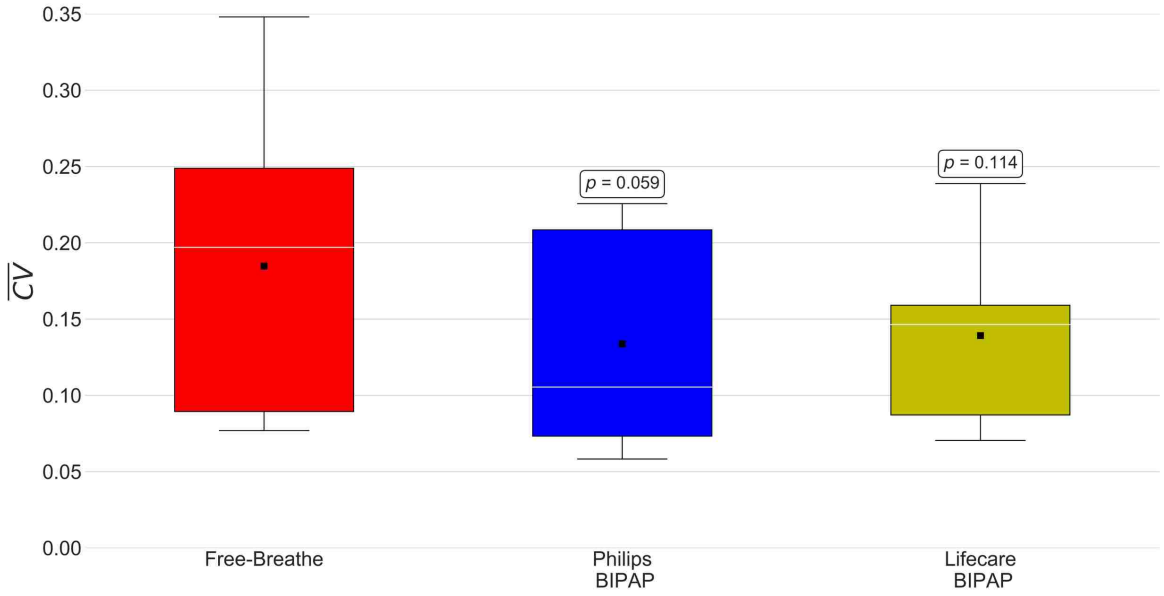

Figure 3.8. Intra-session abdominal surface marker amplitude variation results for all patients. Black boxes indicate the means and white lines indicate the medians. *p*-values shown are compared to free-breathe.

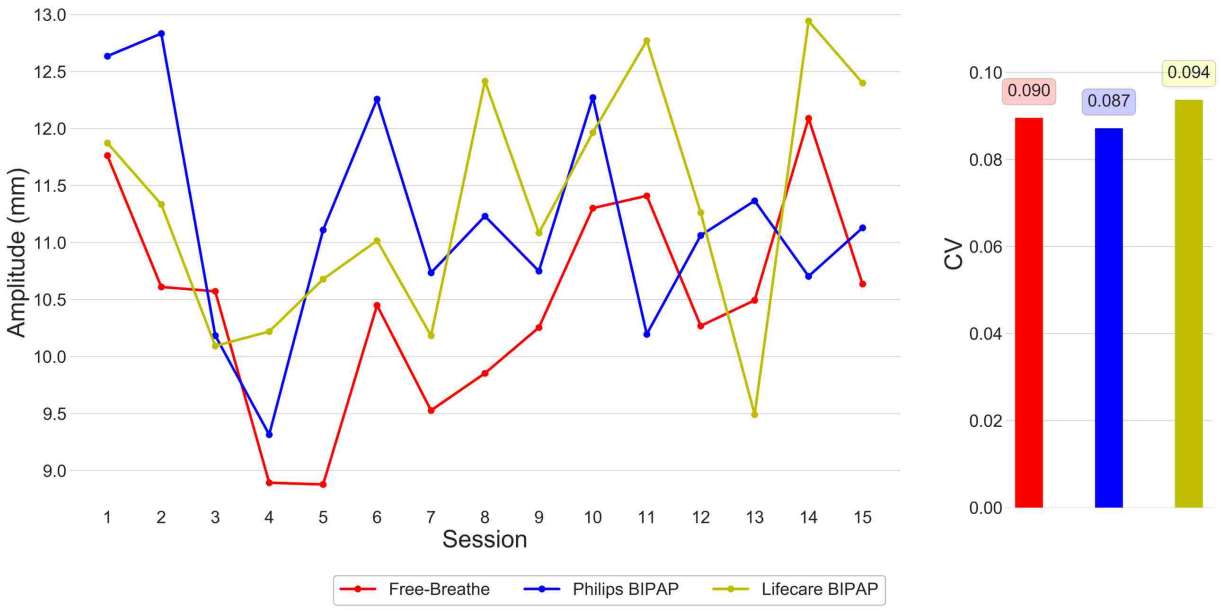

Figure 3.9. Inter-session abdominal surface marker amplitude variation for patient 8. Left: Mean abdominal surface marker amplitudes of each session. Right: CV of the abdominal surface marker amplitude session means. This represents the inter-session abdominal surface maker variation.

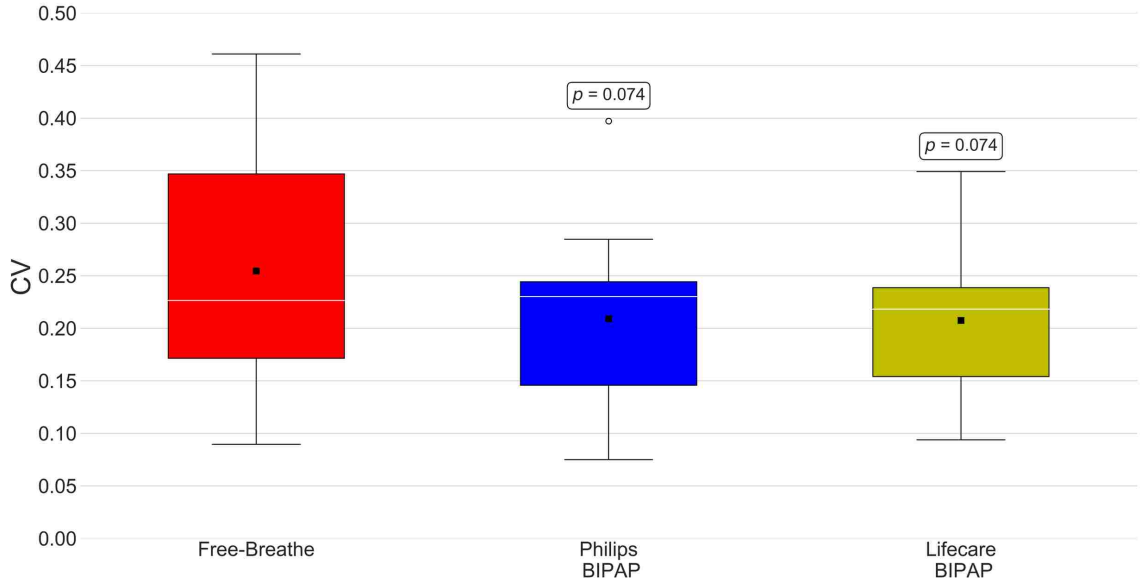

Figure 3.10. Inter-session abdominal surface marker amplitude variation results for all patients. Black boxes indicate the means, white lines indicate the medians, and circles indicate outliers. *p*-values shown are compared to free-breathe.

mean variation reduction of 0.054. The Lifecare BIPAP had the largest mean variation reduction of 0.086.

Inter-session abdominal surface marker period variation for each patient was quantified using the CV of the abdominal surface marker period session means. Patient 8's FB, Philips BIPAP, and Lifecare BIPAP inter-session abdominal surface marker period variation was 0.091, 0.117, and 0.011, respectively (Figure 3.13.). The mean inter-session abdominal surface marker period variation of all patients (Figure 3.14.) was 0.143, 0.124, and 0.048 for FB, Philips BIPAP, and Lifecare BIPAP, respectively. The Philips BIPAP inter-session abdominal surface marker period variation was not significantly lower (p = 0.169) than the FB inter-session abdominal surface marker period variation. The Lifecare BIPAP inter-session abdominal surface marker period variation was significantly lower (p = 0.013) than the FB inter-session abdominal surface marker period variation. The Philips BIPAP had a mean variation reduction of 0.020. The Lifecare BIPAP had the largest mean variation reduction of 0.095.

