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THE EFFECTS OF RESPIRATORY MOTION ON THE IGRT PROCESS IN ESOPHAGEAL RADIOTHERAPY

BY

ASHLEY CLEMENT

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THE EFFECTS OF RESPIRATORY MOTION ON THE IGRT PROCESS IN ESOPHAGEAL RADIOTHERAPY

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Dedication

I’d like to dedicate this work to my supportive family, my mom, dad, sister and my loving partner, Caleb. Taking on a Master’s thesis during Covid-19 has been a valuable learning experience; one that has focused on the importance of adaptability, determination, thinking outside the box and the hardest of all, taking a break. I am so thankful to you all for supporting me and challenging me to find creative ways to make the most of this degree under these difficult circumstances. Your support and encouragement have been a much-needed lifeline over the past year.

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Abstract

Radiotherapy treatment for esophageal cancer requires a daily cone-beam CT (CBCT) scan to ensure target accuracy for treatment. Respiratory motion is known to cause movement of the diaphragm, leading to challenges during image guidance radiation therapy (IGRT). This study quantified the displacement of the diaphragm during daily treatment to reference target displacement, as well as time taken to perform IGRT. Other IGRT factors were assessed. Results show a mean displacement of -0.9 (SD -0.6) cm in the y plane with no significant displacement in x or z. There was no correlation between displacement and IGRT duration, however males were associated with larger displacement in x ($p=0.019$), and non-smokers were associated with larger displacements in y and z ($p<0.001$). Future studies investigating respiratory motion reduction strategies are needed to identify the best approach moving forward.

Keywords: Esophageal cancer, Respiratory motion, Deep inspiration breath hold (DIBH), Image guided radiation therapy (IGRT)

Preface

Due to the difference in breathing patterns between the planning CT scan and the daily CBCT during subsequent radiation treatment for esophageal radiation, there are often challenges during the IGRT process due to the displacement of the diaphragm. This creates image artifacts and reduces target accuracy for treatment. The Thoracic Radiation Oncology group supported the initiation of this study to quantify the displacement of the diaphragm as well as time taken to perform the daily IGRT assessment and to record the IGRT steps that are taken to manage this each day. This study will be the basis for reference in future studies that aim to improve the image quality, accuracy of treatment and IGRT process with reduced respiratory motion in esophageal radiotherapy.

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List of Symbols, Nomenclature, or Abbreviations

IGRT – image guidance radiation therapy

CT – computed tomography

CBCT – cone-beam computed tomography

4DCT – 4-dimensional computed tomography

4DCBCT – 4-dimensional cone-beam computed tomography

DIBH – deep inspiration breath hold

RO – Radiation Oncologist

ITV – internal target volume

CTV – clinical target volume

PTV – planning target volume

Gy – gray

MLD – mean lung dose

MHD – mean heart dose

GEE – generalized estimating equations

UVA – univariate analysis

Chapter 1. Introduction

Esophageal cancer is the seventh most common cancer diagnosis worldwide for men and 13th for women (World Cancer Research Fund, 2018). In 2019, it is expected 1700 men and 500 women will be diagnosed with esophageal cancer in Canada (Canadian Cancer Society, 2019a). Though the prevalence is lower than other cancers, it has one of the fastest rising incidence rates, projected to increase by 40% for men and 50% for women by 2026, and the lowest overall survival rates worldwide (Otterstatter et al., 2012). Five-year survival for both localized and regional esophageal cancer is 43% and 23%, respectively (Canadian Cancer Society, 2019c).

