Fiducial Marker Placement and Selection Study for Real-Time Lung Tumor Tracking

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May, 2023

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Abstract

Introduction: Lung cancer remains one of the most fatal forms of cancer globally. Lung cancer is often treated by surgical removal of the malignant tissue however, surgery is not often an option for lung cancer. Radiation is the next treatment technique for non-small cell cancer. Radiation treatment of lung cancer is complicated by respiratory motion. As a patient breathes their lung inflates and deflates causing the lung tissue and the tumor to move. There are many techniques to account for the lung motion. A technique to accommodate lung tumor motion is tracking. Lung tumor tracking can be performed in multiple ways, but one way is fiducial marker directed tracking. Tracking helps the tumor to be located and treated continuously in real time. This allows the treatment margins to be smaller and gets better patient outcomes. However, the accuracy of the fiducials' motion matching tumor motion has yet to be depicted. This study aims to show how well fiducial motion matches tumor motion. The machine tracks a fiducial centroid, which is the center of mass of one or more objects. The study will also look at what makes fiducial centroids track the tumor well. The dosimetric effect of

switching centroids will be observed. Patterns will be searched for to improve the fiducial marker placement recommendations. The current recommendations for fiducial marker selection are to select the fiducials closest to the tumor. These are not always the best tracking fiducials. The patterns in good fiducial centroids will also be used to improve the fiducial marker selection recommendations.

Methods: This was an IRB approved retrospective study that included 27 patients receiving planning 4DCT for SBRT treatment of either primary or metastatic lung cancer. 20 patients had upper lung tumors with 79 fiducials placed. There were 7 lower lung tumor patients and 23 fiducials. It is expected for there to be more upper lung tumor cases than lower lung tumor cases. In total 102 fiducials were placed. The center of mass (COM) of each fiducial and the pre-contoured tumor were found in every phase of the breathing cycle, using a MATLAB® program. The fiducials were then checked to see if they tracked the tumor well or not. If the fiducial kept a consistent distance within 2 mm of the tumor's COM, it was deemed a good tracking fiducial. Every fiducial combination was found and searched to see what centroid kept the most consistent distance from the tumor and which centroid was closest to the tumor's COM. These centroids were compared with the tracked centroid. The planned dose was shifted by the differences in the centroids locations compared to the tracked centroid. The type of bracketing around the tumor was checked in the centroids of interest. This analysis was done again on upper and lower lung patients separately.

Results: The distance was not a determining factor on if the fiducial would track the tumor well. The centroid that was closest to the tumor's COM was closer than the tracked centroid by 4.1 ± 1.2 mm ($p<0.05$) and the centroid that followed the tumor's

motion the best kept the distance more consistently than the tracked centroid by 0.23 ±0.05 mm ($p<0.05$). The shifted dose profiles were worse for tumor coverage than the original dose profiles but some other organs at risk had better dose sparing. Following analyze of the bracketing present in the centroids of interest, it is most important for the tumor to be bracketed in the superior/inferior and anterior/posterior directions. The superior/inferior bracketing is given higher priority for lower lung tumor patients and the anterior/posterior bracketing is given higher priority for upper lung tumor patients.

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A dissertation

Presented to the faculty of the Department of Physics

East Carolina University

In Partial Fulfillment of the Requirements for the Degree

Doctor of Philosophy in Biomedical Physics

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May, 2023

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Acknowledgements

I would like to start by saying that there are many people whom I want to acknowledge for their help both indirectly and directly in my educational and life path. First I would like to thank my dissertation committee members for taking time out of their very busy schedules to help me throughout the PhD process. A special thanks to Dr. Jung, my research advisor, for always being willing to help with any research questions I had and his willingness to give me advice when asked. I would like to thank the clinical members of my dissertation committee, Dr. Ju and Dr. Sharma as well as non-committee member Dr. Yang, for their assistance in acquiring clinical data and their willingness to allow me to shadow clinical activities and explain different clinical tasks. I would like to thank my final 2 committee members Dr. Shinpaugh and Dr. Dingfelder for their leadership in the department and help throughout my schooling here. I would also like to thank Dr. Sprague for helping me become a better instructor and individual.

Next I would like to give thanks to my family. My parents, especially my father always instilled the importance of education. Thanks to my parents I have always felt comfortable to continue pursing higher education to the highest level of doctorate. A thanks to my late grandparents for their constant belief in me and driving me to better myself. I would also like to thank my sisters and Aunt Jenny for their help and advice throughout my life.

I would like to thank the friends I made while here at school that helped with studying and friendship to get me through the difficult times during graduate school. To name a few Phil Deville, Chris Garcia, Wilson Hawkins, Eric Maertz, Todd Mendenhall,

and Joel Pogue. I would also like to thank my friends outside of East Carolina. I would like to thank the members of the research lab I worked in.

Lastly, I would like to thank my wife, Heather Belcher, whom I met while we both attended graduate school at East Carolina University. Without her belief in me, and willingness to sacrifice for both of our education dreams I do not think I would be here today. I am eternally grateful for her love and support.

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SBRT	Stereotactic Body Radiotherapy	3
SI	Superior/Inferior	10
SRS	Stereotactic Radiosurgery	3
SRT	Stereotactic Radiotherapy	27
TG	Task Group	10
UL	Upper Lung	10
VMAT	Volumetric-Modulated Arc Therapy	10
WHO	World Health Organization	2

Purpose

This research aims to optimize lung tumor tracking by researching fiducial marker placement and selection criteria and guidelines. We looked at the current marker selection protocol with the hopes to update or validate it. The current recommendations are to pick the markers that are closest to the tumor when all markers cannot be tracked. We aimed to give guidance on the placement of fiducial markers relative to the tumor and to improve the specificity in the recommendations when it comes to what fiducials should be selected for tracking. The current recommendation comes from an assumption that closer fiducials will track the tumor better.

Introduction

Lung cancer is one of the most fatal forms of cancer. The World Health Organization (WHO) reported that in 2020 cancer was the leading cause of death globally. The WHO also reported that in 2020 there were 2.21 million new cases of lung cancer, and 1.8 million deaths from lung cancer. This makes lung cancer the second most diagnosed cancer and the deadliest form of cancer. Lung cancer is deadly for two major reasons. First lung cancer is often asymptomatic until it has already reached late stages. Later stages of cancer are more difficult to treat. Treatment is much less likely to be curative at late stages. Secondly, surgical removal of non-small cell cancer is the gold standard of treatment to prevent the spread of disease and increase survival likelihood. However, lung cancer is often inoperable. Later stage cancers are not usually operable because of tumor size and possible nodal involvement. Chance of surgery for lung cancer is further hindered by any comorbidities the patient has, such as chronic obstructive pulmonary disease (COPD), and by the location of the malignancy in the lung. When it comes to radiation treatment of lung cancer it is heavily complicated by the motion of the tumor. Lung tumors move in every direction as you breathe. When you breathe your lung expands and contracts causing your lung tissue and ultimately your lung tumor to do the same. Keeping the radiation beam on target and sparing more healthy tissue will help patient outcomes and survival, which is the goal of this research. Later stage detections and difficulty in treating causes lung cancer to be deadly. This study aimed to provide new guidelines on implantation of fiducial markers and selection of which internal gold markers are tracked to increase the accuracy of the radiation beam.

Background

When it comes to cancer treatment there are multiple treatment modalities. The major treatments for cancer are surgery, chemotherapy, and radiation. These are often used today in combination with one another as well as by themselves. Surgery is often the preferred treatment for non-small cell cancer because it is one of the oldest and most tested treatments. Surgery is also popular because you can cut the malignant cells out of the patient. However, surgery does have its downsides. Some cancer sites are inoperable, and surgery requires a lot of post-operative care as well as having its' own inherent risks. Chemotherapy is a treatment where the patient is given drugs that kill cells administered through an IV. Chemotherapy will kill both cancerous and healthy cells. Chemotherapy is also a difficult treatment for patients to endure. Radiation treatment uses ionizing radiation to kill cells inside the body. This killing technique also does not discriminate; it will kill both healthy and cancerous cells. This is why accuracy is important in radiation therapy, but even more important in the modalities that have fewer treatment fractions and higher dose rates, like stereotactic body radiotherapy (SBRT).

Radiation treatment can be given in multiple ways by multiple machines. There are 3 main treatment techniques, 3D Conformal Radiation Therapy (3D-CRT)/ Intensity Modulated Radiation Therapy (IMRT), SBRT, and Stereotactic Radio Surgery (SRS). These techniques are difficult to compare because each was designed for different treatment goals. The standard LINear ACcelerator (LINAC) often performs 3D-CRT/ IMRT and is a machine that shoots radiation, usually photons or electrons for treatment of cancer. This technique does not often do real time tracking and is used to treat

simple cases of cancer where a high degree of accuracy is not required. Some clinics are working on methods to perform real time tracking with a standard LINAC, but it is not commercially available. The second technique, SBRT, is a high accuracy and high precision modality of treatment. The patient is usually immobilized to reduce patient motion and help increase accuracy. This treatment is used when more precision is required. Some common cancers treated with SBRT are head and neck, lung, and thoracic. These cancers require a more accurate modality because of the surrounding tissue needing to be protected. Treatments using this technique are high dose per fraction and usually around 3-5 fractions or number of treatments, but could be as few as 1. The last type of radiation treatment modality we will mention is SRS. This type of treatment modality is higher dose and higher dose rate than a normally fractionated treatment on a standard LINAC. There are extreme measures used to eliminate any patient motion. It is often used to treat brain cancer. In the case of brain cancer, the patient's head is bolted to a frame and secured to the table to eliminate any chance of motion. This modality is called radio surgery because it is done in a single fraction and has similar results to surgery. This research uses data from patients receiving treatment from Cyberknife which is a SBRT modality.

When it comes to lung cancer there are 6 main motion management techniques. The first technique is not recommended as it calls for irradiation of a large part of the lung. This technique is called free breathing. In this method no motion management technique is used. The patient can breathe freely, and the tumor's motion is considered only in the expansion of the internal target volume (ITV). This will result in a higher amount of healthy tissue being exposed to radiation. The second technique requires the

patient to hold their breath at a certain point in the breathing cycle determined by the treatment plan. This technique treats the patient only while they are holding their breath. This allows the tumor to be treated as static, but it is troublesome because patients usually aren't capable of long breath holds because of their respiratory disease. The third technique does consider patient motion and is called respiratory gating. This technique only has the radiation beam on during a select window of breathing. An area of the breathing cycle is identified, and the radiation beam is on during that area and off when the breathing is at the extremes of max exhale and inhale. This technique does take the lung motion into effect, but it does not track the tumor, and it allows the patient to free breath still. This will decrease the amount of healthy tissue receiving radiation dose but not as much as the fourth method. The fourth method uses markers placed internally to track the tumor. There are different types of markers that can be placed. A common internal marker used is the gold fiducial marker. Gold markers are used in spherical and rod shapes. This is the technique used in this study and we will go into further detail about how it works later in the paper. The fifth technique, a radio-wave emitting marker, was recently approved by the Federal Drug Association (FDA). This marker is called Calypso and was first approved and used for motion management in the prostate.[1] However, a different marker shape had to be produced for possible use of Calypso in the lung due to the spongey material of the lung. [1] When Calypso was first tested in the lung there was a large amount of marker migration meaning that the fiducial was moving after it was implanted. [1] This migration could even carry it outside of the lung and into different parts of the body. [1] Gold markers have been used much longer and are already very stable. We will go into more of a comparison on the gold

versus the Calypso seeds in the other tracking research section. The internal marker methods are the only methods that aims to track and predict tumor location in real time and does not exclude patients based on tumor size. The sixth method markerless tumor tracking also aims to track and predict the tumors location in real time but has excluding criteria not seen with internal marker tracking. When accurate this method will limit the radiation exposure to healthy tissue. Later in the paper we will go over what the excluding criteria is for markerless tumor tracking to have a chance of being possible.

Cyberknife uses a combination of internal and external markers to track the tumor. The internal markers are gold fiducials. The external markers used are 3 infrared emitting diodes. These diodes are placed onto a Velcro vest that the patient is wearing. The infrared emission is detected by an infrared camera in the treatment room. The patient's chest moves up and down as they breath causing motion of the infrared light emitters. The internal gold fiducial markers are seen by 2 orthogonal x-rays that are 45° off-set from the patient and 90° off-set from each other. The gold markers light up bright in the X-ray scan because they have a much higher Hounsfield Unit (HU) than that of air or lung tissue. The HU is dependent upon the linear attenuation coefficient of the material compared with that of water. Multiple x-ray scans are taken to find the marker's location at different phases of the breathing cycle and are called model points. A minimum of at least 8 model points are needed from at least 4 different phases.[2] The breathing cycle is broken into 10 phases with phase 0% usually being end of inhalation and phase 50% usually being end of exhalation. A computer program then builds a correlation between the infrared emitter location and the gold internal marker location.[3] This is done so that the internal markers can be tracked without constant x-ray imaging

giving extra radiation dose to the patient. The internal fiducial and external diode relationship is checked periodically by x-ray imaging to ensure that the predicted gold marker location is close to the actual location. A model point is usually updated every 60 seconds with 3 x-rays shot 1 second apart called an image burst. At this rate the whole model is rebuilt about every 5 minutes.[3] If an error occurs and the correlation error is greater than 5 mm or the need to move the couch in any direction is greater than 25 mm then the correlation model between the external and internal markers is reworked.[2] This is done to ensure the radiation is being deposited accurately into the tumor and sparing the surrounding healthy tissue. The centroid of the internal gold markers is tracked. The centroid is the center of the internal marker cluster that was selected for tracking. Often not all the markers are trackable because of errors such as rigid body error or positioning errors such as shadowing. We will go into more detail about these errors later. The centroid of whichever markers are selected for tracking is used. The CyberKnife beam head then treats the tumor based off the tracking and treatment plan as the patient breathes. This treatment method is long to set up, as each patient must have an individualized breathing cycle found for each treatment. The tumor is treated continuously with the only interruptions being due to error. However, the increased accuracy by tracking the tumor in real time is worth the extra set up time. It does not exclude patients from treatment that have difficulty holding their breath. This is important as lung cancer patients already have respiratory issues. Thus, breath holding for long periods of time is not likely in most patients.