3.2.5. Abdominal Surface Marker Baseline

Intra-session abdominal surface marker baseline variation for each patient was quantified using the mean standard deviation (SD) of the SDs for all sessions. Patient 8's FB, Philips BIPAP, and Lifecare BIPAP intra-session abdominal surface marker baseline variation was 0.787 mm, 0.352 mm, and 0.577 mm, respectively (Figure 3.15.). The mean intra-session abdominal surface marker baseline of all patients (Figure 3.16.) was 0.725 mm, 0.682 mm, and 0.945 mm for FB, Philips BIPAP, and Lifecare BIPAP, respectively. The Philips BIPAP intra-session abdominal surface marker baseline variation was not significantly lower (p = 0.646) than the FB intra-session abdominal surface marker baseline variation. The Lifecare BIPAP intra-session abdominal surface marker baseline variation was significantly higher (p = 0.037) than the FB intra-session abdominal

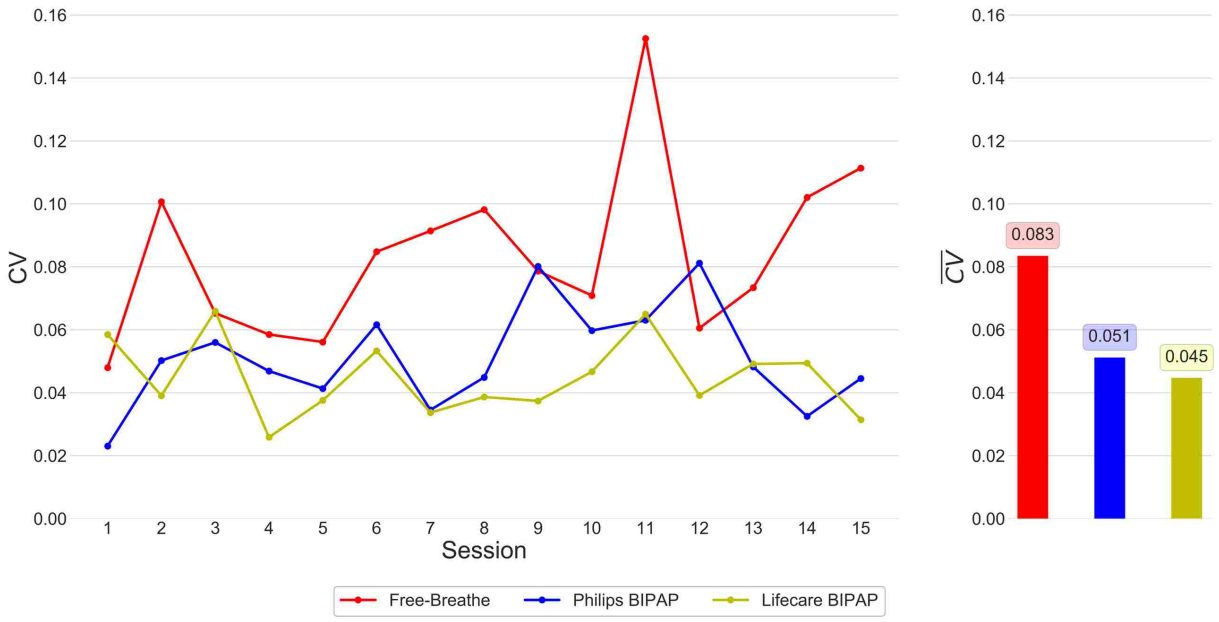

Figure 3.11. Intra-session abdominal surface marker period variation for patient 8. Left: CV of the abdominal surface marker period for each session. Right: Mean abdominal surface marker period CV of all sessions. This represents the intra-session abdominal surface marker period variation.

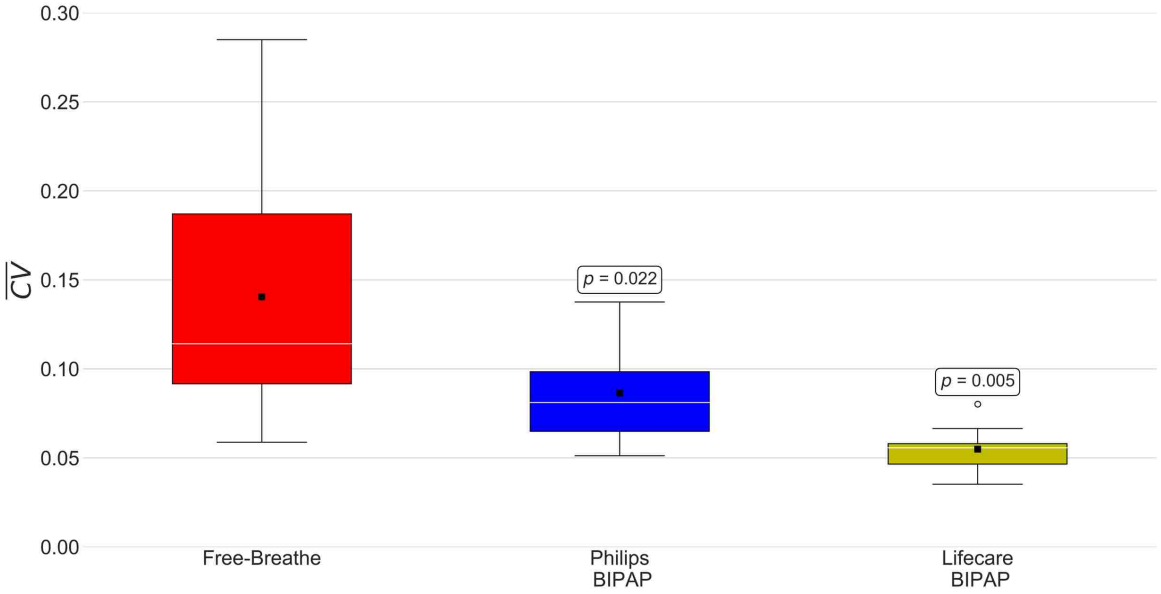

Figure 3.12. Intra-session abdominal surface marker period variation results for all patients. Black boxes indicate the means, white lines indicate the medians, and circles indicate outliers. *p*-values shown are compared to free-breathe.

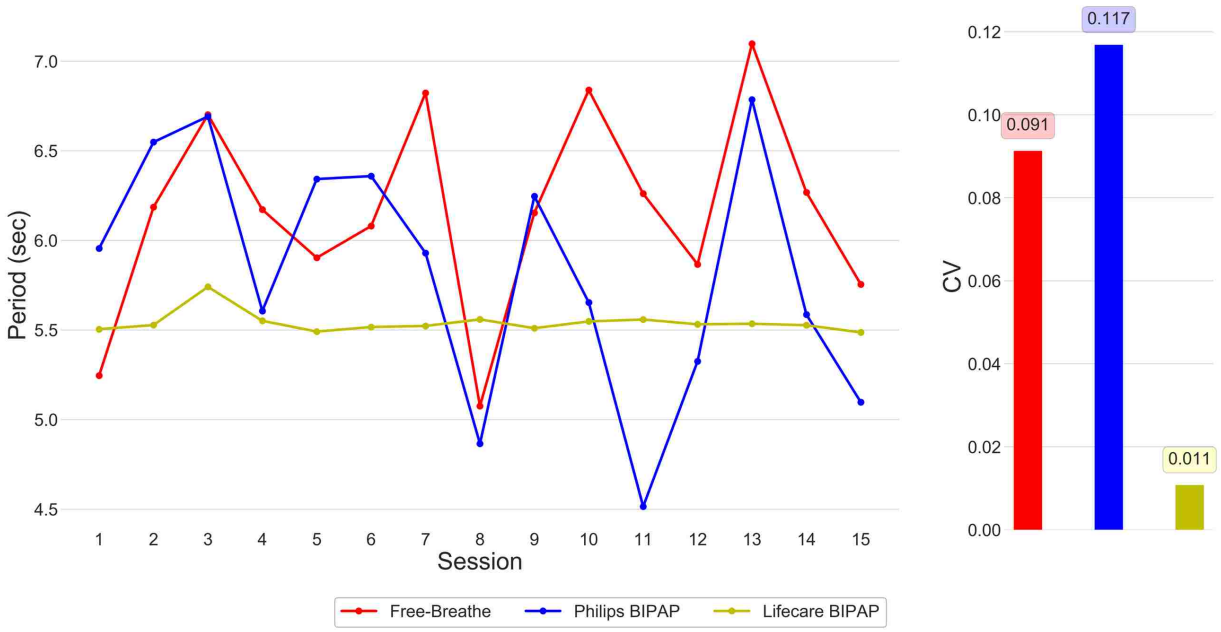

Figure 3.13. Inter-session abdominal surface marker period variation for patient 8. Left: Mean abdominal surface marker periods of each session. Right: CV of the abdominal surface marker period session means. This represents the inter-session abdominal surface marker period variation.