Many patients with esophageal cancer undergo intensive tri-modality treatment including chemotherapy with radiation followed by surgery in the curative setting which impacts both healthy tissues and cancer cells and can have a significant impact on patients' quality of life (Lv et al., 2014). Moreover, patients are required to make multiple visits to the cancer centre for all three treatment modalities and subsequent follow up appointments. Patients undergo radiation treatment as part of the standard of care for a curative approach to esophageal cancer (Canadian Cancer Society, 2019b). Advances in technology for radiation treatment have allowed radiation therapists to perform daily image guidance radiation therapy (IGRT) to improve localization of the treatment area and correct for set-up discrepancies and internal anatomical motion (Goyal & Kataria, 2014). However, despite the improved understanding of respiratory-related tumour motion and the enhancements of IGRT, respiratory motion continues to be a challenging aspect to overcome with IGRT (Goyal & Kataria, 2014). Respiratory motion throughout both the imaging and treatment components of esophageal radiotherapy causes movement of internal structures, including the esophagus (Yoshiko, et al., 2018). As a result, esophageal target volumes are often increased in order to account for this motion during treatment. Increasing these treatment volumes results in greater radiation exposure for healthy tissues and thus, increasing possible side effects (Ghani & Ng, 2018).

Definition of Terms

Deep-Inspiration Breath Hold (DIBH)

A DIBH is a radiation therapy technique where patients take a moderate-deep breath in and hold the breath during radiation delivery (Peter MacCallum Cancer Centre, n.d.).

Active Breathing Coordinator (ABC)

The ABC is an established, non-invasive medical device that was specifically created to reduce respiratory motion during radiotherapy treatment (Swedish Medical Centre, 2019). It includes a mouthpiece, nosepiece, and alert button to help patients perform a DIBH during treatment.

Gray (Gy)

The unit of radiation dose expressed as absorbed energy per unit of mass of tissue (Radiation Emergency Medical Management, 2020).

Organs at Risk (OAR)

OARs are critical anatomical structures that are in close proximity to the tumour, whose radiation dose must be monitored and meet standard tolerance dose criteria (Grosu, Sprague and Molls, n.d.).

Dosimetry

The measurement or calculation used to monitor the dose of radiation for tissues in the body (SNMMI, n.d.). These measurements are completed during the radiation treatment planning process to ensure the appropriate amount of radiation dose is delivered to the target and only a safe amount of radiation is delivered to OARs.

Lung V20

The lung V20 is the percentage of normal lung receiving at least 20 Gy and is dependent on the total lung volume (Bergsma et al., 2014).

Lung V5

The lung V5 is the percentage of normal lung receiving at least 5 Gy and is dependent on total lung volume (Bergsma et al., 2014).

Heart V40

The heart V40 is the percentage of normal heart tissue receiving at least 40 Gy and is dependent on the total heart volume.

Chapter 2. Review of the Literature

Introduction

Organs at Risk (OAR) Toxicity

The impact of radiation doses to surrounding normal tissues, known as OARs, has been studied and resulted in knowing the specific tolerance levels for each individual organ in the body (Bentzen et al., 2010). The heart, lungs and spinal canal are important organs to monitor (in addition to many others) in esophageal radiotherapy due to their proximity to the esophagus and the potential acute and chronic side effects of radiation.

Cardiac toxicity has been widely identified as an independent predictor of survival in radiotherapy for lung cancer, breast cancer and lymphoma, however there is limited data on the impact on survival for esophageal patients undergoing chemoradiation (Oh et al., 2018). Oh et al., (2018) studied the effects of both cardiac and lung toxicity on esophageal patients who underwent chemoradiation. It was also determined that lung dose in esophageal radiotherapy was a significant independent predictor of survival, while cardiac dose was not. Specifically, univariate analysis showed that lung V20, lung V5, and mean lung dose (MLD) in combination with increased age, lower performance status, stage III disease, lack of surgery, and heart V40 showed significant associations with decreased survival (Oh et al., 2018). Due to shorter survival rates, long term cardiac assessment in esophageal patients is limited, and cancer mortality is expected to outweigh the risk of cardiac toxicity (Oh et al., 2018).