Marker placement can occur in two ways. The two methods are bronchoscopic /transbronchial marker placement or percutaneous/transcutaneous placement.

Percutaneous marker placement is when the gold fiducial markers are placed using a needle inserted between the rib cage. The percutaneous placement method allows the markers to be placed wherever the doctor would like. This can ensure that a marker is placed inside the tumor and others are placed bracketing the tumor. However, this treatment comes with risks. The chances of getting a pneumothorax or collapsed lung are high in this procedure. This is because the needle used to place the markers are penetrating the outer layer of the vacuum created that allows people to breathe with their lungs inflating and deflating. When it is punctured there is a chance that the vacuum is not repaired, and the outside pressure collapses the lung. The other marker placement method uses a bronchoscope to look inside the lung. A tool is inserted with the scope that carries the gold fiducial markers. Fluoroscopy is used to help build a picture of the lung's pathways. The planning for this procedure is done using a CT scan. The fluoroscope allows the plan to be modified inside the procedure room to match the actual anatomy. The fiducial wizard program is used to help generate this plan. The risk of pneumothorax for the patient is much lower when using this procedure. Our clinic has a pneumothorax rate less than 3% doing this technique. However, potential marker locations are more limited. This is because the tool for placement must travel through the lung's natural pathways to deposit the marker. This can limit the ability to bracket the tumor with markers. The marker that is meant to go inside the tumor is placed during the biopsy for this placement technique. The current marker placement protocol is for markers to be placed at least 2 cm apart from one another and any 3 markers must be offset by 15°. These protocol rules are meant to help eliminate tracking errors caused by 1 marker shadowing the other for instance. Shadowing occurs when the

fiducial markers are not distinguishable in the x-ray images. If the system cannot distinguish one marker from another then they cannot be tracked. This limits the number of markers that can be tracked. If less than 3 markers are tracked, then the rotational movement of the tumor cannot be tracked. Marker placement is complicated because if you place them too far away from the tumor their motion is assumed to be more likely to be different then the tumors motion. However, if they are placed too close to the tumor, they will shadow one another and not be trackable. Also, if too many markers are placed the chance of shadowing is higher but too few and rotational movement is lost. The manufacturer recommends that markers are placed within 50mm of the tumor and that at least 3 are placed. Since the centroid is tracked if the tumor is not bracketed appropriately then the centroid will not match the tumor.

Other Tracking Research

There is tracking research being done throughout the country and the world. Even though tracking research is being done worldwide we have not come across any published research that is similar to the work we have completed. The previous tracking research was used to gain knowledge and insight into what questions remain unanswered. For the literature survey we began with a paper that shows the need for motion management when doing lung cancer radiation treatment. Next, we will discuss a paper used to validate the use of gold fiducial markers in lung tumor tracking. Then we will go into papers that describe motion management techniques for lung cancer and gives pros and cons and usability of the techniques. The techniques that will be described include free breathing, respiratory gating, tracking without markers, tracking with gold fiducial markers, and tracking with electromagnetic emitting markers. Treatment modalities will also be compared such as lobectomy, SBRT, and Volumetric-Modulated Arc Radiotherapy (VMAT). The recommendations made from the AAPM in Task Group (TG) 76 are included as well as the imaging dose from synchrony as outlined in TG 75.

Seppenwoolde *et al*.[4] published a paper used to validate the need for tumor tracking in lung patients. This paper quantified tumor motion using fluoroscopy and found it to be the highest in the cranial caudal (CC) or superior inferior (SI) direction, with motion being 12 ± 2 mm. The lateral (LAT) or left and right movement was found to be the same as the anterior posterior (AP) movement and was 2 ± 1 mm. The SI motion was found to be highest in lower lung (LL) patients. The location of the tumor LL or upper lung (UL) did not play a role in the AP or LAT movement.**[4]** Eckberg et al.[5]

quantified tumor motion as an average and a range and found them to be SI 3.9 mm (0-12) mm, LAT 2.4 mm (0-5) mm, and AP 2.4 mm (0-5) mm. [5] Eckberg *et al*. agrees with Seppenwoolde *et al*. that SI motion is the largest. A quote from Eckberg *et al*. also acknowledges that some clinics use other bodies to track the tumor such as chest wall movement or diaphragm movement. However, in a study completed by Hanley *et al*.[6] it was discovered that chest wall would move 2-2.5 mm but the diaphragm would move 20-38 mm in the same patients. [6] This demonstrates why tracking only visible motion or external markers are not enough to accurately track the tumor motion.

Kupelian *et al.*[7] discusses the two marker placement techniques and the stability of gold fiducial markers. In that study the transcutaneous method of marker placement had pneumothorax side effects in around 8/15 (53%) of their patients. Kupelian *et al*. claim that the usual risk of pneumothorax from a transcutaneous biopsy procedure is usually around 20-25%.[7] The real danger of a pneumothorax is that if the obstruction gets bad enough it will require the patient to get a chest tube, which is a painful procedure. This can be caused as a side effect from doing the percutaneous procedure and is the reason that percutaneous placement is not a valid option. In Kuplelian *et al.* their 8 patients in the study that had the markers placed bronchoscopically had no incidents of pneumothorax. They found their tumor motion could be up to 40 mm if the tumor was near the diaphragm. The gold fiducial markers were found to be quite stable. The movement from first scan to comparison scan was 2.6 ± 1.3 mm for the markers. The scans were taken an average of 51 days apart with the fewest days being 7 and the most being 118. This migration was defined by finding the difference in location of the tumor's center and the marker's center. Most of the difference in distance can be

attributed to tumor shrinkage, it was reported that <1 mm of the migration was all that could not be attributed to the tumor shrinkage on average.[7]

Table 2 from this Cole *et al.*[8] paper summarizes the different motion management techniques. [8] Using 4D-CT the motion blurring is reduced but it requires more imaging dose than a normal CT. Deep inspiration breath hold (DIBH) is a technique where the patient holds a deep inhale to inflate the lung, displacing lung tissue. This is done to try and limit the dose to healthy tissue and has a shorter treatment time than free breathing. However, the combination of lung density lessening, and increased lung volume can lead to overestimating the dose deposited in the tumor and even local control failure.[8] To further complicate DIBH the patient must be capable of holding their breath for an extended period of time and be compliant with therapist directions. The next technique is abdominal compression where the patient has a plate placed on their abdomen to limit diaphragm movement allowing the patient to breath normally during treatment. There are weight limits associated with this technique because it is difficult to compress an obese patient's diaphragm. It can also create erratic breathing and patients with poor respiratory function are ineligible. A widely used technique respiratory gating has the treatment beam on during a select window of the breathing cycle. It allows treatment margins to be reduced, but it requires more imaging dose and assumes that marker motion matches tumor motion. Gating also requires a more complicated QA procedure. [8] The method CyberKnife uses to track utilizes both internal and external markers. This method significantly reduces treatment margins and has less treatment time than gating. [8] It does have an increase in imaging dose to track the tumor and has the same assumptions about marker and tumor motion matching.

However, it does not need to match as strictly because multiple markers are used. When looking at all the motion management techniques tracking is the best method. The advantages are greater than any other technique and the imaging dose is negligible when compared to the treatment dose. The entrance dose per image with synchrony is between 0.10 milli-Gray (mGy) and 0.50 mGy.[9] Depending on the number of fractions there could be 600-1800 images resulting in a dose of 0.06 Gy to 0.9 Gy. This is much less than the 60 Gy prescribed to the lung tumor and comparable to the 4DCT dose.

Bahig *et al.*[10] describes another tracking method in contrast to using fiducials. This study uses XSight a markerless tracking method that CyberKnife can perform. The paper recommends that the maximum dimension of the tumor must be at least 35 mm to have above an 80% chance of XSight tracking.[10] The study started with 215 patients and only 133 of these patients were even considered for XSight. Out of the 133 patients only 88 could have the XSight tracking done. This results in 41% of the total patient pool being able to have XSight tracking and 66% of those they thought it was possible for.[10] The study also found that the tumor needed to be dense and in the peripheral of the lung with little to no motion in the AP and LAT directions.[10] These criteria limit the patient pool substantially and limits XSight useability. The average tumor size for successful XSight tracking was 15.3 cm^3 and for XSight failure it was 6.5 cm^3.[10] The XSight system is not tracking the tumor on a highly precise scale thus it requires larger treatment margins than tracking with fiducials. The main reason listed against fiducial marking tracking is the risk of pneumothorax associated with percutaneous fiducial placement but as I previously described the risk can be effectively avoided by placing markers using the bronchoscopic method. While XSight fiducial-less tracking might be

possible the extra dose given by larger treatment volumes and the limited patient pool outweighs the gain by avoiding the marker placement procedure. We will describe another tracking method next.

Calypso is a cutting-edge new tracking marker that emits radio waves that was recently approved for use in the lung by the FDA. The calypso markers emit radio waves and the transponders can be tracked with a radio wave detector array placed over the patient. Stability was originally tested in canine subjects. Bronchoscopic implantation was successful in 15/15 transponders but, after 60 days only 6 transponders were still in the lung.[1] These transponders are meant to be permanent implants but keeping them stable throughout the treatment is most important. This presented a problem for stability and the anchoring had to be redesigned for lung stability, as originally calypso was used in the prostate. The calypso study included 7 patients and all had at least 1 calypso transponder placed with stability. 13/14 transponders remained in the lung. Tracking these transponders, was successfully done in 42/53 attempts.[1] The 11 failed attempts were due to the patients becoming uncomfortable because localization took over 10 minutes. It was that study's protocol to terminate any localization attempt that took over 10 minutes. Shah said that the biggest issue with calypso as of that time, 2013, was the initialization process. Shah also said that the motion and position localization is underestimated in importance and respiratory techniques that rely on patients having the same breathing pattern during the course of the treatment over multiple days are insufficient. For lung tumor tracking rotational movement needs more than 1 transponder thus the marker placement and selection research I am working on would still be relevant even if all clinics switched to this

tracking. Memorial Sloan Kettering cancer clinic began using calypso in December 2016. In April of 2018 the FDA approved calypso tumor tracking for use with the lung cancer patients.

Chang *et al.*[11] compared the use of surgery and SBRT for patients who were eligible for surgery. 58 patients were in the study with 37 receiving SBRT and 21 getting surgery. The findings of this pooled study were promising for SBRT. The survival rate at three years was better for SBRT than it was for surgery. SBRT had a 3-year survival rate of 95% while surgery had 79%, a p-value of .037 a significant finding.**[11]** This is largely contributed to the inherent risk in having surgery. Even simple procedures can have adverse side effects and this procedure is invasive as a part of the lung is being removed. The recurrence rates for these procedures were quite similar for SBRT 86% and for surgery 80%. This gave an insignificant p-value of 0.5374. In total 7 patients in the study died. 6 of them were from the surgery group and 1 from the SBRT group.**[11]** 1 of the surgery group deaths was caused by the surgery.

Descovich *et al.*[12] is about another tracking technique called insight. Insight is done using bony structures for that study the bony structure was the spine. The translational and rotational tracking are based off spine alignment.**[12]** There are many issues with bony structure tracking. One such issue is that local control is significantly lower for tumors greater than 40 mm from the spine. An appropriate ITV-PTV expansion are difficult to estimate because unpredictable variations in tumor motion.**[12]** Overall, they summarized tracking with a bony structure by saying it required careful consideration because of the increased margins and chance of missing the tumor. From

this tracking with fiducials is a better option then tracking with bony structures such as the spine.

Casamissima *et al.*[13] found that using synchrony for tumor tracking the treatment margins were reduced by 44% compared to the margins generated from planning done based on end exhale and end inhale scans. Those margins were created by contouring the PTV in both scans then joining the PTV contours. This decreased their normal tissue complication rate from 2.5% to 0.1%.[13] This paper fails to define what a normal tissue complication is for their study though.

The TG report relevant for motion management is *TG 76*.[14] This report cited the American Cancer Society, Cancer Facts and Figures (ACSCFF) saying that 28% of all cancer deaths in the US in 2004 were lung cancer. The 5-year survival rate at that time was 15% even in 2020 the 5-year survival rate was only 18.6% according to the ACSCFF. This report recommends that planning scans need to utilize motion management techniques otherwise the plan loses accuracy. Therefore, 4DCT scans are needed for planning.[14] The patient's lung volume changes greatly based on the type of breathing being performed. During normal breathing the lung volume changes by about 20% but if the patient is doing deep breathing the lung volume can change by 60% or 80%.[14] A notable quote from TG 76 "fiducial markers are also a surrogate for tumor motion, and their accuracy in depicting true tumor motion has yet to be depicted." This is what we worked on. The concern in this report about using IMRT for treatment of the tumor is trying to match tumor motion with MLC motion. TG-76 does recommend that tracking of the tumor needs to be a combination of internal and external tracking with a

correlation model built. This is exactly how the synchrony system used by CyberKnife tracks tumor motion.[14]

Schweikard *et al.*[15] that discusses motion compensation for radiosurgery for both pancreatic and lung cancer patients. The exact spatial position of the tumor must be determined in real time to track the tumor. Tracking the tumor and moving the radiation beam could substantially simplify the procedure because you do not need to turn the beam on and off. This paper addressed the concerns over the infrared detector being affected by the treatment beam. They exposed the infrared detector to the 6 MV treatment beam directly and the noise range created by this was less than 0.01 mm.[15]

Lischalk *et al.*[16] and discusses the benefits of synchrony not being exclusive to patients like immobilization techniques are.[16] Lung cancer continues to be the leading cause of cancer related deaths of men and women worldwide accounting for 18% of all cancer related deaths. A total of 61 patients were used and only 4 had local recurrence of disease. All 4 of these patients died from spread of local disease. The study also noted as I previously said that the risk of pneumothorax was not a factor once placing fiducials bronchoscopically. Their pneumothorax rate actually dropped to 0%.