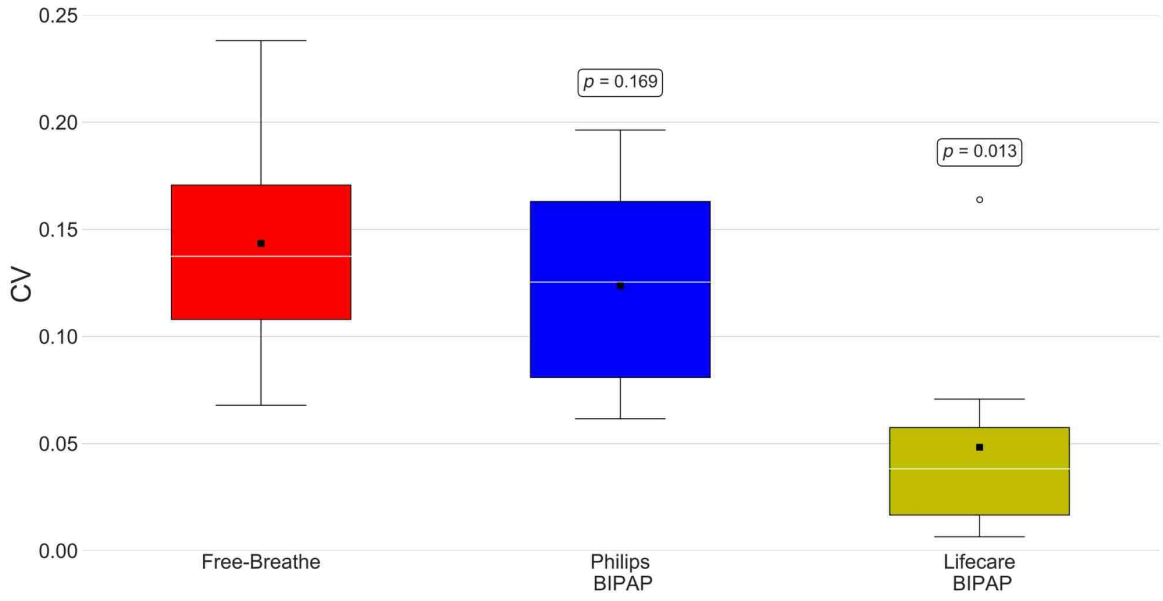

Figure 3.14. Inter-session abdominal surface marker period variation results for all patients. Black boxes indicate the means, white lines indicate the medians, and circles indicate outliers. *p*-values shown are compared to free-breathe.

surface marker baseline variation. The Philips BIPAP had the largest mean variation reduction of 0.043 mm. The Lifecare BIPAP had an increase in mean variation of 0.220 mm.

3.2.6. Compilation of Results

Overall, the Philips BIPAP reduced intra-session and inter-session mean variations for all data components compared to FB (Figure 3.17. and Figure 3.18.); however, only the intra-session tidal volume variation and intra-session abdominal surface marker period variation were significantly lower than the corresponding FB variations (Table 3.1.). The mean ± one SD Philips BIPAP data collection time (first abdominal surface marker peak time to last abdominal surface marker peak time) of all patients was 110.5 ± 6.8 sec. This was not significantly different ($p = 0.721$) than the mean ± one SD FB data collection time of 112.0 ± 5.0 sec.

Overall, the Lifecare BIPAP reduced intra-session and inter-session mean variations for all data components except the intra-session abdominal surface marker baseline, compared to FB (Figure 3.17. and Figure 3.18.); however, the intra-session tidal volume variation and both the intra-session and inter-session abdominal surface marker period variations were significantly lower than the corresponding FB variations (Table 3.1.). The intra-session abdominal surface marker baseline variation was significantly higher than the corresponding FB variation. The mean ± one SD Lifecare BIPAP data collection time (first abdominal surface marker peak time to last abdominal surface marker peak time) of all patients was 75.8 ± 24.3 sec. This was significantly lower ($p = 0.005$) than the mean ± one SD FB data collection time of 112.0 ± 5.0 sec.

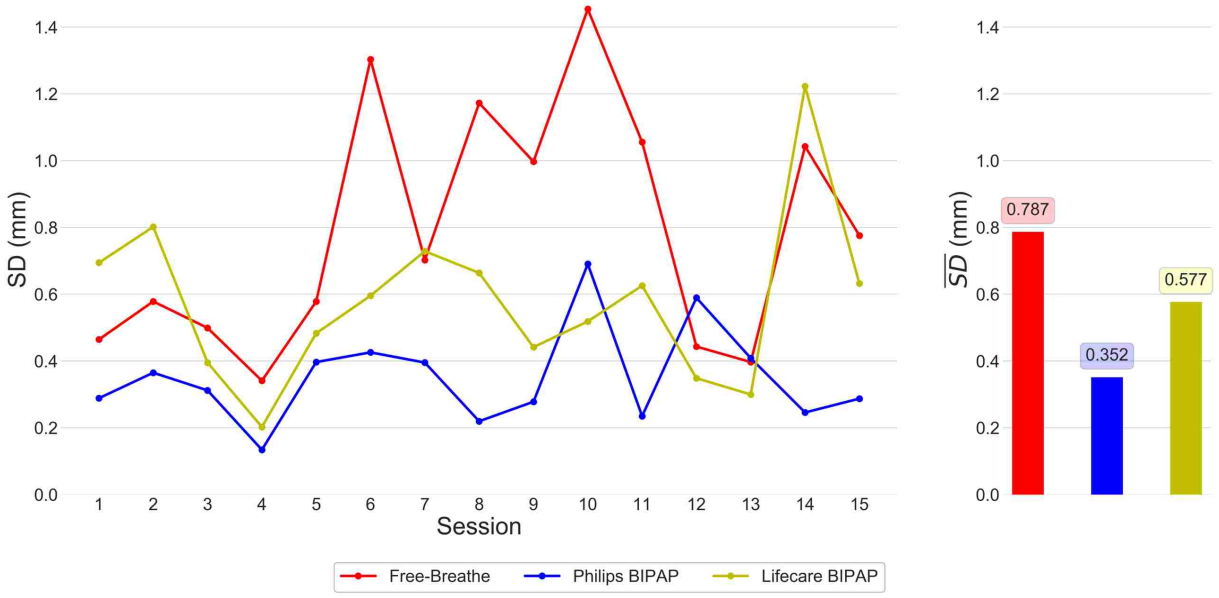

Figure 3.15. Intra-session abdominal surface marker baseline variation for patient 8. Left: SD of the abdominal surface marker baseline for each session. Right: Mean SD of the abdominal surface marker baselines of all sessions. This represents the intra-session abdominal surface marker baseline variation.

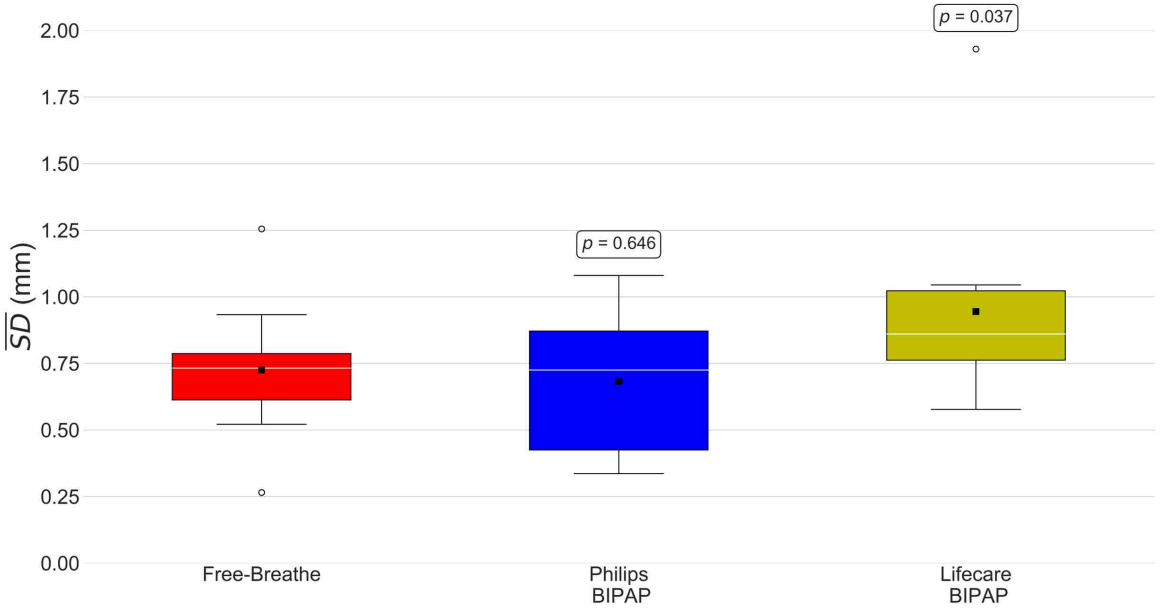

Figure 3.16. Intra-session abdominal surface marker baseline variation results for all patients. Black boxes indicate the means, white lines indicate the medians, and circles indicate outliers. *p*-values shown are compared to free-breathe.