Respiratory-Induced Esophageal Motion

In a study by Zhao et al., (2007), respiratory-induced motion for esophageal tumours near the gastro-esophageal junction (GEJ) was measured for 25 patients using four-dimensional (4D) CT. The movement of the Gross Tumour Volume (GTV) across the different respiratory phases was measured, as well as the internal target volume (ITV) and boundaries. The mean +/- standard deviation of the peak to peak movement of the GTV was 0.39 +/- 0.27cm in the right-left direction; 0.38 +/- 0.23cm in the anterior-posterior direction; and 0.87+/- 0.47cm in the superior-inferior direction showing movement of the tumours near the gastro-esophageal junction (Zhao et al., 2007). The ITV was 75% larger than the CTV defined on the single respiratory phase with variations in tumour boundaries (Zhao et al., 2007). It was noted that target movement due to respiration resulted in larger boundary changes in the left, anterior and superior direction suggesting that asymmetric margins may be useful in these circumstances (Zhao et al., 2007).

Yashamita et al. (2010) quantified patient setup error and daily esophageal motion error in 20 patients undergoing radiotherapy for esophageal cancer. Daily radiation treatment was delivered in a free-breathing state. Male and female participants ranged in age from 53 to 90 years with diagnoses from stage I through IVB; however, tumour location was not identified (Yashamita et al., 2009). Setup error was measured after completing an auto bone match of the vertebral bodies on the cone-beam computed tomography (CBCT) software. The absolute mean and standard deviation (SD) of setup errors were 2 +/- 2mm (maximum 8mm) left/right, 4 +/- 3mm (maximum 11mm) superior/inferior and 4 +/- 3mm (maximum 13mm) anterior/posterior (Yashamita et al, 2009).

A contour of the outer wall of the esophagus was drawn on the data sets with a mediastinal window levelling setting and was compared between the primary computed tomography (CT) scan and the (CBCT). The mean + SD of the daily esophageal motion was 5 +/- 3mm (maximum 15mm) both laterally and vertically (Yashamita et al., 2010). These results were comparable to a study by Yoshiko et al. (2018) who also identified esophageal motion in the free breathing state but noted reduced motion when in a breath hold. These researchers attributed esophageal movement during radiation treatment to respiratory-related motion, cardiac-related motion and peristalsis-related motion (Yoshiko et al., 2018). This study used a breath hold state to account for respiratory-related motion and measured the impact on esophageal movement during radiotherapy treatment. Fiducial markers were implanted into the esophagus of 16 participants (with a total of 19 tumours evaluated) to compare the esophageal movement in free-breathing and breath hold. A 4DCT was used to measure the movement of the fiducial markers in free-breathing through the 0% - 90% breathing phases. Breath hold movement was measured using kilo-voltage (kV) bone matches and CBCT auto bone matches and compared to the planning scan (Yoshiko et al., 2018).

Participants ranged in age from 59-82 years and had early stage (T1-T2b) squamous cell carcinoma of the esophagus. Tumour locations studied included upper thoracic (UT) (n=6), middle thoracic (MT) (n=7) and lower thoracic (LT) (n=6) (Yoshiko et al. 2018). In the free breathing state, the median absolute maximum amplitude (mm) was the largest longitudinally for all tumour locations; UT (3.6), MT (4.8) and LT (8.0) and had the largest reduction in the breath hold state to UT (3.3), MT (3.4) and LT (3.5). Lateral and vertical movements were also improved using breath hold for UT and MT tumours. However, a slight increase in lateral and vertical movement was noted during breath hold for LT tumours despite having the most significant decrease in longitudinal movement (Yoshiko et al., 2018).

These studies indicate that esophageal motion is significantly impacted by respiratory motion (Yashamita et al, 2010; Yoshiko et al, 2018; Zhao et al., 2007). Therefore, incorporating strategies to properly manage or reduce respiratory motion during esophageal radiation is expected to improve image quality and target accuracy, and reduce esophageal motion.