Chan *et al.*[17] compared the dose distributions of CyberKnife and VMAT. The study had 14 tumor plans made with 4DCT for midventalation VMAT and IMRT plans for end-exhale phase CyberKnife. The CyberKnife plans required smaller expansions from GTV to PTV for all 14 tumors. The VMAT PTV was larger on average by 18.7 cm^3.[17] For that study CyberKnife used XSight for tumor tracking. Overall, the paper found that CyberKnife is better than VMAT because less treatment volume is irradiated but, treatment time is longer for CyberKnife.[17] There is also another CyberKnife versus

VMAT comparison paper written by Yoon *et al.*[18] that came to the same findings about CyberKnife needing to irradiate a smaller volume during treatment.[18] Yoon *et al.* found that active breath-holding was not suitable for 40% of the patients receiving SBRT.[18]

Khadige *et al.*[19] was conducted on 95 patients and 100 tumors and studied how the tracking technique affected local control rates of the tumor. That study included 71 primary tumors and 29 secondary tumors. Overall CyberKnife has good local control with literature reporting it between 90-97% at 2-3 years. That study claims that tracking errors decreases with more than 3 markers and cited the manufacturer recommendation of 4-6 gold fiducials being placed. However, the current manufacturer recommendation states that at least 3 fiducials should be placed. CyberKnife also recommended that the fiducials should be placed within 50-60 mm of the target. That study had 35 tumors tracked with gold seeds, 15 with coils, 7 with XSight Lung and the remaining 43 were tracked with XSight Spine. Of their fiducial tracking patients only 11 of the 50 had 3 fiducials placed and only 3 were able to have all 3 fiducials tracked. 24 patients had 2 fiducials placed with 15 having both fiducials tracked. Lastly 15 patients only had 1 fiducial placed.[19] That clinic at the time performed marker placement percutaneously leading to pneumothorax complications. The two big findings for local control rate with fiducial tracking was the size of the tumor and the distance from the marker to the tumor. The study found that tumors with a size less than 35 mm had a control rate of 92% while larger tumors had a control rate of 54%. Markers placed within 50 mm of the tumor had a local control rate of 95% with further away markers giving 69%.[19] The paper concluded suggesting that fiducials be placed within 50 mm and that 2 fiducials should be placed. This recommendation for number of fiducials placed came with the

admittance that they found rotational tracking nearly impossible. The number of fiducials being placed is something this study is looking into.

Willmann *et al.*[20] validates the need for internal fiducial markers and patient specific real time tumor tracking. That study showed that internal fiducial motion was significantly associated with tumor motion in the AP and SI directions. Their study included 28 patients who were treated with a prospective IRB approved protocol for DIBH that was gated through use of internal electromagnetic transponders an external infrared reflective block.**[20]** Their electromagnetic transponders included a gold-nickel-copper coil that allowed it to be visualized in a 4DCT scan. They used the passive radiopaque marker for their study not the electromagnetic transponder. They quantified distances for their objects by defining phase 50% as a reference point for each object and finding their distance in the current phase to that reference point. They used a linear-mixed model to compare the correlation between the fiducial motion and the GTV motion. However, this came with admittance that their population based correlative model should not be used to attempt to predict tumor location or motion or influence target definitions but only be used as a benchmark to compare different motion management techniques.**[20]** The study had similar findings to previously reported data of tumor motion be largest in the SI direction. Their internal markers had similar motion in all directions compared to the tumor, but the external marker only had AP motion quantified and it was nearly double that of the tumor.**[20]** They mentioned a tumor motion more than 7 mm would have more significant day to day motion and an external surrogate only would not be accurate enough to track the tumor alone. They recommended real time tumor tracking with imaging or electromagnetic

transponders.[20] Another paper by Anastasi *et al.*[21] surveyed 200 centers from 41 different countries and found that the most common type of respiratory motion management used was an external surrogate.[21] As previously discussed though external motion cannot be used alone to accurately track lung tumor motion in real time. Lung tumors had the highest percentage of tracking being used at 10%. The study also found that roughly 75% of respondents used or wished to use real time motion management for respiratory motion for lung cancer patients.[21]

Dhont *et al.*[22] discusses the long and short term variability of breathing induced tumor motion for both lung and liver cancer patients and both primary and metastatic cancers. [22] They discussed how a 4DCT only has about 15 total breathing cycles used in generating the 4DCT. They say this means the scan has no day-to-day variability in the 4DCT and is why active tumor tracking must be performed and not passive tumor tracking. [22] The tumor location and tracking in their study was performed by tracking a single fiducial they placed percutaneously in or within a cm of the tumor, and all their patients had motion larger than 7 mm on the pretreatment 4DCT. [22] All of their lung tumor patients had their largest motion be in the SI direction. They found that 8 of their 19 lung tumor patients had interfraction amplitude variability of greater than 5 mm. [22] The study mentions the need to do repeated verification of the lung tumor position to due to the high variability of motion. That paper shows that passive lung tumor tracking is not accurate enough and should be abandoned for active tumor tracking modalities. [22]

Uijtewaal *et al.*[23] shows the feasibility of performing MLC tracking with a MRI guided imaging LINAC.[23] This was done on an Elekta Unity system which has been

shown recently to be the first MRI guided LINAC capable of tracking respiratory motion. It is important to note that the study only considered motion in the SI direction. This is much less accurate than the current capabilities of SBRT with x-ray guided imaging and has no chance of tracking rotational movement. Their treatment plan differs from traditional SBRT doses. They treated with 7.5 Gy/fx for 8 fractions or 18 Gy/fx in 3 fractions. Another limitation of this type of tracking was imaging frequency. The study mentioned that the system images at 4 or 8 Hz.[23] This causes the system to track an outdated tumor position and needs to try to correct this with a prediction model. Prediction can be complicated by irregular breathing patterns. There is also a latency in between telling the MLC where it should be positioned and it moving to that location. The study also admitted that 3d tracking was needed to reduce treatment margins more and that it was not ready for clinical use.[23]

Research Questions

This research was hoping to help answer a multitude of questions all leading to better lung tumor tracking. The first question we sought to answer was if the distance between the tumor and fiducial could be used to determine the fiducial's ability to match the tumor's motion. Another question we had was if the fiducial's relative positioning to the tumor i.e. superior or inferior, proximal or distal, and anterior or posterior had any effect on the fiducials tracking accuracy. We also sought to see if any relative position was present more than its counterpart when placing fiducials. Another fiducial marker placement question we had was if the fiducial was placed within the tumor target. It was our hope that all patients would have at least 1 fiducial placed within the tumor target. We were also seeking to answer questions about the combined fiducials' centroid instead of individual fiducials. To start we looked at different combinations of fiducials' centroids compared to the GTV's center of mass (COM). First was the centroid from the previously determined 2 fiducials that individually tracked the GTV's COM the most consistently, as well as the centroid from the 2 fiducials that were closest to the GTV's COM, and lastly the centroid from all implanted fiducials. That was done as a preliminary data analysis. We then took a look at all of the different possible centroid combinations to see what centroid was the closest to the GTV's COM and which centroid followed the GTV's COM the best. We also looked at what number of fiducials were used to create these centroids. We also were seeking to quantify how much better our proposed centroids were than the centroid that was tracked. This quantification will be determined by how much closer it is to the GTV's COM or how much more consistent the motion tracks and the dosimetric effect of changing the marker selection.

We also sought to see how often the different centroids were inside the tumor target. All of this can be used to help the treatment staff select which markers should be used for tracking and where the markers are best suited to be placed.

Specific Aims

Specific Aim I: Determine what makes a fiducial track the tumor well.

The distance between each fiducial and the tumor was tracked through the entire breathing cycle. If the distance between the fiducial and the GTV's COM stayed constant within 2 mm throughout the entire breathing cycle, then the fiducial motion matched that of the tumor motion well enough to be deemed good tracking. Markers deemed good tracking by the above method were grouped into their relative positioning with respect to the tumor to see if a trend emerges. This was checked for lower lung and upper lung separately because the different areas of the lung exhibit different motion. It was also checked to see how many of the fiducials were placed inside the tumor target. Again, this was checked for upper and lower lung tumor patients separately.

Specific Aim II: Determine what fiducials should be selected for optimal tracking.

The centroid for each possible combination of fiducials was compared and they were found in all phases of the breathing cycle. After finding every possible centroid combination we searched for the combination that was closest to the tumor's COM and what centroid combination had the smallest change in distance from the tumor's COM throughout the entire breathing cycle. The average distance between the centroid closest to the GTV's COM and the tumor was found and it was compared to the distance between the centroid used during tracking and the GTV's COM using a two-mean t-test. The discrepancy in motion was compared for the centroid that kept the distance to the GTV's COM the most consistent and the centroid that was tracked using

a two-mean t-test. Using those combinations, we searched for patterns that can be applied to provide optimal treatment in most patients. We looked at the position for the individual fiducials making up the centroids of interest relative to the GTV's COM. The fiducial's position data was analyzed to see if there were any trends in where fiducials were placed relative to the GTV's COM and if that affected their ability to accurately match tumor motion. This was done to check if the fiducials bracket the GTV's COM and if so in what direction. Another trend that was analyzed was if the centroid was inside the tumor target. This will be used to make recommendations on what fiducials should be used when selecting fiducials to track the GTV.

Specific Aim III: Determine what number of fiducials should be tracked.

To check what number of fiducials should be tracked we found every possible centroid combination and saw what combination provided optimal tumor tracking. Then we found what number of fiducials was most common in these centroids. We also found what type of relative positioning or bracketing is present in these centroids. These techniques allowed this research question to be answered.

Specific Aim IV: Determine the dosimetric effect of changing marker selection.

We found what the effect was on the GTV and organs at risk (OAR) when the marker selection was changed. A dose volume histogram (DVH) comparison was made for the unaltered treatment plan, and the treatment plan being shifted to the 2 different centroids of interest. The mean, maximum, and minimum dose were compared for the GTV and relevant OAR as well for each centroid combination. This data shows what can happen if the centroid being tracked is shifted because of GTV motion not matching

fiducial motion. It can be used as an estimate to the worst case scenario of dose distribution.

Specific Aim V: Determine the type of bracketing needed for upper and lower lung patients separately.

We found the type of bracketing present in the centroids of interest separately for upper and lower lung patients. This was done because it was assumed the different areas of the lung would have differing motions.

Methods

This is a retrospective IRB approved study that uses real patient data from patients treated at Vidant medical center in Greenville, North Carolina. 2 sequential series of patients were selected for the study that were receiving 4DCT simulation of a CyberKnife Stereotactic Radiotherapy (SRT) treatment for lung cancer with relative radiation start dates in spring of 2017 or in the fall of 2020. Patients with both primary and metastatic tumors were included in the study. The patient having their four-dimensional Computed Tomography (4DCT) scan was a necessary component for the research. The 4D-CT scan is crucial for this study because it allows the scans to be broken into their breathing phases. This allows us to examine data in all phases of the breathing cycle. The 4D-CT works similar to a normal CT scan but, the scan takes multiple images over time so that images can be broken into their parts of the breathing cycle. The breathing cycle is broken into 10 phases and these phases are determined from the scan at different times and it creates a normal CT scan at each different phase of the breathing cycle. As mentioned earlier phase 0% usually represents end of inhalation and phase 50% usually represents end of exhalation. The average size of the patient's GTV in this study was 9.74 ± 1.35 cm^3, with the largest GTV being 27.1 cm^3, and the smallest being 1.8 cm^3.

The radiation oncologist contours the tumor's GTV which is the tumor volume that can be seen in the scan. One important issue that our hospital does a good job of controlling is keeping the tumor contour consistent no matter which doctor does the contouring. Still not every doctor is the same so the GTV contour needed post-processing in the study in every phase to eliminate physician contouring bias. Caldwell

et al.[24] shows that physician bias is a real issue when doing a study that could possibly have different people preforming GTV contouring.[24] In that study 3 different radiation oncologist attempted to contour the same patients GTV. The contours were compared for each radiation oncologist and a ratio of largest to smallest was created. Those ratios ranged from 1.06 to 7.66 depending on the patient.[24] That study did admit that they only used patients with difficult to define margins and thus the ratio for the general population would likely be smaller.

The fiducials were contoured in a group as one object by the clinic so for this study the fiducials needed to be recontoured and renamed. The recontouring and renaming had to be done in every phase of the breathing cycle for every fiducial for every patient. The fiducials were labeled from superior to inferior as fiducial 1 to 4 and any 2 fiducials that showed up in the same superior inferior plane the fiducial located closest to the spine or most proximal to the patients center line was given the earlier numbering. Once all objects were contoured the post-processing could be done.

Now that all the objects were contoured the post-processing was done to eliminate noise, make the experiment more reproducible, and try to eliminate any physician bias in the GTV contouring. A scan was done on the objects that the COM was to be calculated for and checked the pixel values of each pixel inside that object's contour. A range of numbers was input that the fiducial or GTV should have and then any pixel inside that range was assigned a value of 1 and any pixel outside that range was assigned a value of 0. Now the geometric COM was calculated and only pixels with a value of 1 for each object was used in the calculation. This post processing was done on each phase of the breathing cycle for each patient and had to be done for the GTV

and the fiducials separately because they have different expected pixel values. This allowed the COM to be calculated with physician bias being accounted for and without allowing the noise from motion blurring affecting it.

Since all the COM's are known in every part of the breathing cycle, motion was compared for the fiducials and the GTV. When looking at the individual fiducials their tracking success was based on if the distance between the fiducial and GTV stayed consistent within 2mm. When this distance stayed constant then the fiducial motion matched the GTV motion. A discrepancy value of 2 mm was used to separate the fiducials into good tracking and bad tracking subgroups. These subgroups were analyzed to look for any indications in what caused the marker to track the GTV's COM well or not. Distance and relative position around the tumor were the most likely areas to look for patterns in the data. All statistical testing was done with t-tests except the relationship between relative position and tracking ability which was checked with a chi-squared test.

With all the fiducials COM's located different centroid combinations were found. A centroid is the center of two or more objects. The centroid of whatever fiducials were selected by the system is how synchrony and CyberKnife track. While figuring out which individual markers track well is important, figuring out which centroids track well is more clinically relevant because that is how the system actually tracks the tumor. The work with the induvial fiducials was a method of figuring out what contributes to the centroids being more accurate. Different centroid combinations were found for analysis. The combinations we found were the centroid from all implanted fiducials, the centroid from the 2 closest fiducials, and the centroid from the 2 fiducials that kept the most constant

distance to the GTV from the method described earlier. These centroids were compared with the tumor's COM in all phases of the breathing cycle for preliminary analysis.