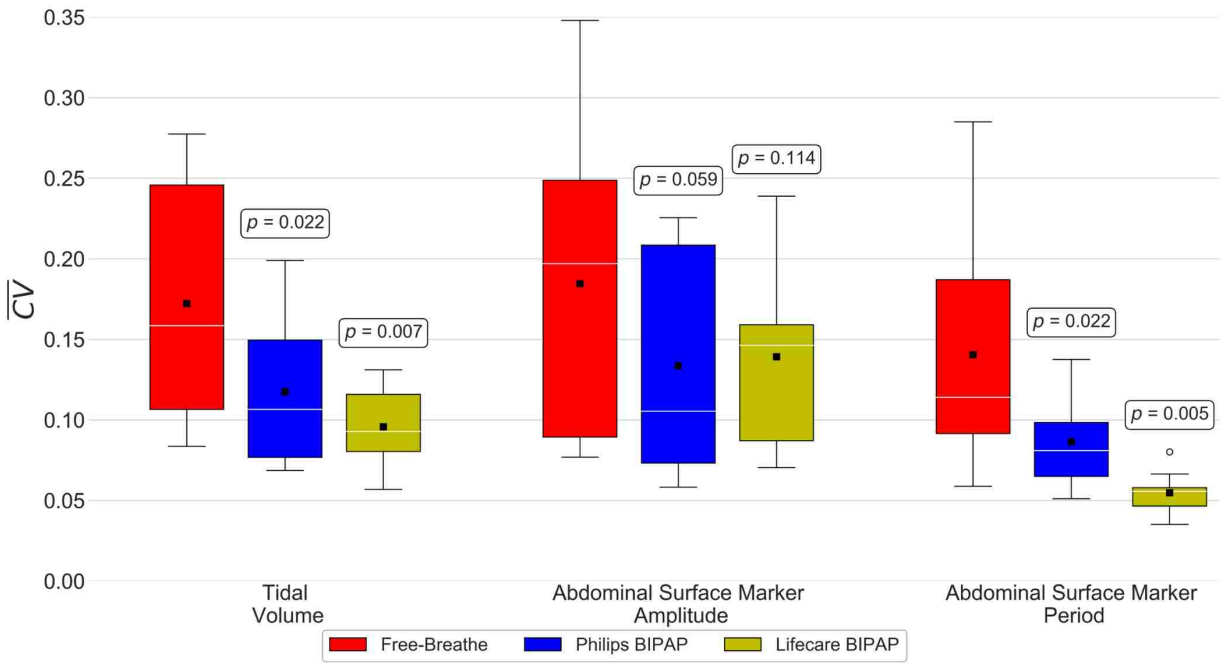

Figure 3.17. Summary of intra-session variation results, excluding the abdominal surface baseline results. Black boxes indicate the means, white lines indicate the medians, and circles indicate outliers. *p*-values shown are compared to free-breathe.

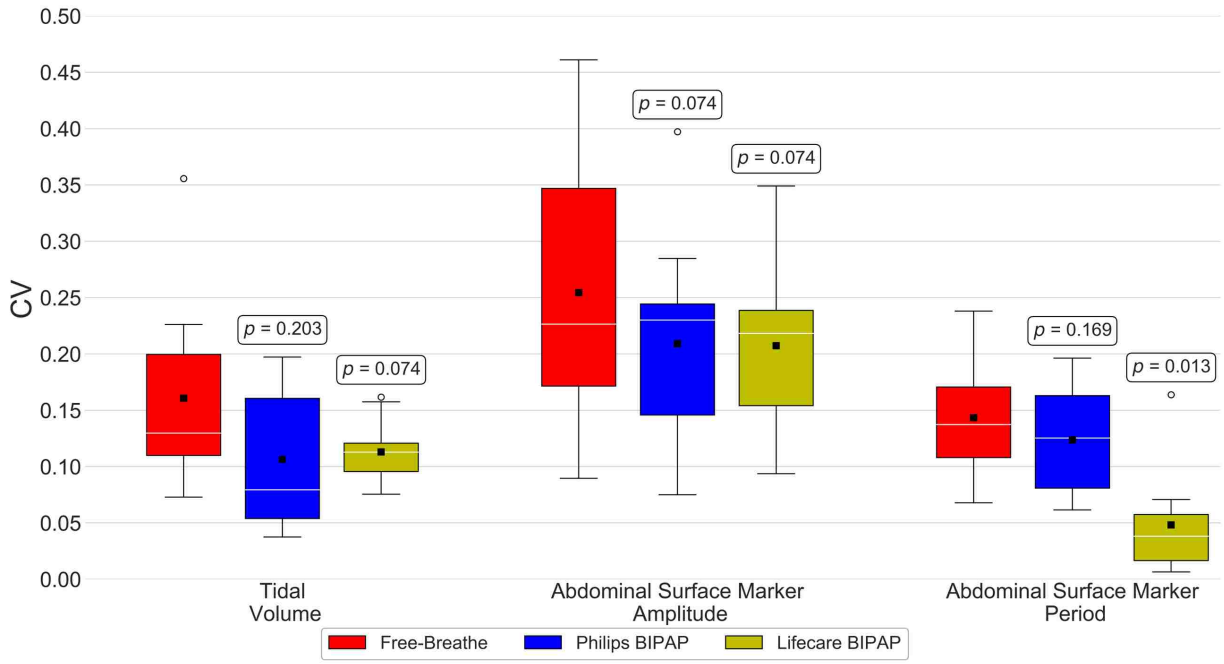

Figure 3.18. Summary of inter-session variation results. Black boxes indicate the means, white lines indicate the medians, and circles indicate outliers. *p*-values shown are compared to free-breathe.

Table 3.1. Statistical summary of results for all patients (1-10). CV difference (unless otherwise indicated) from FB shown. Green indicates a variation reduction. Red indicates a variation increase. P indicates the Philips BIPAP and L indicates the Lifecare BIPAP. Statistical significance was determined for each comparison (FB vs. Philips BIPAP and FB vs. Lifecare BIPAP) using the non-parametric Wilcoxon signed-rank test, with a significance level of 0.05.

	Intra-session variation								Inter-session variation					
	Tidal Volume		ASM$^{\lozenge}$ Amplitude		ASM$^{\lozenge}$ Period		ASM$^{\lozenge}$ Baseline$^{\mu}$		Tidal Volume		ASM$^{\lozenge}$ Amplitude		ASM$^{\lozenge}$ Period	
	$FB_{\overline{CV}}$-$P_{\overline{CV}}$	$FB_{\overline{CV}}$-$L_{\overline{CV}}$	$FB_{\overline{CV}}$-$P_{\overline{CV}}$	$FB_{\overline{CV}}$-$L_{\overline{CV}}$	$FB_{\overline{CV}}$-$P_{\overline{CV}}$	$FB_{\overline{CV}}$-$L_{\overline{CV}}$	$FB_{\overline{SD}}$-$P_{\overline{SD}}$	$FB_{\overline{SD}}$-$L_{\overline{SD}}$	FB_{CV}-P_{CV}	FB_{CV}-L_{CV}	FB_{CV}-P_{CV}	FB_{CV}-L_{CV}	FB_{CV}-P_{CV}	FB_{CV}-L_{CV}
1	0.080	0.130	0.122	0.134	0.086	0.157	0.064	-0.997	0.035	0.045	0.121	0.114	0.029	0.141
2	0.154	0.176	0.183	0.149	0.214	0.233	-0.024	-0.002	0.153	0.110	0.203	0.150	0.059	0.142
3	0.022	0.025	0.019	0.001	0.037	0.065	0.383	0.210	-0.088	-0.007	-0.016	-0.005	-0.028	0.035
4	0.017	0.020	-0.000	0.058	0.017	0.047	-0.559	-0.315	0.077	0.029	0.052	0.067	0.093	0.113
5	0.041	0.104	0.008	0.031	-0.012	0.045	0.109	-0.009	0.022	0.051	-0.048	-0.008	-0.055	-0.050
6	-0.016	-0.010	-0.014	-0.062	0.006	0.000	-0.071	-0.326	-0.052	-0.007	-0.017	-0.001	-0.006	0.009
7	0.033	0.047	0.014	0.001	-0.014	0.033	-0.156	-0.298	0.096	-0.024	0.074	0.015	0.047	0.072
8	0.038	0.028	0.029	0.017	0.032	0.039	0.435	0.210	0.041	-0.002	0.002	-0.004	-0.026	0.081
9	0.203	0.197	0.164	0.160	0.129	0.162	-0.010	-0.390	0.298	0.233	0.064	0.112	0.042	0.232
10	-0.025	0.047	-0.016	-0.035	0.044	0.074	0.259	-0.280	-0.038	0.047	0.018	0.030	0.041	0.178
Mean	0.055	0.077	0.051	0.045	0.054	0.086	0.043	-0.220	0.054	0.048	0.045	0.047	0.020	0.095
p-value	**0.022**	**0.007**	0.059	0.114	**0.022**	**0.005**	0.646	**0.037**	0.203	0.074	0.074	0.074	0.169	**0.013**

BOLD indicates statistical significance
◊ Abdominal Surface Marker (ASM)
μ Difference in mm

Comparing the two BIPAPs against each other shows mixed results. The Philips BIPAP had significantly lower intra-session abdominal surface baseline variation compared to the corresponding Lifecare BIPAP variation. The Lifecare BIPAP had significantly lower intra-session tidal volume variation, intra-session abdominal surface marker period variation, and inter-session abdominal surface marker period variation than the Philips BIPAP (Table 3.2.).

Table 3.2. Statistical comparison of the Philips BIPAP to the Lifecare BIPAP. Mean CV values (unless otherwise indicated) of all patients are displayed. Statistical significance was determined for each comparison using the non-parametric Wilcoxon signed-rank test, with a significance level of 0.05.