Management of Respiratory Motion

4DCT

One of the most common techniques used in lung radiotherapy to account for respiratory motion is the 4DCT because it can be used to identify tumour movement throughout the different breathing phases while reducing image artifacts and improving the quality of the image (Ghani & Ng, 2018). The 4DCT can allow for Internal Target Volume (ITV) margins that are created to reflect the movement of the tumour across all breathing phases. A Planning Target Volume (PTV) margin is then created by expanding the ITV by 5mm based on our institutional policy to account for additional set up errors. This process, while accounting for tumour motion during respiration and improving accuracy of treatment, can create larger treatment volumes, exposing a greater amount of healthy tissue to radiation (Ghani & Ng, 2018). However, a 4DCT from CT simulation is not necessarily representative of the patient's breathing pattern throughout the course of their radiotherapy treatment (Ghani & Ng, 2018). To account for this, a 4-dimensional cone-beam computed tomography (4DCBCT) can be used for daily treatment verification. This process allows for the evaluation of tumour motion for each daily treatment, reduced motion artifacts (therefore improved image quality), excellent soft tissue contrast and is feasible for lung Stereotactic Body Radiation Therapy (SBRT) and adaptive planning (Ghani & Ng, 2018). The disadvantages of this approach are the significantly longer acquisition time and reduced image quality in comparison with the CT Simulation (Ghani & Ng, 2018). While 4DCT can improve image quality, the creation of the ITV margin can increase radiation exposure to surrounding OARs and lead to worsening side effects (Ghani & Ng, 2018).

Respiratory Gating

Another technique to manage respiratory motion is respiratory gating. This technique uses a device that monitors the patient's breathing cycle and is connected to the treatment machine. By monitoring the breathing cycle, the treatment machine is then programmed to only be able to deliver radiation when the patient is within a specific respiratory phase that is determined during the treatment planning process (Ghani & Ng, 2018). Typically, this allows for reduced PTV margins and therefore reduced radiation exposure to OARs. However, the target respiratory phase can be different for different patients, and different target respiratory phases can lead to varying degrees of OAR exposure (Ghani & Ng, 2018). In theory, this technique is ideal to ensure target accuracy and reduce margins by only delivering treatment when the patient is within the most appropriate breathing cycle; but it relies heavily on consistent, regular breathing, so the accuracy of the technique for patients with irregular breathing patterns is limited (Ghani & Ng, 2018). Another disadvantage of this technique is that it requires significantly more time for treatment delivery, leading to longer time for patients on the bed and longer appointment times on the treatment machines (Ghani & Ng, 2018). While this technique offers an opportunity to manage respiratory motion during radiotherapy and reduce PTV margins, there are also strategies to reduce or eliminate respiratory motion altogether.

Reducing Respiratory Motion

Deep Inspiration Breath Hold (DIBH)

Using a DIBH for radiotherapy treatment can result in stationary targets (Ghani & Ng, 2018). By reducing or eliminating respiratory motion during radiotherapy, image quality is improved resulting in increased treatment accuracy and decreased PTV margins (Ghani & Ng, 2018). Because of this, DIBH has been studied in a variety of cancers to reduce PTV margins, reduce OAR exposure and therefore improve short- and long-term side effects (Ghani & Ng, 2018).

Breast Cancer. Dosimetric improvements with respiratory management were initially noted and put into practice for breast cancer patients and lymphoma patients receiving radiation therapy. One study for left-sided breast cancer with a moderate Deep Inspiration Breath Hold (mDIBH) using the Active Breathing Coordinator (ABC) showed a significant 20% reduction in mean heart dose (MHD) for 88% of patients (n=81) and a statistically significant reduction in left lung dose (Eldredge-Hindy et al., 2015). Only patients with a breath hold of 20 seconds or greater were included in the study, and patients with MHD reduction of 5% or greater underwent their full course of radiation with the ABC. Procedural success was also measured and defined as the proportion of patients who could perform the mDIBH with a resulting dosimetric benefit (Eldredge-Hindy et al, 2015). Researchers identified that the increased exposure to ionizing radiation for two CT scans was justified due to the anticipated benefit to OARs with the study participation (Eldredge-Hindy et al., 2015). Overall, patients tolerated the ABC treatment well with a 72% procedural success rate.

A study by Comsa et al. (2013) confirmed the use of a moderate DIBH and ABC in left-sided breast cancer had a positive impact on OARs and a minimal increase in treatment delivery time. The study noted statistically significant differences between heart dose and lung dose between FB scans and moderate DIBH scans and five-to-ten minute increases in treatment time, depending on the technique (Comsa et al., 2013). The implementation process did not impact the ability to meet provincial guidelines and has led to moderate DIBH with ABC becoming the standard of care for left-sided breast cancer in this regional cancer centre (Comsa et al., 2013).