Next every possible centroid combination was found for the patients. Patients with 4 fiducials placed had a total of 11 different centroids that needed analysis. There was 1 patient that had 6 fiducials implanted and this vastly increased the number of possible centroids to 57. This will allow the best tracking centroid to be determined. From this we hoped to find patterns in the number of fiducials used to generate the centroids, as well as their relative position. This allowed us to answer the research questions about the number of fiducials that should be implanted, and what the best places for them are. This data was also used to quantify how much better our proposed centroids were than the centroid that was tracked.

A program in MATLAB® was used that shifted the isocenter of a dose profile. The distance between the tracked centroid and the 2 centroids of interest were found in every phase of the breathing cycle. A breathing trace from a patient was analyzed to estimate the amount of time that was spent in each part of the breathing cycle. The time spent in each phase was then divided by the total time of the breathing cycle to find the proportion of time the patient was in each phase of the breathing cycle. This was done because people do not spend equal amounts of time in each phase of the breathing cycle. Inhalation is an active process where the muscles of the diaphragm constrict, allowing the lung space to fill with air and expand. Exhalation on the other hand is the passive process of the lungs deflating. The body wants to spend less time in the active process using energy thus, patients spend more time in the exhale portion of the breathing cycle. A single patient's breathing trace was used to find the proportionate

amount of time that the patients were in that phase and a scaling factor for the shifts was generated. People spend around twice as long in exhale than they do inhale so each patient should spend equal proportions of time in each phase. The breathing trace that was used to generate the scaling factors was compared with breathing traces from 2 other patients. The scaling factors used agreed within four-hundredths for the proportion of time spent in each phase of the breathing cycle for the 2 comparison patients, thus it was determined that only the one set of scaling factors were needed. The dose profile was shifted from the tracked centroid to the 2 centroids of interest for each phase of the breathing cycle and the amount of shift was scaled by the amount of time spent in that phase relative to the whole breathing cycle. Sparing healthy lung tissue is very important. Lung tissue is considered a parallel tissue. Parallel tissue that receives radiation above the threshold dose limit is considered disabled. For parallel tissue approximately 1/3rd the total volume needs to be functioning for the organ to function.[25] Critically it is also necessary that the functioning part of the tissue is connected to the part of the organ that carries the function away.[25] The lungs critical volume is about 1500 cm^3 and the threshold dose is different for SBRT. For 3 fraction (fx) treatments the dose is 10.5 Gy and for 5 fx it is 12.5 Gy.[26] The dose constraints are outlined in TG 101, but they are listed with a precaution as early dose constraints and that more research is needed into SBRT dose constraints.[26] DVH's were generated to compare the dose of the GTV and any possible OAR for that patient. The mean, maximum, and minimum dose were found and compared for the unaltered dose profile and the 2 shifted dose profiles. Some patients had their centroids of interest be the

same centroid or had their tracked centroid match one of the centroids of interest. In these cases the dose profile was only shifted once.

Once all the possible centroids were found, we found the centroid that was closest to the GTV's COM and the centroid that followed the GTV's COM the best, as previously stated. The fiducials that created those centroids were analyzed to look for patterns in what created them. The position of the fiducial relative to the GTV's COM was found first. These were analyzed to see if a certain relative position appeared more often than its counterpart. This would mean that the fiducials were being placed on one side of the GTV more often than the other. This analysis was repeated after separating the patients based on if their tumor was in the upper or lower part of the lung. We felt the necessity to separate the patients by tumor location for this part of the study because the upper and lower parts of the lung have different types of respiratory motion. The location of the fiducial relative to the tumor was then analyzed with that fiducials success in tracking the GTV's COM. This was done to see if fiducials placed on one side of the tumor did better at tracking than its counterpart side. The centroids were then analyzed to see what if any types of bracketing were present in the combination of fiducials that created that centroid. This was done to improve the recommendations for fiducial marker placement and selection. Similar to the relative position analysis this was repeated on upper and lower lung patients separately. The types of bracketing in the centroids of interest were checked to see if they matched the tumor's largest direction of motion. This was again checked on the upper lung tumor and lower lung tumor patients separately. This was done to show that upper and lower lung patients exhibit different types of motion and require different fiducial placement and selection recommendations.

It was also checked to see if the fiducials were placed inside the GTV. This was done by looking at the 4DCT and seeing if any of the fiducials were inside the tumor target. It was also checked to see if the centroids of interest and the tracked centroid were inside the tumor target. A flow of my method at looking at fiducials and centroids can be seen in diagram 1.

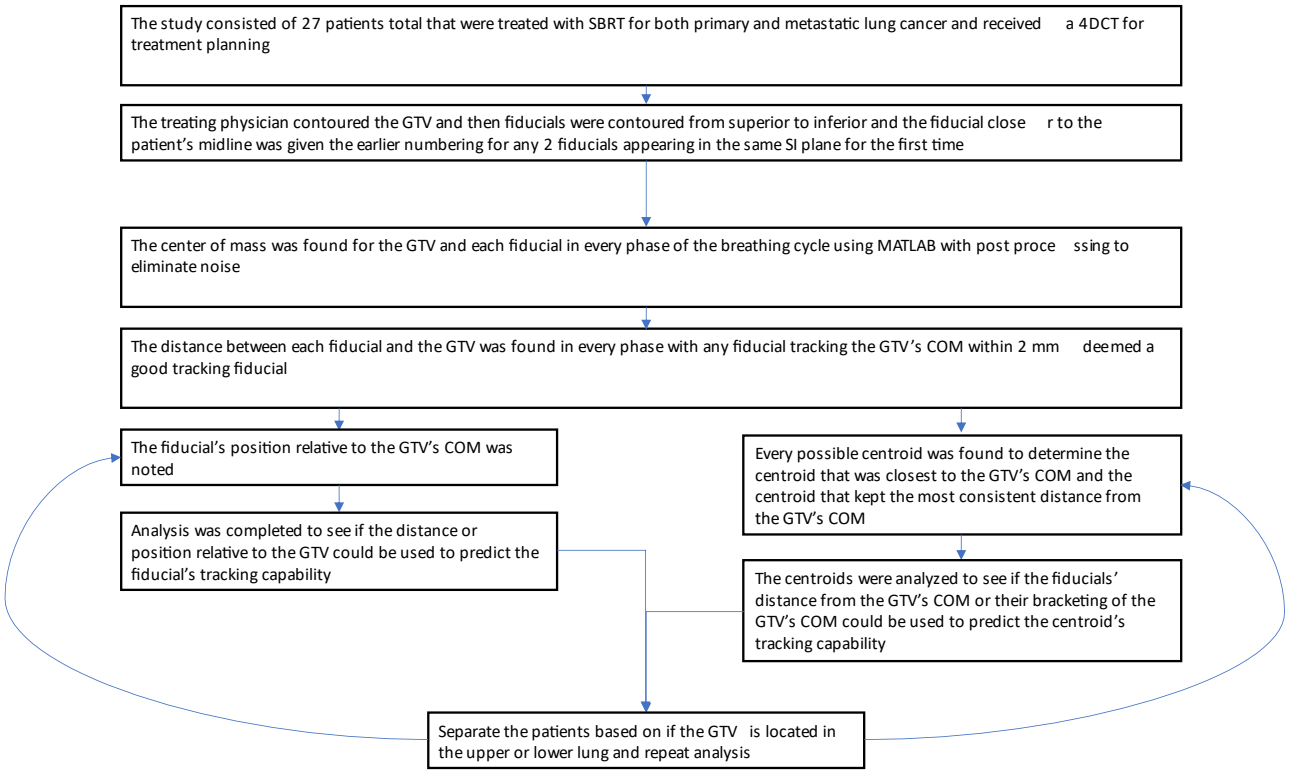

Diagram 1: Describing the workflow

Results

For the 27 patients the COM for the GTV and each fiducial were found first. The first analysis we did was seeing which fiducials had a constant distance to the GTV within 2 mm. The average distance away from the GTV's COM for "good" and "bad" tracking fiducials can be seen in *Table 1.* Our initial hypothesis was that distance would be a significant factor here. When analyzing the data, it was found that distance was not a significant factor ($p=0.165$), this did not support our initial hypothesis. One of the "bad" tracking fiducials was excluded from the study because it was deemed an outlier. It was determined to be an outlier using the 1.5*Interquartile Range (IQR) method. This method involved finding the IQR or the difference between the third and first quartile then multiplying by 1.5. That number is added to the third quartile and subtracted from the first quartile. Any number outside this range created is deemed an outlier. In our study we had 1 "bad" tracking fiducial that was 6.79 cm away from the GTV's COM but the top of our acceptable data range was at 5.92 cm. If we do not remove the outlier the distance is still not significant, but the finding is closer to it ($p=0.108$). The analysis was completed using a two-mean T-test with a significance threshold of $p \leq 0.05$. The closer a fiducial was to the tumor did not mean that it would keep a more constant distance from the GTV than a further fiducial. This led us to the conclusion that a fiducials ability to match the motion of the GTV is far more complicated than just proximity to the tumor. Therefore, we wanted to look at the relationship between relative positioning of the fiducial and the GTV to see if the "good" tracking fiducials are more often superior to the GTV or inferior or any certain direction. Next, we investigated what factor the distance from the GTV's COM has on fiducials when they are being used as parts of a centroid

and not looked at individually, as they were in *Table 1*. The centroid for the 2 closest fiducials, the centroid from the 2 “most constant” tracking fiducials, and the centroid from all fiducials were compared. The distributions are shown in *Figure 2.* The 2 closest fiducials had the centroid closest to the GTV’s COM. When comparing the 2 closest and the 2 most constant it was significant (p=0.004) and when comparing the 2 closest with the centroid from all the fiducials the data was still significant (p=0.007). The comparison with the other 2 combinations was not significant (p=0.276). This would support that distance from the tumor is important in the fiducials ability to track the tumor when looked at as part of a grouping.

	Good	Bad
Average Distance (cm)	2.64	2.87
Standard Error (cm)	0.16	0.18
N	52	49

Table 1: Fiducial’s Distance from the GTV

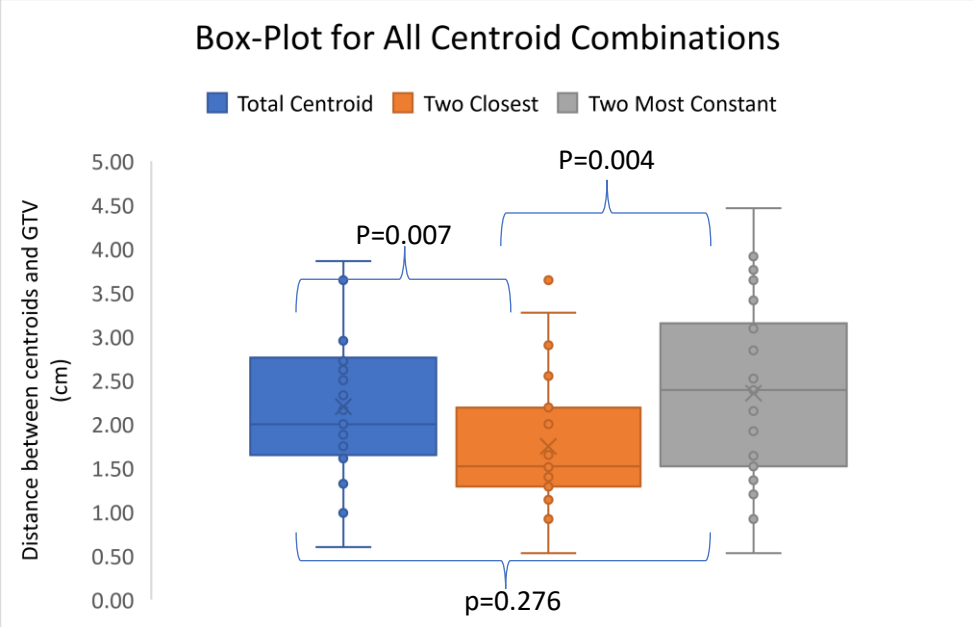

Figure 2: Boxplot showing the distributions of Centroid data

In *Figure 3 panels A-C* and *E-G* show the motion in all three directions for each centroid combination and the GTV's COM in every phase of the breathing cycle for an upper lung tumor and a lower lung tumor patient respectively. In *Figure 3 panels D* and *H* the distance between the centroid for each combination and the GTV's COM are shown in all phases of the breathing cycle for the same patients. In *Figure 3 panel C* the motion in phase 20 does not match the GTV for any of the centroids' combinations.