	Intra-Session Variation			Inter-Session Variation		
	Philips	Lifecare	p-value	Philips	Lifecare	p-value
Tidal Volume CV (SD)	0.118 (0.047)	0.096 (0.024)	**0.047**	0.106 (0.063)	0.113 (0.029)	0.799
ASM◊ Amplitude CV (SD)	0.134 (0.070)	0.139 (0.058)	0.386	0.209 (0.096)	0.207 (0.074)	0.575
ASM◊ Period CV (SD)	0.086 (0.031)	0.055 (0.013)	**0.007**	0.124 (0.047)	0.048 (0.046)	**0.005**
ASM◊ Baselineμ SD (SD)	0.682 (0.262)	0.945 (0.384)	**0.037**			

BOLD indicates statistical significance
◊ Abdominal Surface Marker (ASM)
CV: Coefficient of variation
SD: Standard deviation
μ Units are mm

4. Discussion

4.1. Summary of Findings

This study evaluated using BIPAP ventilation assistance to help patients improve their respiratory reproducibility. In Aim 1, we modified equipment which allowed us to collect patients' breathing data. In Aims 2 and 3, we collected and evaluated patients' free-breathe (FB) and BIPAP ventilation-assisted breathing data. Data components of each platform (i.e. FB, Philips BIPAP, and Lifecare BIPAP) included the tidal volumes, and abdominal surface marker amplitudes, periods, and baselines. We calculated and compared intra-session (breath-to-breath) and inter-session (day-to-day) variations of the FB and BIPAP breathing data components to evaluate respiratory reproducibility.

Based on the high correlation of respiratory volume (i.e. tidal volume) to tumor motion,[16] we assumed that the tidal volume was an acceptable surrogate for tumor motion. We also used an abdominal surface marker to provide a monitoring system that was independent of the tidal volume measurements and consistent across both the FB and BIPAP ventilation data collection platforms. We used the abdominal surface marker amplitudes, periods, and baselines to provide spatial and temporal information about the respiration pattern.

We observed that patients' FB tidal volume respiratory patterns demonstrated both intra-session and inter-session variations. Dosimetrically, breath-to-breath and day-to-day tumor motion variations could alter the tumor coverage or require larger treatment margins to ensure full tumor coverage. The negative consequences of tumor motion variations could include overexposing normal tissues or worse, underexposing the tumor. Thus, it is crucial that patients reduce tidal volume respiratory pattern variations. Our results showed that BIPAP ventilation assistance reduced both intra-session and inter-session tidal volume variations, compared to

unassisted free-breathing; however, only the intra-session tidal volume variation was significantly reduced. Although no studies have previously investigated using BIPAP ventilation assistance to improve respiratory reproducibility, our intra-session findings are consistent with a similar respiratory reproducibility study by Lim *et al.*[17] Their results included significant ($p < 0.05$) reductions in the intra-session standard deviations of the tidal volumes by providing visual feedback of the real-time breathing pattern to 10 healthy volunteers. The reductions in intra-session and inter-session tidal volume variation with BIPAP ventilation assistance could lead to improvements in both image quality during image acquisition and radiation treatment accuracy during radiation delivery;[15] however, the magnitude of these improvements needs to be investigated. We can translate our results to an estimation of the reductions in tumor motion variation by making a few assumptions such as a mean tumor motion of 1-3 cm and a one-to-one correlation between tidal volume and tumor motion.[4, 16] These assumptions indicate that a 0.06 tidal volume CV reduction (mean of BIPAPs intra-session and inter-session CVs) could result in a 0.1-0.2 cm reduction in tumor motion variation (i.e. standard deviation). This improvement in respiratory reproducibility could lead to the tumor being in the PTV more during radiation delivery or even a reduction of the PTV margins added using the motion-encompassing methods, which currently are 0.2-0.5 cm.[24]

Analogous to our tidal volume respiratory pattern observations, patients' FB abdominal surface marker amplitudes, periods, and baselines demonstrated both intra-session and inter-session variations. We found that BIPAP ventilation assistance reduced both intra-session and inter-session abdominal surface marker amplitude and period variations, compared to unassisted FB, although only the period variations were significantly lower. A similar observation has been documented by Neicu *et al.*, who suggests that a reproducible abdominal surface marker period is

required to predict tumor position and synchronize the radiation field to the tumor motion.[25, 26] The significant reductions in intra-session and inter-session abdominal surface marker period variations with BIPAP ventilation assistance could lead to improvements in tumor position predictions or even in respiratory gating techniques where reproducible tumor motion periods are desirable.

The pure ventilation characteristics (i.e. permits patient triggering) of the Philips BIPAP required that patients actively control their respiratory pattern. The use of the Philips BIPAP was well-tolerated and none of the patients mentioned any discomfort. The controlled ventilation assistance characteristics (i.e. does not permit patient triggering) of the Lifecare BIPAP provided more control of the tidal volume each breath, compared to the Philips BIPAP; however, patients were still required to synchronize their breathing pattern to the fixed air volume output of the Lifecare BIPAP. Some patients had difficulty using the Lifecare BIPAP, especially breathing at the fixed breathing period, and ultimately could not use it for more than a short amount of time. The use of the Lifecare BIPAP was tolerated, although not as well as the Philips BIPAP. Most of the patients that had trouble using the Lifecare BIPAP mentioned that it felt restrictive or that their breaths were "cut off." We attribute these problems to our coaching methods (e.g. only using green "inhale" and red "exhale" visual cues) and imperfect patient-specific Lifecare BIPAP ventilator settings (i.e. breathing periods), which were determined during the first session and used for subsequent sessions.

After comparing the Philips BIPAP against the Lifecare BIPAP, it is not clear which is the best at improving respiratory reproducibility. We believe that combining certain capabilities of each BIPAP, specifically the air volume output limit of the Lifecare BIPAP and the adaptive Auto-Trak Sensitivity of the Philips BIPAP (1.1.7 Bi-Level Positive Airway Pressure (BIPAP) Ventilation),

would result in even lower intra-session and inter-session variations. The mixed results, in addition to patients' comments, indicate that developing a hybrid BIPAP, with capabilities of the Philips BIPAP and Lifecare BIPAP, would be the logical next step.

4.2. Response to Hypothesis

The Philips BIPAP and Lifecare BIPAP intra-session tidal volume variation was significantly reduced compared to unassisted free-breathe, which supported the hypothesis.

The Philips BIPAP and Lifecare BIPAP inter-session tidal volume variation was reduced, although not significantly compared to unassisted free-breathe, which did not support the hypothesis.

4.3. Limitations of This Study

This study has several limitations beyond using a small sample size of 10 patients. These limitations include patients missing or skipping sessions on treatment days, Lifecare BIPAP data collection times for some patients, short data collection times relative to typical treatment times, the placement of the abdominal surface marker each session, a Philips BIPAP volume waveform calculation issue, and an imperfectly sealed Lifecare BIPAP patient circuit.

Patients participated in daily sessions which occurred either before or after their radiation therapy treatments. All patients had sessions on more than 50% of their treatment days; however, patients were permitted to skip sessions on treatment days when they were not feeling well, running late, or had other appointments (i.e. physician visits, chemotherapy, etc.). Subsequently, the overall impact of using ventilation assistance was not fully investigated, which would have required having sessions on all treatment days.

Seven patients did not have mean Lifecare BIPAP data collection times longer than 90 seconds. The patients that had difficulty could not use it for more than a short amount of time before they had to open their mouth and "catch their breath." During the first session, the Lifecare BIPAP

data collection ended if patients had to open their mouth to catch their breath or if they notified the investigator that they could not follow the Lifecare BIPAP any longer. On subsequent sessions, patients were expected to match the data collection times from their first session.

We collected breathing data during two-minute intervals, which simulated a typical volumetric modulated arc therapy radiation treatment beam-on time. In reality, typical treatment sessions can last up to and beyond 30 minutes due to patient setups, daily imaging, and multiple radiation beams. Based on the feedback from patients in this study and the data collection time results for the Lifecare BIPAP, requiring patients to use BIPAP ventilation assistance throughout the entire treatment session is most likely not feasible. Instead, a relief valve could be inserted into the patient circuit that would permit patients to breathe freely during times when they are not required to use the BIPAP (e.g. time between patient setup and daily imaging).

The abdominal surface marker was placed midway between the xiphoid process and umbilicus and rested on a thin piece of acrylic. Indexing on the couch was used to ensure abdominal surface marker placement reproducibility for each session; however, patients could have been lying on the couch slightly angled or rotated (i.e. patient's abdominal surface was not normal to the abdominal surface marker) from session to session. These differences in abdominal surface marker positioning would have led to a systematic inflation of the inter-session amplitude variation for FB, Philips BIPAP, and Lifecare BIPAP. Intra-session abdominal surface marker amplitude variation would not have been impacted by any differences in abdominal surface marker positioning.

The Philips BIPAP provided an LCD color touchscreen that displayed the real-time volume waveform. Functionally, the Philips BIPAP monitors the real-time flow and calculates the real-time volume using numerical integration. The real-time inhalation volume is calculated while the

monitored flow is positive. During this time, the BIPAP applies the inhalation pressure. Once the Philips BIPAP senses that the user has ceased inhalation, it reduces the pressure. During this time, the BIPAP applies the exhalation pressure. The calculation of the inhalation volume is subsequently stopped (i.e. inhalation volume has achieved its maximum value). If the Philips BIPAP falsely senses that the patient has ceased inhalation, meaning that the patient continues to inhale even though the Philips BIPAP has reduced the pressure, the displayed volume value will be incorrect. The root of the problem is the sensitivity of the Philips BIPAP's Auto-Trak Sensitivity feature, which monitors when the user has ceased inhalation. Unfortunately, we were not able to adjust the sensitivity. This error was accounted for by recording and monitoring both the real-time flow and volume waveforms. If the flow waveform indicated the patient continued to inhale and the volume waveform achieved its maximum value or "flat-lined", the breath was ignored. In total, 4.9% of all breaths using the Philips BIPAP were ignored because of this issue.