Lymphoma. Charpentier et al. (2014) studied the use of the ABC to perform a mDIBH for Hodgkin's lymphoma and Non-Hodgkin's lymphoma and compared the doses in free breathing (FB) and mDIBH. It was found that a mDIBH significantly improved mean lung dose (MLD) (FB: 11.0 Gy; mDIBH: 9.5Gy; $P<0.0001$), V20 (FB: 28%; mDIBH: 22%; $p<0.0001$), and MHD (FB:14.3Gy; mDIBH 11.8Gy; $p=0.003$), while noting an increase in mean breast dose (FB:3.0Gy; mDIBH: 3.6Gy; $p=0.0005$). Patients were treated to a total dose ranging from 20Gy to 36Gy. The magnitude of the inhalation for mDIBH was associated with dosimetric benefit for heart and lung doses (Charpentier et al., 2014). These dosimetric benefits have also been studied and identified in esophageal cancer.

Esophageal Cancer. A study by Dieters et al. (n.d.) identified the difference in dose to surrounding OARs, specifically the heart and lungs between free-breathing and breath hold for esophageal radiotherapy. The standard clinical plan was compared to three study protocols: 4D FB, deep inspiration breath hold (DIBH) and exhale breath hold (EBH). The standard clinical plan involved a free breathing scan for patients and a partial Volumetric Modulated Arc Therapy (VMAT) beam in combination with intensity modulated radiation therapy (IMRT) as a treatment plan. The FB, DIBH and EBH scans were all used to create full VMAT treatment plans. The MHD was reduced from 22 Gy in the clinical plan to 19.2 Gy (VMAT FB), 17 Gy (EBH) and 13.8 Gy (DIBH), where $p=0.02$. In addition, V30 heart was lowered to 21.8% (VMAT FB), 15.4% (EBH) and 10% (DIBH) when compared to the clinical plan at 29.5% ($p<0.01$) (Dieters et al., n.d.). The use of a full VMAT technique, an increase in lung volume to spare the heart, and the lack of an Internal Target Volume (ITV) margin due to stabilized breathing all contributed to reducing heart toxicity with the DIBH plan (Dieters et al., n.d.). Overall, the DIBH scan had the largest impact on heart dose reduction ($p=0.02$) and heart volume reduction ($p<0.01$). However, the reduction in heart toxicity in the FB plan shows that changing to a full VMAT technique alone has a positive impact, despite being less effective than the combination of VMAT and DIBH. LMD and V20 lung were slightly reduced in both the EBH and DIBH plans but with a non-statistically significant result (Dieters et al., n.d.). Both the EBH and DIBH plans did show a statistically significant increase in overall lung volume ($p<0.01$) which is noted as a contributing factor to reducing the heart dose. The FB scan had similar results to the clinical plan for LMD and V20.

Yin, Liu and Zhai (2012) performed a similar study by comparing heart and lung doses during esophageal radiotherapy between a FB IMRT plan, FB VMAT plan and the DIBH VMAT plan. Ten participants underwent two CT scans, one in FB and one in

DIBH using ABC. The FB planning target volume (PTV) was 0.5cm larger than the PTV for DIBH and overall heart volume was larger in the FB plan ($p<0.05$) (Yin et al., 2012). DIBH showed an increase in lung volume and a corresponding reduction in MHD compared to FB (Yin et al., 2012) The overall results showed a significant reduction in both heart and lung toxicity using DIBH VMAT with a negligible difference in target coverage (Yin et al., 2012).