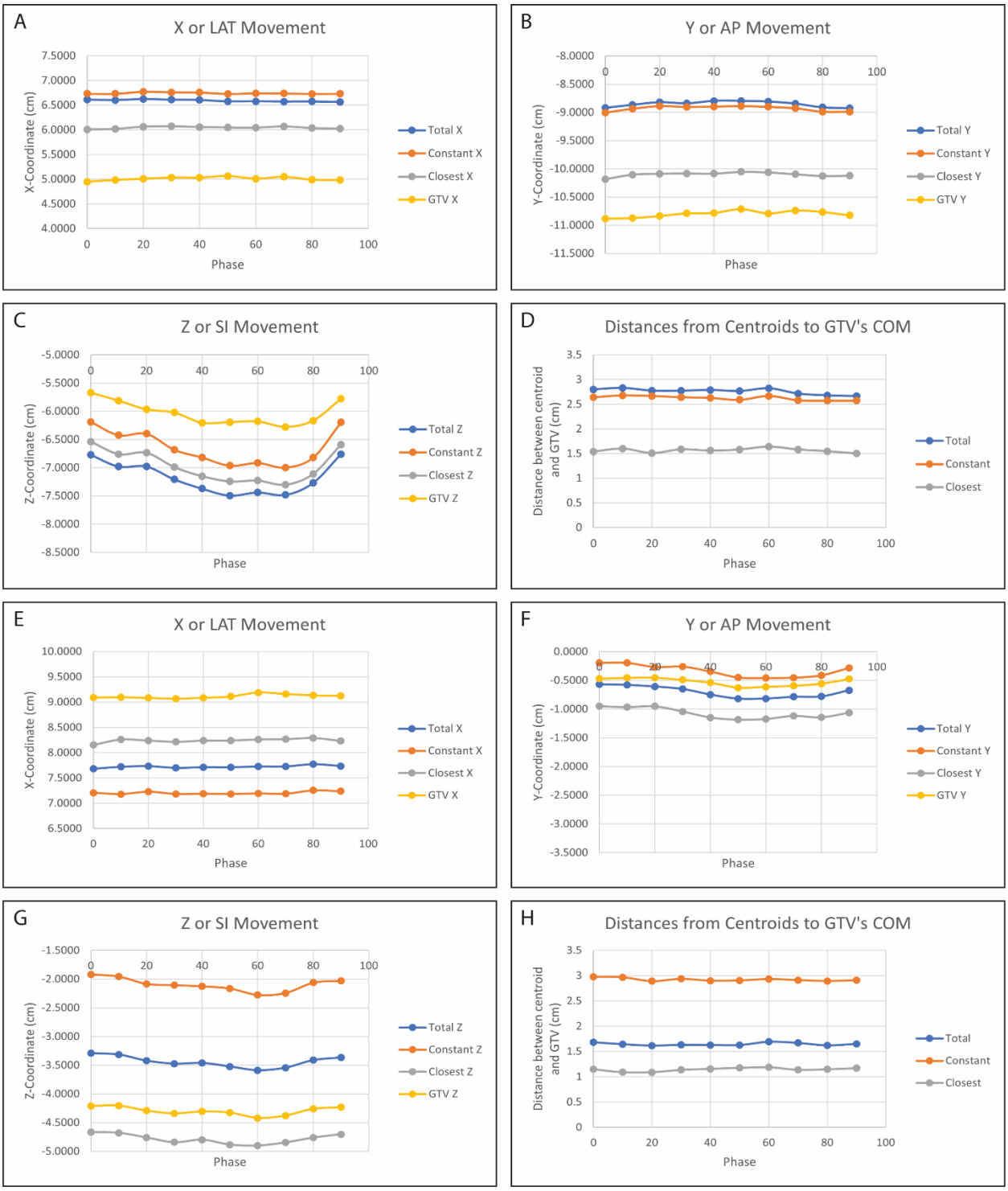

Figure 3:(A-C, E-G) Motion of the Centroids and GTV COM in all phases and directions. (D,H) Distance between the Centroids and GTV COM in all phases

It is possible that the discrepancy in motion could be caused by an error in data acquisition or the splitting of the 4DCT into the phases. However, if this is a true indication of the actual motion then tumor tracking has failed in that phase. The deviation in motion in phase 20 is caused by 3 or 4 of the fiducials moving in the opposite z-direction in phase 20 then the GTV is. This might make these fiducials not trackable in a real clinic scenario. Next, we quantified just how much better the tracking could be based off this research. A total analysis has been completed on the 27 patients. The values can be seen in *Table 2*. The closest centroid was closer to the GTV's COM than the tracked centroid by 4.1 ± 1.2 mm (p=0.001). This analysis excluded one patient as an outlier. The patient was determined an outlier the same way as previously described. This outlier was again at the top end of the data set, thus if it was included it would make the difference larger and the data more significant but, we did not want any outliers skewing our data even if the skew was in our favor. The tracked centroid was the centroid from the fiducials actually tracked in the clinic during treatment. These 27 patients have also had their smallest discrepancy centroid compared with discrepancy of the tracked centroid. We defined the discrepancy in terms of the standard deviation of the distance between the centroid and GTV's COM for each patient over the whole breathing cycle. The centroid that tracked the tumor the most consistently had significantly smaller discrepancy than the tracked centroid by 0.23 ± 0.05 mm (p=0.00003). This too is listed in *Table 2B*.

	Tracked-Closest Distance (mm)
Average	4.1
Standard Error	1.2

Table 2A: Summary Statistics for the Difference in the Tracked Centroid and the Centroid Closest to the GTV's COM

	Tracked-Smallest Std Dev (mm)
Average	0.23
Standard Error	0.05

Table 2B: Summary Statistics for the Difference in Tracking Accuracy for the Tracked Centroid and the Centroid that

The shift from the tracked centroid to the centroids of interest has been completed for all 27 patients. The analysis was repeated on 5 patients who had a shift smaller than 1 cm on average. The shift between the fiducial centroids was less than 1 cm but the dosimetric effect was large. The amount shifted in each direction and total for both shifts on average for those 5 patients are shown in *Table 3*.

Shift From Tracked	X (mm)	Y (mm)	Z (mm)	Total (mm)
Closest	1.8	3.3	2.7	5.4
Smallest	2.9	2.7	2.5	5.5

Table 3: Average Centroid Shift Distances

The change in dose to the GTV and the relevant OAR are shown in *Table 4* for the 5 patient's with less than 1 cm shift on average. The closest to the GTV COM shift is where the original dose profile has been shifted by the difference between the distance from the GTV's COM for the tracked centroid and the distance from the GTV's COM for

the closest centroid in each phase with the appropriate scaling factor applied. The left column shows the difference in the original tracked dose and the closest to the GTV's COM shift. Similarly, the smallest discrepancy shift was found except it uses the distance from the GTV's COM to the centroid that had the least discrepancy in motion compared to the GTV. The right column shows the difference in the tracked dose and the smallest discrepancy shifted dose. The GTV coverage drops for both the shifted centroids. The difference in the GTV maximum and minimum dose is significant for both shifts as is the difference that 95% of the GTV volume receives. The dose to the ribs is lower for both shifts but the difference is not significant. The dose to the other OAR was better for the both the closest to the GTV's COM shift and the smallest discrepancy shifted dose profile. There was a significant difference for OAR#3 mean dose on average and the shift to the closest centroid had a significant difference for OAR#2 mean dose. *Figure 4* shows the DVH comparison for both of the shifted centroids described earlier for a single patient. In each graph the dotted line is from the original dose profile created and the solid line was generated from the shift in the isodose profile based on shifting the fiducial centroid to a different combination than what was tracked.

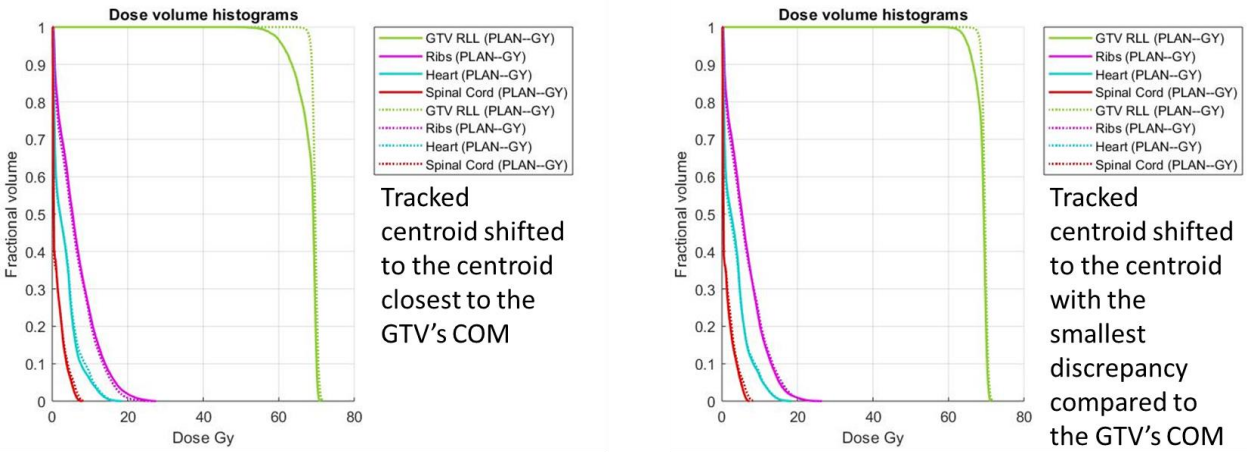

Figure 4: DVH Comparison for both Shifted Centroids(The dotted line represents unshifted and the solid line represents shifted)

Different Dose Metrics	Difference in dose between original and shift to the closest centroid	Difference in dose between original and shift to the most consistent centroid
GTV Mean	**3.47**	**3.53**
GTV Max	2.16	**0.6**
GTV Min	**14.9**	**14.9**
GTV 95% Volume	**10.2**	**10.2**
Ribs Mean	0.31	0.43
Ribs Max	2.26	2.7
OAR #2 Mean	**0.12**	0.09
OAR #2 Max	3.1	3
OAR #3 Mean	**0.16**	**0.24**
OAR #3 Max	0.9	1.3

Table 4: Summary of Dose Profiles Gy

We then examined how often these fiducial centroids were the same. Also, how often the fiducials that were individually the closest to the GTV's COM made the centroid that was closest to the GTV's COM. The closest fiducials were used to make the centroid that was closest to the GTV's COM in 70% (19/27) of patients. The centroid that was closest to the GTV's COM was selected for tracking in 26% (7/27) of the

patients. The centroid that kept the most consistent distance from the GTV's COM was used in tracking for 19% (5/27) patients. Lastly, the ideal scenario would have the centroid closest to the GTV's COM be the same as the centroid that kept the most consistent distance, but this was seen in only 33% (9/27) patients. These can be seen in *Table 5*. We next examined the number of fiducials that were used to generate these centroids. This will be helpful in improving the recommendations for both fiducial marker placement and selection. 3 or more fiducials were tracked in 19% (5/27) of patients. 3 or more fiducials are needed for any chance of tracking rotational movement. The tracked centroid and 2 centroids of interest were created most often by 2 fiducials. The number by number and different centroids can all be seen in *Table 6*.

% Closest Fids = Closest Centroid	70% = 19/27
% Closest Centroid = Tracked	26% = 7/27
%Smallest (Max-Min) = Tracked	19% = 5/27
% Closest Centroid = Smallest (Max-Min)	33% = 9/27

Table 5: Comparison Statistics

Number of Fiducials	Tracked	Closest Centroid	Most Consistent Centroid
1	15% = 4/27	0% = 0/27	0% = 0/27
2	67% = 18/27	89% = 24/27	78% = 21/27
3	3% = 1/27	11% = 3/27	15% = 4/27
4	15% = 4/27	0% = 0/27	7% = 2/27

Table 6: Statistics by number of fiducials

Figure 5 shows 2 different CT images from the same patient in the same phase of the breathing cycle. The crosshairs are lined up at 2 different fiducial centroid locations. The orange contour shows where the GTV is located. The small blue contour

on the right image is showing the location of a fiducial. The image on the left has the crosshairs lined up with the centroid closest to the GTV's COM and the image on the right has the crosshairs lined up at the centroid that kept the most consistent distance from the GTV's COM. This shows while the distance between centroids is less than 1 cm, the change in anatomy can be large.

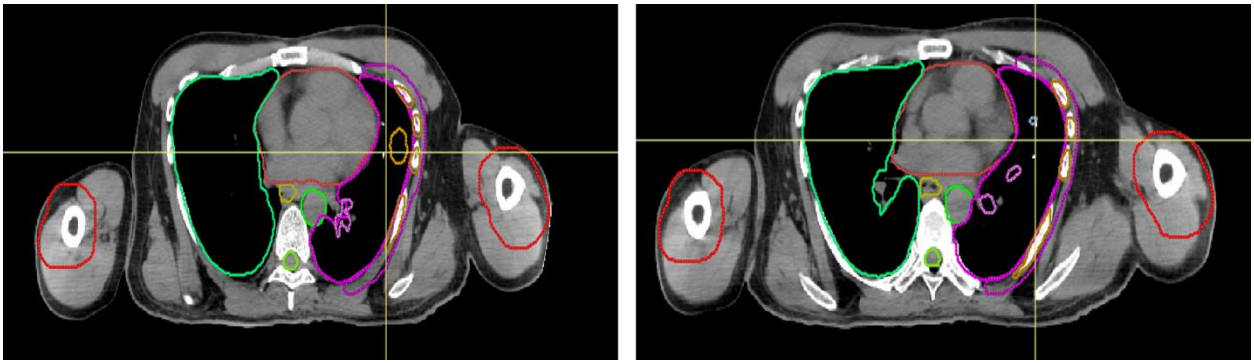

Figure 5: CT Images of The Same Patient

The placement of fiducials determines if any bracketing is possible and the selection of fiducials for tracking determines if any type of bracketing occurs. The tracked centroid and the 2 centroids of interest had their fiducials examined to see the type of bracketing that occurred and check to see if any patterns were found. In addition we checked to see if the centroids had bracketing in the same direction as the GTV's largest dimension of motion. When we looked at the placement of the fiducials there were more fiducials placed inferior than superior. There were 60 fiducials placed inferior and 42 placed superior. The difference in placement was found to be significant when looking at the patients with upper lung tumors. In the upper lung patients, there were 52 fiducials placed inferior and 27 superior. There were also more fiducials placed distal than proximal for upper lung tumor patients. There were 49 placed distal and 30

proximal. The difference was significant when looking at these placements. There were also more fiducials placed anterior than posterior. However, the difference was not significant for either upper or lower lung tumor patients. This data is shown in *Table 7*. The bolded data entries are to signify a statistical significance occurred.

Fiducials Location Relative to the GTV		
	Superior	Inferior
Upper Lung	**27**	**52**
Lower Lung	15	8
	Proximal	Distal
Upper Lung	**30**	**49**
Lower Lung	15	8
	Anterior	Posterior
Upper Lung	45	34
Lower Lung	9	14

Table 7: Number of fiducials placed relative to the GTV split by location of the tumor

We then looked at how the tracked centroid and the 2 centroids of interest bracketed the tumor. This was done to look for patterns in bracketing to improve fiducial placement and selection. This analysis was done separately for upper and lower lung tumor patients because we assumed the motion would be different for the different groups of patients. There was an equal occurrence of anterior-posterior bracketing, distal-proximal bracketing, and a lack of bracketing by the chosen fiducials in the centroid that was tracked in the clinic for upper lung tumor patients. The lack of bracketing is due to the fiducials that were chosen were placed on the same side of the GTV. In the tracked centroid for upper lung tumor patients superior-inferior bracketing occurred 1 less time than the others. Those types occurred in 7 of the 20 patients while superior-inferior occurred 6. For the centroid that was closest to the GTV's COM it had

bracketing occurring most often in the anterior-posterior direction. This occurred in 10 of the 20 patients. For the closest to the GTV's COM centroid superior-inferior bracketing occurred 2nd most often in 9 out of 20 patients. For the centroid that kept the most consistent distance from the GTV's COM bracketing occurred most in the anterior-posterior direction. Anterior-posterior bracketing was present in 10 of the 20 patients. Superior-inferior bracketing was 2nd most in this centroid as well occurring in 8 of the 20 patients. The data is shown in *Table 8*. There is no double counting present in the table thus the sum of each column will be 20.