The Lifecare BIPAP patient circuit consisted of a six-foot-long, ¾" diameter piece of flexible plastic tubing which connected the BIPAP air output port to the patient's nasal mask. A water solenoid valve was inserted into the circuit to permit patient exhalation. Unfortunately, the patient circuit was not a completely sealed circuit. Air could be inhaled, if forcefully enough, through the one-way water solenoid valve. This unavoidable leak in the patient circuit system was a consequence of our experimental design and could have resulted in increased intra-session and inter-session tidal volume variations for the Lifecare BIPAP.

4.4. Future Work

The results of this study warrant future work into the possible clinical benefits of BIPAP ventilation assistance. This work should include developing a hybrid BIPAP ventilator, performing a healthy volunteer study to assess their variation reductions and receive coaching

feedback, and performing an investigation of the impact on tumor motion variations using BIPAP ventilation assistance.

Our results showed that variations in respiratory patterns were reduced using BIPAP ventilation assistance. Comparing the Philips BIPAP against the Lifecare BIPAP showed mixed results about which one was better, indicating that developing a hybrid BIPAP would be the best next step. Ideally, the simplest solution to combining the useful attributes of both BIPAPs would be to limit the volume of air output by the Philips BIPAP each breath, similar to the Lifecare BIPAP. Unfortunately, after discussions with Philips, there seems to be little to no possibility of implementing a "tidal volume limit feature" in the Philips BIPAP. Newer models of the Lifecare BIPAP, specifically the Lifecare PLV 102b, come standard with a mode named Synchronized Intermittent Mandatory Ventilation (SIMV) mode. In the SIMV mode, the ventilator delivers a minimum breathing rate at a preset tidal volume; however, the patient may breathe spontaneously at a rate higher than at the set level. We hypothesize that utilizing this mode would alleviate some of the difficulty in using the Lifecare BIPAP by allowing patients to breathe spontaneously, similarly to the Philips BIPAP, but still have a preset tidal volume output. Further investigation and research is needed to assess the possibility of using a newer model of the Lifecare BIPAP.

This study collected and evaluated ventilation assistance data on patients, who are the intended users of BIPAP ventilation assistance. Patient compliance was necessary to use both the Philips BIPAP and Lifecare BIPAP successfully. Performing a similar study on healthy volunteers, who would represent ideal compliance, would hopefully reveal the best possible intra-session and inter-session variation achievable with BIPAP ventilation assistance. Feedback could also be obtained to aid in improving our coaching method.

The results of this study show that respiratory variations were reduced with BIPAP ventilation assistance. Because tidal volume highly correlates to tumor motion, an investigation is needed to determine the reduction in tumor motion variations using BIPAP ventilation assistance. This investigation would shed light on the possible clinical benefits of using BIPAP ventilation assistance.

4.5. Conclusion

This study tested the feasibility of using BIPAP ventilation assistance to help patients improve their respiratory reproducibility. The results showed that variations in respiratory patterns were reduced using BIPAP ventilation assistance. Reducing variations of the respiratory patterns could reduce variations of tumor motion. Future work will include an investigation into the possible clinical benefits of using ventilation assistance to reduce tumor motion variations.

References

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2018.* CA: A Cancer Journal for Clinicians, 2018. **68**(1): p. 7-30.

2. Ettinger, D.S., et al., *NCCN Guidelines Insights: Non–Small Cell Lung Cancer, Version 5.2018.* Journal of the National Comprehensive Cancer Network, 2018. **16**(7): p. 807-821.

3. Tortora, G.J. and B. Derrickson, *Principles of anatomy and physiology*. 2011, Hoboken, N.J.: Wiley.

4. Keall, P.J., et al., *The management of respiratory motion in radiation oncology report of AAPM Task Group 76a).* Medical Physics, 2006. **33**(10): p. 3874-3900.

5. Landberg, T., et al., *Report 62.* Journal of the International Commission on Radiation Units and Measurements, 1999. **os32**(1): p. NP-NP.

6. Vedam, S.S., et al., *Quantifying the predictability of diaphragm motion during respiration with a noninvasive external marker.* Medical Physics, 2003. **30**(4): p. 505-513.

7. Ramsey, C.R., D. Scaperoth, and D. Arwood, *Clinical experience with a commercial respiratory gating system.* International Journal of Radiation Oncology • Biology • Physics, 2000. **48**(3): p. 164-165.

8. Rietzel, E., T. Pan, and T.Y. Chen George, *Four-dimensional computed tomography: Image formation and clinical protocol.* Medical Physics, 2005. **32**(4): p. 874-889.

9. Underberg, R.W.M., et al., *Use of maximum intensity projections (MIP) for target volume generation in 4DCT scans for lung cancer.* International Journal of Radiation Oncology • Biology • Physics, 2005. **63**(1): p. 253-260.

10. Kwa, S.L.S., et al., *Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients.* International Journal of Radiation Oncology • Biology • Physics, 1998. **42**(1): p. 1-9.

11. Hope, A.J., et al., *Modeling radiation pneumonitis risk with clinical, dosimetric, and spatial parameters.* International Journal of Radiation Oncology • Biology • Physics, 2006. **65**(1): p. 112-124.

12. Kini, V.R., et al., *Patient training in respiratory-gated radiotherapy.* Medical Dosimetry, 2003. **28**(1): p. 7-11.

13. Ge, J., et al., *Planning 4-Dimensional Computed Tomography (4DCT) Cannot Adequately Represent Daily Intrafractional Motion of Abdominal Tumors.* International Journal of Radiation Oncology • Biology • Physics, 2012. **85**(4): p. 999-1005.

14. Worm, E.S., 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 Oncologica, 2013. **52**(7): p. 1437-1444.

15. Pollock, S., R. Keall, and P. Keall, *Breathing guidance in radiation oncology and radiology: A systematic review of patient and healthy volunteer studies.* Medical Physics, 2015. **42**(9): p. 5490-5509.

16. Hoisak, J.D.P., et al., *Correlation of lung tumor motion with external surrogate indicators of respiration.* International Journal of Radiation Oncology • Biology • Physics, 2004. **60**(4): p. 1298-1306.

17. Lim, S., et al., *Guiding curve based on the normal breathing as monitored by thermocouple for regular breathing.* Medical Physics, 2007. **34**(11): p. 4514-4518.

18. Strollo, P.J., Jr., M.H. Sanders, and C.W. Atwood, *POSITIVE PRESSURE THERAPY.* Clinics in Chest Medicine, 1998. **19**(1): p. 55-68.

19. Simon, S. and N. Collop, *Latest Advances in Sleep Medicine: Obstructive Sleep Apnea.* Chest, 2012. **142**(6): p. 1645-1651.

20. Katz, J.A. and J.D. Marks, *Inspiratory work with and without continuous positive airway pressure in patients with acute respiratory failure.* Anesthesiology, 1985. **63**(6): p. 598-607.

21. Goldstein, J.D., et al., *Continuous Positive Airway Pressure for Motion Management in Stereotactic Body Radiation Therapy to the Lung: A Controlled Pilot Study.* International Journal of Radiation Oncology • Biology • Physics, 2015. **93**(2): p. 391-399.

22. Mehta, S. and N.S. Hill, *Noninvasive Ventilation.* American Journal of Respiratory and Critical Care Medicine, 2001. **163**(2): p. 540-577.

23. Palma, D.A., et al., *New developments in arc radiation therapy: A review.* Cancer Treatment Reviews, 2010. **36**(5): p. 393-399.

24. Edelman, M.J., et al., *Randomized Phase II Study of Preoperative Chemoradiotherapy ± Panitumumab Followed by Consolidation Chemotherapy in Potentially Operable Locally Advanced (Stage IIIa, N2+) Non–Small Cell Lung Cancer: NRG Oncology RTOG 0839.* Journal of Thoracic Oncology, 2017. **12**(9): p. 1413-1420.

25. Neicu, T., et al., *Synchronized moving aperture radiation therapy (SMART): improvement of breathing pattern reproducibility using respiratory coaching.* Physics in Medicine & Biology, 2006. **51**(3): p. 617.

26. Neicu, T., et al., *Synchronized moving aperture radiation therapy (SMART): average tumour trajectory for lung patients.* Physics in medicine and biology, 2003. **48**(5): p. 587.