Type of Bracketing	Tracked Centroid	Closest to the GTV Centroid	Most Consistent Distance Centroid
None	7	4	4
SI	1	4	3
AP	4	3	5
DP	3	2	1
SI/AP	1	1	0
SI/DP	2	0	2
AP/DP	0	2	2
SI/AP/DP	2	4	3

Table 8: Breakdown of the type of bracketing by fiducials of the GTV found in the centroids of interest and tracked centroid for upper lung patients

We then examined the type of bracketing occurring in the centroids of interest and the tracked centroid for the lower lung patients. Similar to the upper lung patients the tracked centroid for the lower lung patients had no bracketing appear most. Occurring in 3 of the 7 patients. The centroid that was closest to the GTV's COM for lower lung tumor patients had bracketing most in the superior-inferior direction. This occurred in 4 of the 7 patients. Superior-inferior bracketing occurred most in the centroid

that kept the most consistent distance from the GTV's COM appearing in 6 of the 7 patients. All of the bracketing can be seen in *Table 9*. There is no double counting in the table, meaning the sum of the columns will be 7.

Type of Bracketing	Tracked Centroid	Closest to the GTV Centroid	Most Consistent Distance Centroid
None	3	2	1
SI	1	3	2
AP	1	1	0
DP	1	0	0
SI/AP	0	0	1
SI/DP	0	0	0
AP/DP	0	0	0
SI/AP/DP	1	1	3

Table 9: Breakdown of the type of bracketing by fiducials of the GTV found in the centroids of interest and tracked centroid for lower lung patients

It was found that there were significantly more fiducials placed outside the GTV than inside the GTV. This was an expected finding. There were 88 fiducials placed outside the GTV out of the 102 total fiducials. 13 of the patients had at least 1 fiducial be placed inside their tumor target. The centroid that was closest to the GTV's COM was more often found inside the tumor target than the other centroids but the difference was not significant. The centroid closest to the GTV's COM was inside the GTV's contour in 8 of the 27 patients. The tracked centroid had the next highest number with 5 of the 27 patients having their centroid inside the GTV's COM. Lastly, the centroid that followed the GTV's COM the most consistently had the fewest with 4 being inside the GTV's COM contour. The data can be seen in *Table 10*.

Location of Fiducial	Individual Fiducials	Tracked	Closest Centroid	Most Consistent Centroid
Outside	88	22	19	23
Inside	14	5	8	4
Total	102	27	27	27

Table 10: Statistics of Inside/Outside the GTV's Contour

Of the 88 fiducials placed outside the GTV 70 of them were in the upper lung tumor patients. That means the remaining 18 were in the lower lung tumor patients. 9 of the 14 fiducials that were placed within the GTV were in the upper lung tumor patients. The remaining 5 were in the lower lung tumor patients. There was a higher percentage of lower lung tumor patients that were able to have a fiducial placed within the GTV. The percentage was 57.1% or 4/7. The percentage of upper lung tumor patients with a fiducial placed within the GTV was 45% or 9/20. The data can be seen in *Table 11.* *Figure 6* also shows a fiducial that is placed within the GTV for a patient.

Fiducials Placed	Outside GTV	Within GTV
Upper Lung Tumor	70	9
Lower Lung Tumor	18	5

Table 11: Fiducials placed inside or outside the GTV by Tumor Location

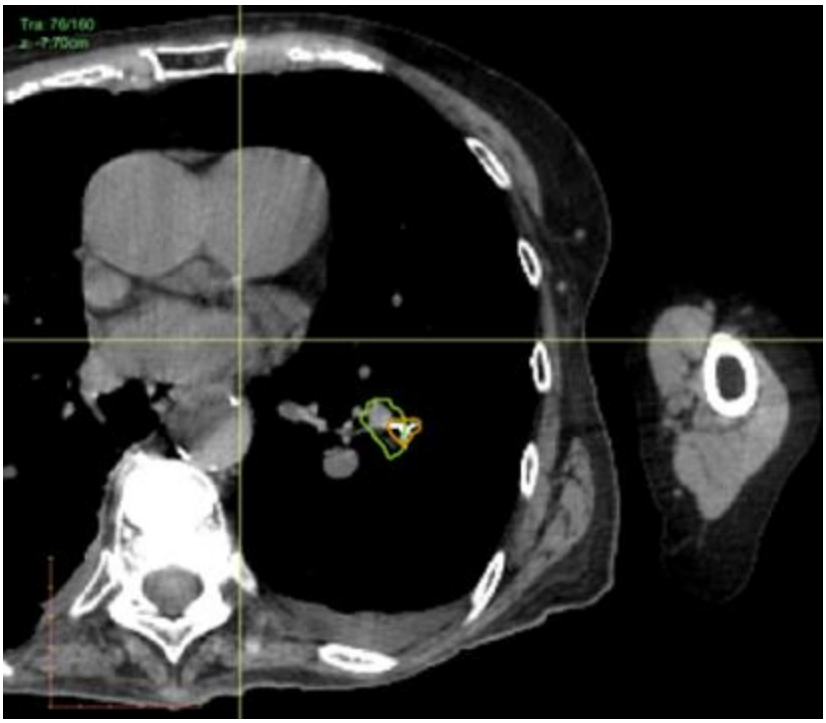

Figure 6: A fiducial within the GTV

It was also examined to see if the placement of the fiducial relative to the GTV's COM could predict the fiducials tracking ability. This was checked for all of the fiducials placed and in each relative direction. This was then checked again for upper and lower lung patients separately. There was only a significant finding for patients with lower lung tumors and only when looking at the anterior and posterior directions. The data is shown in *Table 12*. There were significantly more bad tracking fiducials placed anteriorly and more good tracking fiducials placed posteriorly in reference to the GTV's COM. A chi-square test was performed on the 2x2 contingency table, and the significance was determined because the p-value was less than 0.05.

Fiducial's Position	Good Tracking Fiducials	Bad Tracking Fiducials
Posterior	9	5
Anterior	2	7

Table 12: 2x2 contingency table of relative positioning and fiducial tracking ability

Discussion

Now that the data has been presented, we will provide some conclusions and discussion on what it all means for our research questions and the findings. While we found that distance from the GTV's COM was not able to significantly determine if a fiducial would track the tumor within 2 mm, we would still recommend that fiducials be placed closer to the GTV when possible. The fiducial that did track the GTV's COM well were placed closer on average.

Our initial look at some centroids showed distance from the centroid to the GTV's COM could be used to draw some statistical significance. The centroid created by the 2 closest fiducials was significantly closer to the GTV's COM than the centroid from all fiducials placed or the centroid from the 2 fiducials that followed the GTV's motion the best. Therefore, when selecting fiducials to create a centroid the closer fiducials do significantly impact the closeness of the centroid. However, the centroid created from the 2 fiducials that followed the GTV's COM the best was not significantly closer than the centroid from all the fiducials. When determining if the centroid will be closest to the GTV's COM the fiducials ability to keep a consistent distance from the GTV's COM seems to not be a determining factor.

While looking at the motion of the GTV's COM over the entire breathing cycle it can be seen that the lateral movement is lowest. Followed by anterior-posterior movement and superior-inferior movement is the highest. A discrepancy similar to that shown in phase 20 of *Figure 3* in the superior-inferior direction is not present in most patients but is indicative that tracking research is needed to increase accuracy. The

patient in the first 4 panels had an upper lung tumor the graphs are similar in shape, except the discrepancy, for lower lung tumor patient too. Both of these patients had their highest dimension of motion in the SI direction.

We found that the centroid that was tracked in the clinic during treatment was significantly further away from the GTV's COM than the centroid that was closest to the GTV's COM. The tracked centroid also did not have the smallest discrepancy in motion compared to the GTV's COM. This shows there is improvement to be made in the field of fiducial marker facilitated tumor tracking. It is important to note that most of the time not all the fiducials implanted in the patient are capable of being tracked during treatment in the clinic. This study did not exclude any fiducials from analysis, so it is possible some of the centroids of interest we generated were not capable of being used during treatment.

The dosimetric effect of changing the centroid from what was tracked in the clinic was estimated by shifting the dose in each phase from the tracked centroid to the centroids of interest. We showed that while the total shift can have a large dosimetric effect. As shown in *Figure 4* and *Table 4* the dosimetric effect of shifting the centroid resulted in worse dose to the GTV. This was shown by the dotted line representing the unshifted dose profile having a steeper curve than the shifted solid line in the DVH. For OAR the shifted dose line is lower, meaning there is less dose, than the unshifted, while that is bad for the GTV it is good for the OAR. It often the case in treatment planning where a change might be better for OAR it creates worse coverage for the GTV. It should be noted that this is an estimation created by shifting the planned dose profile and not an actual dose measurement.

When looking at how often the centroids of interest were the same or how often they were the tracked centroid, we found they weren't often the same. The centroid closest to the GTV's COM was not often selected for tracking. The centroid with the least discrepancy in motion compared to the GTV's COM was tracked less than the closest to the GTV's COM centroid. Further, ideally the centroid closest to the GTV's COM would also be the centroid that had the least discrepancy in motion compared to the GTV's COM but this occurred in only a 3rd of the patients. This means that a choice on which centroid of interest is selected for tumor tracking because they are not often the same. It was promising though to see that the closest fiducials to the GTV's COM created the closest centroid to the GTV's COM usually.

Another unexpected finding was that the centroids of interest and the tracked centroid were rarely created from 3 fiducials. As previously stated, the system needs to track at least 3 different fiducials to have any chance at tracking rotational movement instead of just translational movement. The most common number of fiducials creating the centroids of interest and the tracking centroid was 2 fiducials. This knowledge and knowing that often not all fiducials are trackable in the clinic will help in making our recommendations for number of markers placed and used in the clinic. *Figure 5* visualizes what 2 different centroids look like with the surrounding anatomy.

The upper lung patients having significantly more fiducials placed inferior could be a limitation of the bronchoscopic fiducial marker placement technique. It is also possible that it is a limitation created naturally by the tumor placement. If the tumor is in the upper part of the lung, it is possible that there is not enough lung tissue superior of the lung for a fiducial to be placed there.

Fiducials bracketing of the tumor is a goal of fiducial marker placement. Another usual goal of fiducial marker placement is to place a fiducial inside the GTV. When looking at the location of fiducials placed, lower lung patients had a more equal distribution of fiducial placement. Lower lung patients had no statistical difference in the location of their placement. The upper lung tumor patients had significantly more fiducials placed inferior and distal. This could be caused by the location of the tumor for upper lung patients being more superior and proximal.

However, all of the fiducials are not usually trackable. This means that the type of bracketing present in the centroids being used for tracking depends on which fiducials are selected for tracking as well as where they are placed. We examined the bracketing needs for upper and lower lung patients separately because it was assumed motion of lower lung tumors and upper lung tumors would be different. The directions of bracketing for upper lung tumor patients in the tracked centroid occurred almost equally in every direction. For the types of bracketing in the 2 centroids of interest anterior-posterior bracketing and superior-inferior bracketing were most important, with a slightly higher occurrence of anterior-posterior. This shows that when placing fiducials and when selecting fiducials for upper lung patients anterior-posterior and superior-inferior need to be prioritized over lateral or distal-proximal bracketing.

For the lower lung tumor patients, the distribution of bracketing in the tracked centroid was nearly the same for all directions with 2 out of 7 patients. Except a lack of bracketing occurred in 3 out of 7 patients. Superior-inferior bracketing occurred most in both the centroids of interest. It appeared in all but one of the most consistent distance centroids for the lower lung patients. Therefore superior-inferior bracketing should be

given priority in fiducial marker placement and fiducial marker selection for patients with lower lung tumors.

It was expected that not all the patients would have a fiducial within their tumor target because of the bronchoscopic method of fiducial placement. Bronchoscopic fiducial marker placement is much safer for the patient but limits the possible fiducial marker placement locations. It was surprising that 1 patient had 2 fiducials placed within their tumor target. This was surprising because fiducials need to be at least 2 cm apart from one another to attempt to avoid shadowing errors from occurring. It was expected that the centroid closest to the GTV's COM had the most cases of being within the GTV's contour. However, it was surprising that there were more cases with it outside the GTV's contour than within.

As shown in *Table 12* there are more of our previously defined "bad" tracking fiducials placed anterior and good tracking fiducials placed posteriorly for the lower lung patients. This would suggest that the anterior part of the lung from the GTV's COM should be avoided when placing fiducials for lower lung tumor patients. Our data set included 7 patients with a total of 23 placed fiducials. It is usual that there are fewer lower lung tumor patients than upper lung tumor patients. Our data has 74% upper lung tumor cases and 26% lower lung tumor cases. Previous studies have published 70% upper lung tumors and 30% lower lung tumors and 64% upper lung tumors and 36% lower lung tumors. [27],[28]

This study is not without limitations. Our analysis is based on a planning 4DCT and not actual tumor motion during patient treatment. It is assumed that the tumor and fiducial motion during the planning 4DCT would match motion during treatment. Our

estimate of the dosimetric effect is based on differences in centroid locations for each phase of the breathing cycle being used to shift the dose and not from actual dose measurements using different centroids. Our work also assumes that every fiducial was capable of being tracked which is likely not true.

Conclusions

Now we will draw some conclusions and make some recommendations based on our findings. We would recommend that fiducials be placed 2.7 cm or closer to the GTV's COM. This recommendation comes from the examining the average distance from GTV's COM that the "good" tracking fiducials were and allowing a slightly further distance to allow more options, while not being within 1 standard error of the "bad" tracking fiducial average distance. If the clinic is only using 2 fiducials for tumor tracking, then the 2 fiducials closest to the GTV's COM should be selected to create the centroid closest to the GTV's COM. The 2 fiducials that bracket the GTV in either the anterior-posterior or superior-inferior direction should be selected to try and achieve the centroid that keeps the most consistent distance from the GTV's COM.

The usual motion for the GTV's COM has lateral, distal-proximal or left and right motion the lowest. Thus, tracking the tumor in this direction seems least important. The anterior-posterior movement and the superior-inferior movement are larger and need to be accounted for more so than lateral movement.

The dosimetric effect of shifting the dose profile based on centroid locations showed that small changes in location of the isocenter can create large effects. While our dosimetric effect was generated from estimation of changing existing planned dose profiles it shows how important accuracy is for the dose profile. There was a decrease in dose coverage for the GTV because of the shifts.

The tracked centroid was statistically further away from the GTV's COM than the closest centroid and had statistically more discrepancy in motion compared to the most

consistent centroid. These centroids were found assuming all of the placed fiducials could be tracked. Ideally, we could make one fiducial marker selection recommendation that would work for both centroids of interest and all patients, but we showed that the 2 centroids of interest are rarely the same. We would recommend that the clinic select 2 fiducials to be used for tracking as this was the most commonly seen number used to create both of our centroids of interest. When it comes to our fiducial placement and bracketing recommendations, we need to make separate recommendations for upper and lower tumor patients. For upper lung tumor patients fiducial marker placement and selection should be given priority for anterior-posterior bracketing. If possible, superior-inferior bracketing should also be achieved in fiducial marker placement. For lower lung tumor patients the emphasis for fiducial marker placement and selection should be in the superior-inferior direction.

It should be expected that with bronchoscopic fiducial marker placement that not all patients will have fiducial placed within the GTV. About half of the patients from our data set 48.2% or 13/27 had at least 1 fiducial placed within their tumor target. The centroid closest to the GTV's COM was only within the tumor target in approximately three-tenths of the data, 8 out of 27 (29.6%). This could imply that the benefits of choosing the closest to the GTV's COM centroid might not be great enough to justify choosing it over the most consistent distance centroid. We will make recommendations for selection of fiducials for both centroids and each clinic can decide which centroid fits their needs.

To summarize fiducials should be placed within 2.7 cm of the GTV's COM. There should be 3 to 4 fiducials placed to allow for not all of the fiducials being trackable and

to generate the desired tumor bracketing. The upper lung tumor patients should have anterior-posterior bracketing prioritized for both fiducial marker placement and selection. If two types of bracketing can be achieved or anterior-posterior bracketing is not possible than superior-inferior bracketing has 2nd priority for upper lung tumor patients. Lower lung tumor patients should have superior-inferior bracketing prioritized for fiducial marker placement and selection. The clinic needs to decide which of our centroids of interest they wish to track. The centroid closest to the GTV's COM should have the 2 closest fiducials selected for tracking and the centroid that kept the most consistent distance from the GTV's COM should have the bracketing we recommended earlier selected for tracking.

Future Direction of Work

There were a few questions that arose from our work that could be researched in the future. Where we shifted the dose profile it would be interesting to see the dosimetric effect of changing the selection of which fiducials will be used for tracking during treatment planning. This would be another way to estimate the dosimetric effect of changing the fiducial centroid that is tracked. Another possible research project would be building a respiratory modeling device and measuring dose with different centroids being used for tumor tracking.

A logical future project would be doing a prospective IRB where our work is used to help recommend fiducial placements and selection for tracking, since all the work completed on this project was for a retrospective IRB. This could be done on a select group of patients with their dose and treatment outcomes being compared with a standard group of patients. Another potential prospective IRB that could be completed is using a prospective 4DCT scan to look for potential fiducial placement locations. This scan could be analyzed to see what areas of the lung had motion that matched the tumor's motion. It could then be used to give patient specific recommendations for fiducial placement locations. It would also be possible that this data could be input into an artificial intelligence machine learning program. This would allow a 4DCT to be input into the program and it could identify possible fiducial placement locations. This artificial intelligence program would need to assume that lung motion was similar for different people that have lung tumors in similar areas though.

It would also be interesting to see all of this work repeated with a different type of tracking marker being used, such as the previously described calypso marker. It is theorized that the type of marker should not make a difference in the work but would be interesting to see.

Another possible future project would be to repeat the experiments with only lower lung tumor patients. This would most likely need to be a pooled analysis from multiple clinics because there are far fewer lower lung tumor patients than upper lung tumor patients. The pooled analysis would be required to gather enough patients for analysis to be completed in a reasonable time frame.

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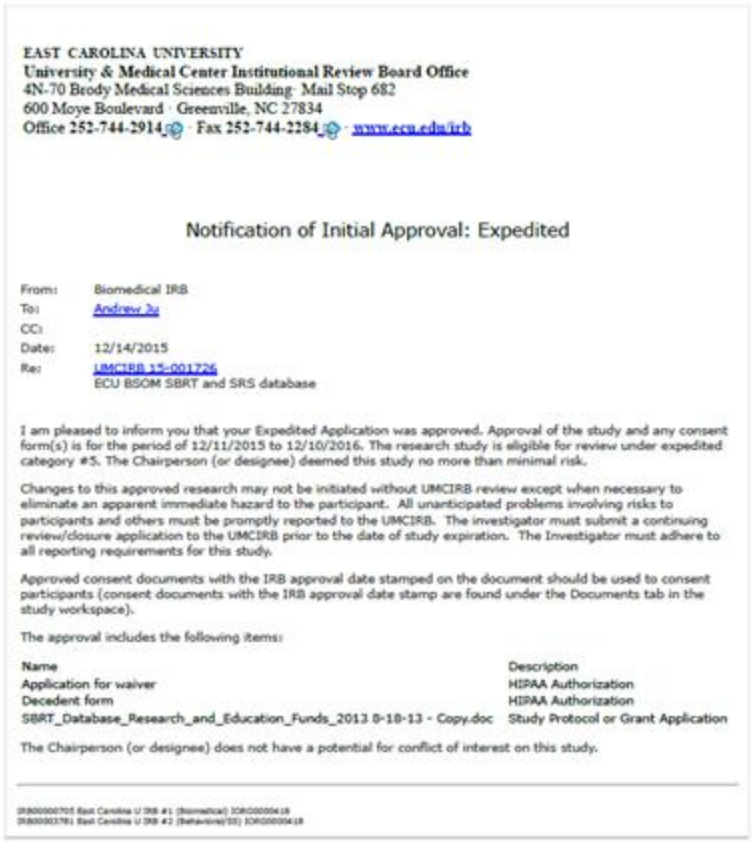
Appendix A

This research involved data gathered from human cancer treatments. The study was conducted retrospectively, meaning no human was used as a subject. Data gathered from normal treatment procedures were used in the study. The study was titled ECU BSOM SBRT and SRS database with Study ID: UMCIRB 15-001726. Dr. Andrew W. Ju is the principal investigator. The description of the study is as follows, “We will establish a quality improvement database to record the clinical and quality of life outcomes of patients treated with SRS or SBRT or various malignancies, including but not limited to CNS, lung, prostrate, liver, and head and neck malignancies. We will analyze the information in this database to find factors affecting clinical outcomes that may be used to guide treatment decisions within our clinic for future patients with these malignancies.”



EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board Office
4N-70 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office 252-744-2914 · Fax 252-744-2284 · www.ecu.edu/irb

Notification of Initial Approval: Expedited

From: Biomedical IRB
To: Andrew Ju
CC:
Date: 12/14/2015
Re: UMCIRB 15-001726
ECU BSOM SBRT and SRS database

I am pleased to inform you that your Expedited Application was approved. Approval of the study and any consent form(s) is for the period of 12/11/2015 to 12/10/2016. The research study is eligible for review under expedited category #5. The Chairperson (or designee) deemed this study no more than minimal risk.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The Investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Name	Description
Application for waiver	HIPAA Authorization
Decedent form	HIPAA Authorization
SBRT_Database_Research_and_Education_Funds_2013 8-18-13 - Copy.doc	Study Protocol or Grant Application

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

IRB00000705 East Carolina U IRB #1 (Biomedical) IORG0000418
IRB00003781 East Carolina U IRB #2 (Behavioral/SS) IORG0000418

Appendix A Figure 1: Letter of Initial Approval for the IRB

Appendix B

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** ·
www.ecu.edu/ORIC/irb

Notification of Amendment Approval

From: Biomedical IRB
To: Andrew Ju
CC:

Suzanne Kelly
Date: 7/6/2018
Re: Ame9_UMCIRB 15-001726
UMCIRB 15-001726
ECU BSOM SBRT and SRS database

Your Amendment has been reviewed and approved using expedited review for the period of 7/5/2018 to 10/23/2018. It was the determination of the UMCIRB Chairperson (or designee) that this revision does not impact the overall risk/benefit ratio of the study and is appropriate for the population and procedures proposed.

Please note that any further changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. A continuing or final review must be submitted to the UMCIRB prior to the date of study expiration.The investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Document	Description
Adding study staff member Wesley Belcher to the study	

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

IRB00000705 East Carolina U IRB #1 (Biomedical) IORG0000418
IRB00003781 East Carolina U IRB #2 (Behavioral/SS) IORG0000418

Appendix B Figure 1: Letter of Approval for Amendment to IRB that added me to the study

Appendix C

In this appendix we will show some of the raw data. In *Appendix C Table 1* the location of a GTV is shown in all phases of the breathing cycle. In the following *Appendix C Tables 2-5* the location of each implanted fiducial will be shown. This is done to show what some of the raw data looks like for a single patient.

Phase	X	Y	Z
0	-3.454	-1.332	-11.418
10	-3.514	-1.450	-11.289
20	-3.530	-1.502	-11.286
30	-3.445	-1.326	-11.470
40	-3.451	-1.331	-11.461
50	-3.448	-1.352	-11.433
60	-3.454	-1.427	-11.380
70	-3.531	-1.500	-11.268
80	-3.521	-1.487	-11.246
90	-3.513	-1.484	-11.262

Appendix C Table 1: GTV Location for a patient

Phase	X	Y	Z
0	-6.953	-0.543	-13.469
10	-6.897	-0.520	-13.544
20	-6.856	-0.456	-13.548
30	-6.860	-0.435	-13.542
40	-6.875	-0.428	-13.530
50	-6.919	-0.514	-13.466
60	-6.960	-0.560	-13.456
70	-7.011	-0.584	-13.343
80	-6.935	-0.588	-13.425
90	-6.926	-0.488	-13.441

Appendix C Table 2: Fiducial 1 Location for a patient

Phase	X	Y	Z
0	-7.454	-1.787	-12.518
10	-7.415	-1.764	-12.548
20	-7.344	-1.6370	-12.738
30	-7.332	-1.631	-12.775
40	-7.338	-1.673	-12.795
50	-7.423	-1.708	-12.725
60	-7.484	-1.836	-12.518
70	-7.481	-1.866	-12.425
80	-7.426	-1.824	-12.485
90	-7.399	-1.727	-12.562

Appendix C Table 3: Fiducial 2 Location for a patient

Phase	X	Y	Z
0	-6.011	-0.525	-11.009
10	-6.074	-0.476	-10.930
20	-6.106	-0.627	-10.795
30	-6.021	-0.431	-11.057
40	-5.954	-0.464	-11.049
50	-5.971	-0.450	-11.054
60	-6.067	-0.611	-11.070
70	-6.108	-0.646	-10.800
80	-6.063	-0.607	-10.795
90	-5.893	-0.461	-10.918

Appendix C Table 4: Fiducial 3 Location for a patient

Phase	X	Y	Z
0	-8.768	-2.156	-10.929
10	-8.835	-2.295	-10.788
20	-8.849	-2.355	-10.783
30	-8.808	-2.010	-11.036
40	-8.782	-2.047	-11.054
50	-8.782	-2.081	-11.046
60	-8.837	-2.191	-10.934
70	-8.864	-2.351	-10.816
80	-8.852	-2.359	-10.773
90	-8.799	-2.272	-10.798

Appendix C Table 5: Fiducial 4 Location for a patient

The distance between each fiducial and the GTV was found for each phase of the breathing cycle and then the average distance and the difference between their maximum and minimum distance. These can be seen in *Appendix C Table 6*. Fiducial 3 was the closest to the GTV's COM. Fiducial 1 was second furthest away from the GTV's COM but kept the distance the most consistent.

Phase	GTV & Fid 1	GTV & Fid 2	GTV & Fid 3	GTV & Fid 4
0	4.132	4.174	2.713	5.401
10	4.171	4.112	2.762	5.411
20	4.157	4.084	2.765	5.411
30	4.092	4.112	2.578	5.424
40	4.102	4.125	2.682	5.395
50	4.109	4.194	2.706	5.397
60	4.165	4.207	2.755	5.455
70	4.154	4.132	2.755	5.419
80	4.148	4.111	2.723	5.422
90	4.170	4.105	2.613	5.364
Average	4.140	4.135	2.724	5.410
Max-Min	0.079	0.123	0.151	0.090

Appendix C Table 6: Distance Statistics for Each Fiducial from the GTV

Every possible combination of fiducials was used to find every possible centroid. The centroids of interest can be seen in *Appendix C Table 7*. For this particular patient, the tracked centroid was also the centroid that kept the most consistent distance from the GTV's COM. The closest centroid to the GTV's COM is closer on average than the tracked and most consistent centroid by approximately 0.80 cm. The tracked and most consistent centroid has more consistency in maximum minus minimum by approximately 0.03 cm and in standard deviation by 0.008 cm.

Phase	Tracked & Most Consistent Distance Centroid	Centroid Closest to the GTV's COM
0	4.071	3.237
10	4.056	3.261
20	4.033	3.228
30	4.042	3.234
40	4.084	3.203
50	4.084	3.228
60	4.102	3.293
70	4.061	3.256
80	4.048	3.225
90	4.060	3.202
Average	4.061	3.237
Max-Min	0.069	0.092
Std Dev	0.020	0.028

Appendix C Table 7: Distance Statistics for the Centroids of Interest from the GTV

The two centroids of interest both bracketed the GTV's COM. The tracked centroid and centroid that kept the most consistent distance from the GTV's COM bracketed the GTV's COM in the anterior-posterior direction. The centroid that was closest to the GTV's COM bracketed the GTV's COM in the superior-inferior direction. This patient had an upper lung tumor with the tumor's largest dimension of motion

occurring in the superior-inferior direction, matching the bracketing present in the centroid that was closest to the GTV's COM.