Appendix A. Institutional Review Board Protocol

Our Lady of the Lake College IRB Study number 2018-029
Amendment 2 Approved: 14-SEP-2018

A Pilot Study for the First Augmented Ventilation for Reproducible Respiration Evaluation
Mary Bird Perkins – Our Lady of the Lake Cancer Center

Purpose/Background:

For cancers specifically located in the lung and abdomen, radiation therapy can be complicated by tumor motion due to breathing. Radiation treatment planning typically relies on a series of 3D computed tomography images to document tumor motion, location and shape throughout the respiratory cycle. This technique is referred to as 4DCT. These patients, throughout the 4DCT imaging process, are coached to maintain normal breathing efforts. However, many patients fail to maintain the same regular, reproducible breathing pattern during subsequent treatments. The images obtained during the 4DCT are used during radiation treatment planning to achieve 2 goals: (1) enlarge the planning target volume (PTV) to account for uncertainties which, in this case, include an increased safety margin due to the potential breathing variability during treatment and (2) minimize a PTV, which is exposed to high prescription doses, to spare the surrounding healthy tissue as much as possible, thus reducing radiation induced side effects and toxicity. It has been a primary objective during the treatment planning process to achieve goal 2 while not sacrificing goal 1. Achieving a better balance between the two may result in improved outcomes for many patients.

Currently in the field of radiation therapy, breathing is not typically monitored for most patients, and there is no effective solution for patients who would benefit from PTV reduction but are unable to maintain consistent breathing patterns. The purpose of this pilot research study is to assist patients in producing a more consistent breathing pattern during the 4DCT imaging process and each subsequent treatment. This consistency in breathing, achieved through bi-level ventilation, will ensure the patient tumor motion is reproducible throughout the course of treatment, helping to improve the healthy tissue sparing through reduction in PTV margins and potential to support more effective “gated” radiation delivery strategies in the future.

Design:

Equipment and phase of Study:

Through the use of a non-invasive assisted breathing device, a program will be established that utilizes a combination of coaching and the breathing device to improve a patient’s breathing reproducibility during imaging and treatment. We intend to utilize and adapt a full featured Bilevel Positive Airway Pressure (BPAP) machine for this project. A Philips Respironics V60 non-invasive BPAP ventilator will be used for the first of a two phase project.

Those undergoing a 4DCT, typically lung patients are eligible to participate in the trial.

The initial pilot phase of the project will be concentrated on establishing patient training procedures, ventilation parameter optimization and augmented reproducibility of respiration in the imaging suite

and treatment planning stages. Each patient will have a recording session for each daily treatment using the equipment to practice/track reproducibility.

Healthy subjects (ie, volunteers without cancer) are also eligible to participate in the trial. Healthy subjects will have zero ionizing radiation and will solely be used as a comparison group (ie, establishing a baseline) of using the non-invasive BPAP.

The second phase of the project will focus on implementation in treatment delivery rooms. The existing BPAP equipment used in the first phase above will not be used for treatment as it is not specifically adapted to the requirement of radiation treatment conditions which require remote control and monitoring. This will require additional funding for equipment modification or the design must be adapted specific to treatment delivery room needs The second phase will depend on the outcome of the pilot phase of study and available funding.

Eligibility Criteria:

- Patients:Patients with pathological or cytological proven lung carcinoma
- Must be able to speak and understand English
- ≥ 18 years of age
- Presenting to cancer center for fractionated radiation therapy requiring a 4DCT imaging procedure and to be treated with normal breathing during treatment as ordered by a participating radiation oncologist
- Patients must be non-claustrophobic and able to tolerate wearing a ventilation mask
- Patients must be amenable to coaching.
- Patients that require nasal oxygen cannula assist are also eligible.

Healthy Subjects:

- Volunteer without cancer and a non-smoker
- Must be able to speak and understand English
- >= 18 years of age
- Healthy subjects must be non-claustrophobic and able to tolerate wearing a ventilation mask
- Healthy subjects must be amenable to coaching.

Study Randomization:

The patient is asked to match the breathing pattern he/she establish during imaging used for radiation planning. If the patient with breathing assistance can repeat the same respiration pattern during each session/treatment, it is definitively 100% successful. Each patient is his/her own control when not using the breathing assistance.

Similar to patient data collection, healthy subjects breathing will be recorded during daily sessions, with and without ventilation assistance. The healthy subject will act as his/her own control.

This non-randomized pilot study will be aimed as efficacy of active assistance in reproducibility of patient breathing during all fractionated treatments matching as close as the initial 4DCT image scan captured at one point in time with a particular state of patient's normal breathing upon which a radiation plan was designed. Before each daily treatment over the course of fractionated radiation therapy, a recording of "warmup" session of the same patient with and without active breathing assistance is its own study and control comparison.

Sample Size:

The expected enrollment for this study is 30 total participants overall (20 cancer patients and 10 healthy subjects).

Methods:

Patients who report to the Mary Bird Perkins-Our Lady of the Lake Cancer Center Radiation Oncology Center for radiation treatment planning with a cancer diagnosis will be eligible for this study. Only English speaking patients will be included. The principal investigator (PI) will identify potential patients for the study through computer review of the weekly schedule. Potential subjects will be approached by the PI for discussion of informed consent and study participation usually on the day of the initial patient consult by the radiation oncologist. The informed consent discussion will take place in a private exam room. To avoid any implication of coercion, the treating radiologist will not be involved in any aspect of the consenting process. Potential patients will be instructed that declining participation in this pilot study will in no way affect their radiation treatment plan. The study will be conducted starting at the initial Imaging simulation day.

Healthy subjects who approach or contact the PI about volunteering for this study will be eligible. The PI will make the study known by posting a flyer in the radiation oncology department in addition to word-of-mouth. Healthy subjects that contact the PI about the study will have a discussion of informed consent. No monetary compensation will be given to healthy subjects that volunteer.

For **cancer patients** - The study will involve the following steps:

1. At the initial 4DCT imaging stage, the patient will be coached to establish a natural breathing pattern. An inhale/exhale ventilation pattern will be customized to closely match it. The patient is expected to wear a BPAP ventilation mask, per manufacturer's guidelines during the whole process. Note, the low bi-level pressure air-flow ventilation is non-invasive in nature, i.e., it is a voluntary inhale/exhale process.
2. The patient will practice the customized breathing pattern until it can be matched consistently.

3. The patient will go through the normal patient immobilization simulation setup on the CT couch.
4. A 4DCT imaging scan will be done with the patient wearing the BPAP mask and breathing the fixed ventilation pattern. Note the patient does not have to follow the driving pattern but only as required as follows. It is expected the patient to breath and match the ventilation pattern consistently only during the CT scanning time of 1-2 minute intervals. The patient will be prompted to start and will ramp up to breathing consistency after a few breath cycles before the "beam" turn on.
5. The patient is expected to practice with the equipment for about 10-15 minute session before each treatment time if the patient is not asked to use the BPAP machine during treatment. All such arrangements will be done ahead of time to avoid patient scheduling confusion.
6. Depending on the stage of our study (2nd stage), the patient may be asked to use the BPAP machine during all radiation treatments. If so, it is expected for the patient to follow the breathing pattern consistently during radiation beam-on time of 1-2 minute intervals. There may be between 5-10 intervals of such beam-on demands during each treatment.

For **healthy subjects** the study will involve the following steps:

1. During the first session, the healthy subject will first go through normal patient immobilization simulation setup on the CT couch. This process is only needed to create an immobilization device that the healthy subjects will use during subsequent sections.
2. The healthy subject will be coached to establish a natural breathing pattern. An inhale/exhale ventilation pattern will be customized to closely match it. The healthy subject is expected to wear a BPAP ventilation mask, per manufacturer's guidelines during the whole process. Note, the low bi-level pressure air-flow ventilation is non-invasive in nature, i.e., it is a voluntary inhale/exhale process.
3. The healthy subject is expected to practice with the equipment for about 10-15 minutes during daily sessions.

Informed consent will be obtained by Connel Chu or a staff member who has been trained in research procedures under the direction of ~~Dr.~~ Mr. Chu. The informed consent will be signed by the patient or legally authorized representative as well as the person obtaining consent.

Analysis Methods:

The principal investigator will analyze patient breathing patterns through the use of a BPAP machine that has been adapted for this research study.

Data points will be based on respiration volume per cycle. There will be # of respiration cycles in 1-2 minute period for each fractionation in a fractionated course per patient. The patient's classification will be normalized to lung differential (inhale/exhale) volume per tumor motion distance.

Analysis will be respiration volume variance per cycle, per fraction of 1-2minute period, per daily fractions all correlated to tumor movement distance.

Appendix B. Calculating Volume from Flow Signal

Free-breathe volume data and Lifecare BIPAP volume data was recorded using the Sensirion SFM 3000 mass flow meter (Sensirion AG, Switzerland) shown in Figure 2.9., which uses complementary metal-oxide-semiconductor (CMOS) technology to measure air flow at rates up to 200 standard liters per minute (slm) and with an accuracy of ± 0.05 slm. The SFM 3000 flow meter was connected to the same dedicated computer as the camera for the Philips BIPAP. Under software control, the sensor sampled the air flow approximately every eight milliseconds and logged the flow signal in a comma separated variable file.

The flow signal (Figure B.1.) was integrated using the cumulative trapezoidal numerical integration (cumtrapz) function in MATLAB®. The cumtrapz function computes the approximate cumulative integral of the input (i.e. flow signal) via the trapezoidal method with non-uniform spacing (i.e. flow signal sample time) and outputs the result (i.e. raw volume).