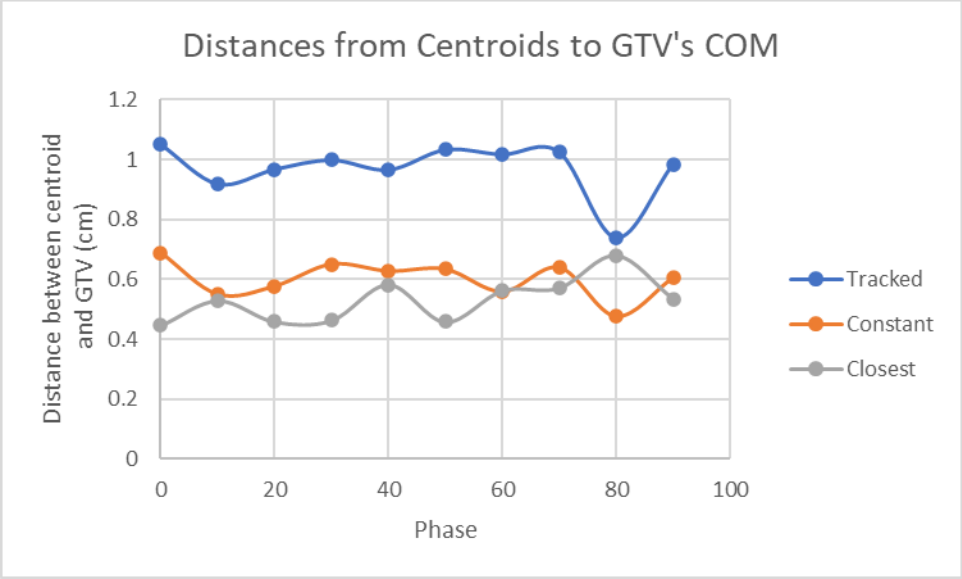
Appendix D

The amounts shifted, the motion of the centroids compared to the GTV's COM in all phases and dose differences between the unshifted and shifted dose profiles are shown for additional patients that had both of their shifts be less than 1 cm on average. This occurred in a total of 5 patients. One of the patients already had their amount shifted and dose differences shown in the main text. In *Appendix D Table 1* the amount shifted for each of these patients on average is shown.

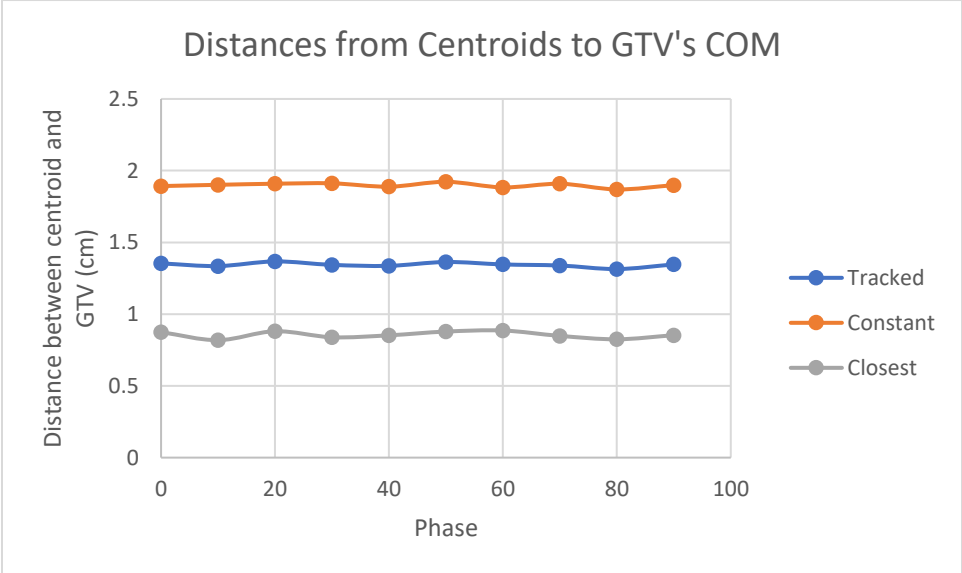
Patient	Shift From Tracked	X (mm)	Y (mm)	Z (mm)	Total (mm)
1	Closest	0.6	4.2	4.1	5.9
	Smallest	2.9	1.0	2.9	4.2
2	Closest	0.4	3.7	4.3	5.7
	Smallest	0.4	4.2	4.3	6.0
3	Closest	0.2	3.1	3.4	4.6
	Smallest	0.2	3.1	3.4	4.6
4	Closest	3.2	1.8	0.6	6.5
	Smallest	6.2	1.8	0.6	6.5
5	Closest	1.8	3.8	0.9	4.3
	Smallest	5.0	3.7	1.1	6.3

Appendix D Table 1: Centroid Shift Distances

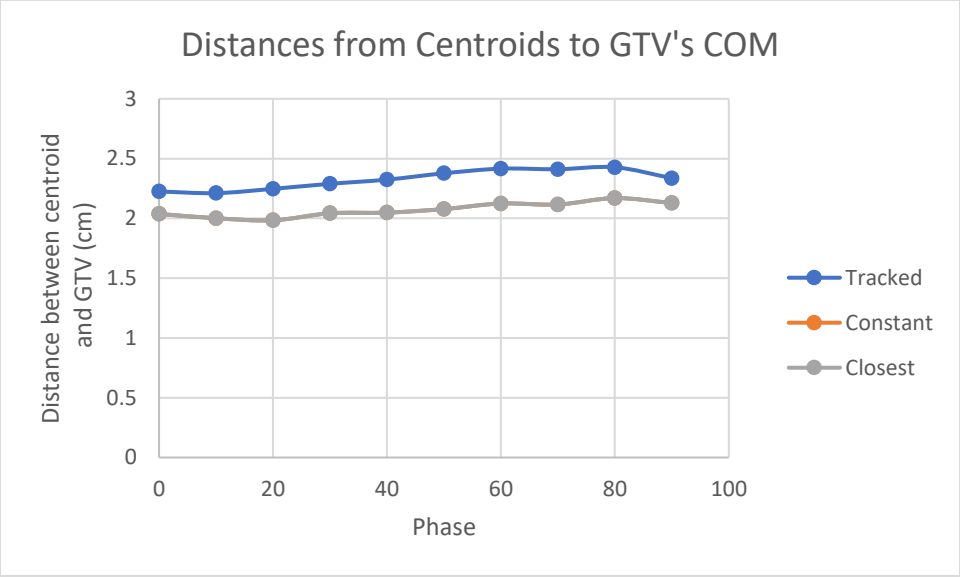
In *Appendix D Figure 1-5* we will show the motion of the centroids compared to the GTV's motion for each phase of the breathing cycle.



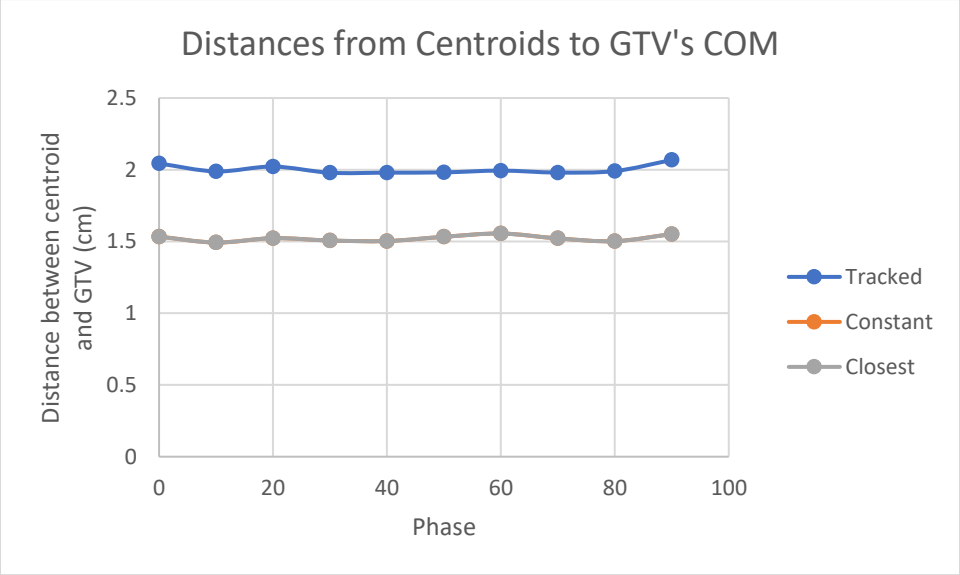
Appendix D Figure 1: The distance between the centroids and the GTV in each phase of the breathing cycle for patient A



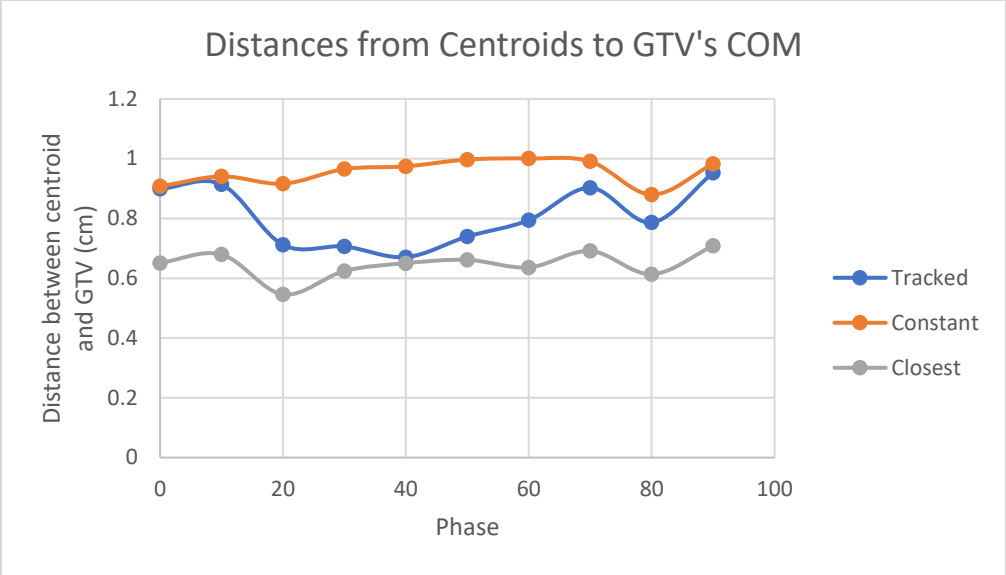
Appendix D Figure 2: The distance between the centroids and the GTV in each phase of the breathing cycle for patient B



Appendix D Figure 3: The distance between the centroids and the GTV in each phase of the breathing cycle for patient C



Appendix D Figure 4: The distance between the centroids and the GTV in each phase of the breathing cycle for patient D



Appendix D Figure 5: The distance between the centroids and the GTV in each phase of the breathing cycle for patient E

In *Appendix D Figure 1* the constant centroid is closer than the closest centroid for 1 phase. In phase 80 you can see that the constant centroid is closer than the closest centroid however, the closest centroid is closer on average. In *Appendix D Figure 3 and 4* there are only 2 lines present on the graph because the centroid closest to the GTV's COM is also the centroid that followed it the most consistently.

In *Appendix D Table 2(A-E)* the differences in dose are shown for patients A-E. A negative value in this table means the dose increased after the shift. The GTV dose coverage drops for these patients and depending on the patient the dose sparing to the ribs or other OAR could be better or worse.

Different Dose Metrics	Difference in dose between original and shift to the closest centroid	Difference in dose between original and shift to the most consistent centroid
GTV Mean	1.79	0.77
GTV Max	0.8	0.6
GTV Min	15.8	6.6
GTV 95% Volume	7	3
Ribs Mean	-0.39	-0.05
Ribs Max	-1	0.2
OAR #2 Mean	0.14	-0.06
OAR #2 Max	0.2	0.4
OAR #3 Mean	0.06	0.12
OAR #3 Max	0.8	1.4

Appendix D Table 2A: Summary of Dose Profiles for Patient A in Gy

Different Dose Metrics	Difference in dose between original and shift to the closest centroid	Difference in dose between original and shift to the most consistent centroid
GTV Mean	3.24	3.98
GTV Max	1	0.4
GTV Min	11.8	13.4
GTV 95% Volume	9	11
Ribs Mean	0.44	0.35
Ribs Max	1.2	1.8
OAR #2 Mean	0.05	0.24
OAR #2 Max	3	3.6
OAR #3 Mean	0.19	0.34
OAR #3 Max	1.8	2.2

Appendix D Table 2B: Summary of Dose Profiles for Patient B in Gy

Different Dose Metrics	Difference in dose between original and shift to the closest centroid	Difference in dose between original and shift to the most consistent centroid
GTV Mean	3.98	3.98
GTV Max	1.2	1.2
GTV Min	18.2	18.2
GTV 95% Volume	13	13
Ribs Mean	0.31	0.31
Ribs Max	7.5	7.5

Appendix D Table 2C: Summary of Dose Profiles for Patient C in Gy

Different Dose Metrics	Difference in dose between original and shift to the closest centroid	Difference in dose between original and shift to the most consistent centroid
GTV Mean	7.81	7.81
GTV Max	0.2	0.2
GTV Min	20.4	20.4
GTV 95% Volume	21	21
Ribs Mean	1.35	1.35
Ribs Max	4.6	4.6

Appendix D Table 2D: Summary of Dose Profiles for Patient D in Gy

Different Dose Metrics	Difference in dose between original and shift to the closest centroid	Difference in dose between original and shift to the most consistent centroid
GTV Mean	0.54	1.1
GTV Max	0.4	0.6
GTV Min	8.2	16
GTV 95% Volume	1	3
Ribs Mean	-0.15	0.2
Ribs Max	-1	-0.6
OAR #2 Mean	0.18	0.08
OAR #2 Max	6	5
OAR #3 Mean	0.22	0.25
OAR #3 Max	0.2	0.2

Appendix D Table 2E: Summary of Dose Profiles for Patient E in Gy