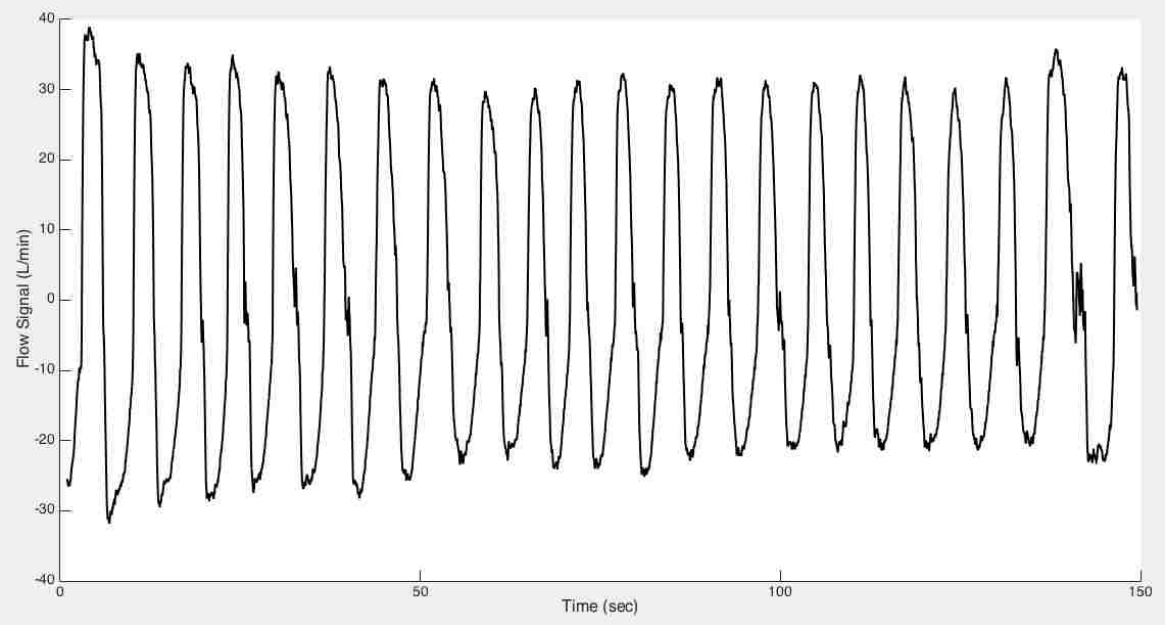

Figure B.1. Example of recorded flow signal.

Linear trends were often observed in the raw volume (Figure B.2.). These linear trends resulted from an imperfectly sealed system (i.e. slight leaks around the nasal mask) and were removed from the raw volume using the detrend function in MATLAB®. The detrend function computes the least-squares fit of a straight line to the input data (i.e. raw volume) and subtracts the resulting linear function from the input data. The raw volume was manually cut to only include the data that was analyzed (i.e. from recording start (notification to patient) to end) and then was detrended. The detrended volume was further processed to have every breath start at zero (Figure B.3.). Each breath's tidal volume value was determined by calculating the volume amplitude of each breath or the exhale volume amount. We validated our flow signal to volume calculation method using a 3L calibration syringe.

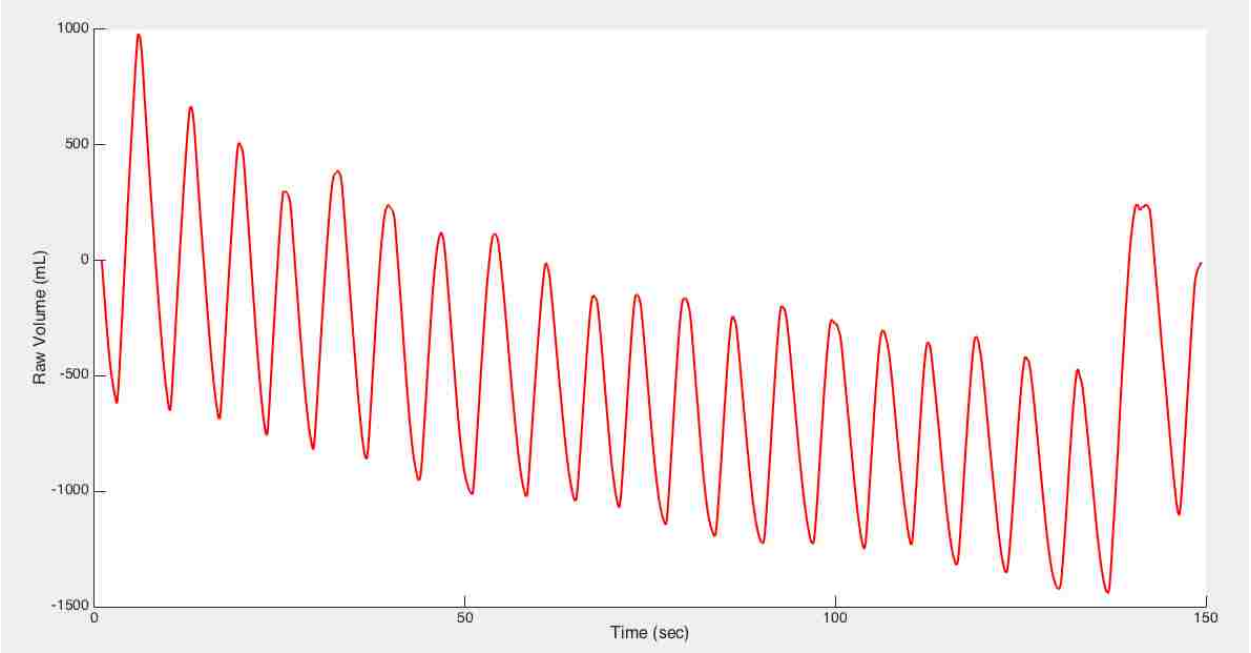

Figure B.2. Raw volume calculated by integrating the corresponding flow signal from Figure B.1.

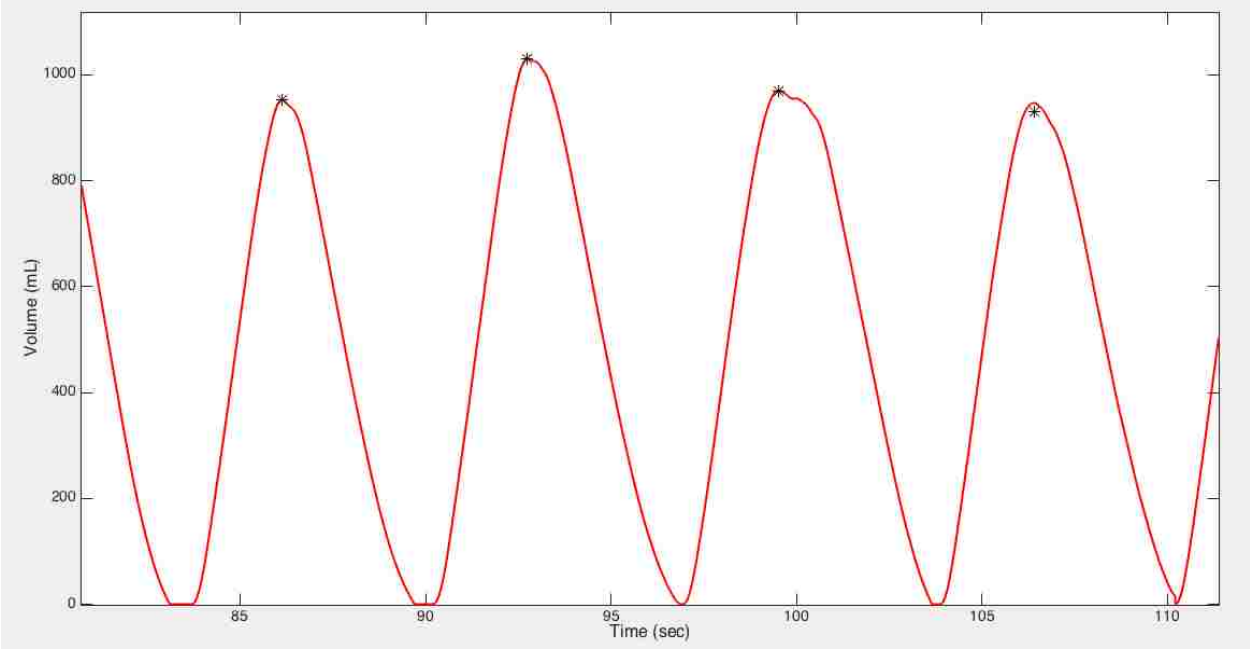

Figure B.3. Post-processed volume. The black asterisks indicate the tidal volume of each breath.

Vita

Cameron Sprowls was born in Bedford, Pennsylvania in 1992. Upon graduating high school in 2010, he received a golf scholarship to play at Wilmington University in New Castle, Delaware. In 2012, Cameron transferred to West Chester University in West Chester, Pennsylvania where he received a Bachelor of Science degree in Physics in December of 2015. Cameron matriculated into the LSU Medical & Health Physics Graduate Program in Baton Rouge, Louisiana in the fall of 2016. After completing the M.S. degree requirements in May of 2019, Cameron plans to continue his medical physics education by seeking a medical physics residency position.