Gong et al. (2013) studied the effect of using a mDIBH with VMAT on both target and OAR doses for thoracic esophageal cancer. Fifteen participants (5 females, 10 males) aged 42-65 years with squamous cell carcinoma of the thoracic esophagus were studied. All participants had good cardiopulmonary function, Karnofsky performance status (KPS) scores between 80-90, a minimum breath hold of 30 seconds, and no communication barriers (Gong et al., 2013). Both a FB IMRT plan and a FB VMAT plan were compared to a VMAT DIBH plan. VMAT DIBH decreased heart volumes by 19.85% and increased lung volume by 52.54% compared to FB ($p<0.05$) (Gong et al., 2013). Compared to FB IMRT and FB VMAT, the VMAT DIBH plan reduced MLD by 18.64% and 17.84% respectively, where $p<0.05$. Additionally, V5, V10, V20, and V30 lung doses were reduced using VMAT DIBH (Gong et al., 2013). This study also compared the total number of monitor units (MUs) and time for treatment delivery, with VMAT DIBH having the lowest of each (Gong et al., 2013). The researchers also identified the ABC device as a practical approach to improving precision of targets for thoracic and abdominal cancers due to its ability to reduce respiratory motion and subsequently reduce Clinical Target Volume (CTV) and PTV margins. (Gong et al., 2013). The use of DIBH increases overall lung volume allowing for normal lung tissue sparing, which has been studied in both breast cancer and lymphoma with positive results (Gong et al., 2013). Additionally, the varying degrees of breath hold allow for an increased spatial relationship between targets and OARs (Gong et al., 2013).

An interesting study by Zhao et al., (2018) also discussed the important difference between using a thoracic DIBH and an abdominal DIBH, noting that this can have an impact on the radiation dose to the target and OARs. There were 22 Chinese participants in this study with left-sided breast cancer and a mean age of 46.9 years. Participants were asked to perform a thoracic DIBH, whereby the diaphragm and chest muscles perform the inhalation leaving the abdomen mostly stabilized, and an abdominal DIBH, where the abdominal muscles are used to perform the inhalation and the thoracic cage remains mostly stable (Zhao et al., 2018). All DIBH were performed with the assistance of the ABC device. Both conformal and IMRT plans were created for each DIBH scan as well as a FB scan which showed than an abdominal DIBH IMRT plan had the lowest dose to the heart and left lung, compared to FB plans, conformal abdominal DIBH and both thoracic DIBH plans (Zhao et al., 2018). The MHD was better with the abdominal DIBH plan compared to thoracic DIBH where $p<0.001$. MLD was lower in abdominal DIBH compared to thoracic DIBH with a $p <0.05$. Lung V5 had no statistically significant improvements however V20 improved in abdominal DIBH with a $p <0.05$. Overall, findings from this study indicated that an abdominal DIBH can reduce cardiac and lung dose further than a thoracic DIBH, and that specification and instruction on the type of DIBH for patients to use is relevant (Zhao et al., 2018).

Tumour Location. One study by Doke et al. (2017) separated the data based on tumour location. Doses to OARs with DIBH were compared between proximal and distal esophageal tumours. Proximal tumours were located near the level of the carina, while distal tumours were located near the gastro-esophageal junction (GEJ). Using a 2-tailed paired t-test, the study identified that proximal tumours had a statistically significant reduction in MLD as well as V5, V10 and V20 using DIBH, where $p<0.01$. MHD had a non-statistically significant reduction. In distal tumours, there was a statistically significant increase in MHD using DIBH, $p<0.01$. There were also increases in MLD and V5, V10, and a decrease in V20, which were not statistically significant (Doke et al., 2017). Increases in lung dose for distal tumours was associated with including the celiac nodes in the treatment volume (Doke et al., 2017). This study suggested that location of esophageal tumours could have contrasting impacts on OAR doses (Doke et al., 2017).

Gaps in the Literature

While there are many studies discussing the best strategy to manage or reduce respiratory motion in esophageal radiotherapy, there is a gap in the literature regarding measuring the impact of respiratory motion on the day to day workflow challenges in esophageal IGRT. In addition, while studies identify the dosimetric benefits of using a DIBH technique in treating a variety of cancers and have resulted in changes to standard clinical practice, it is challenging to locate studies that address the feasibility of the DIBH treatment technique through a full course of radiation (25 treatments) for esophageal patients. Studies drawing comparisons between strategies such as DIBH or 4DCBCT during IGRT for esophageal radiation to measure the differences from standard free-breathing or standard imaging practices are difficult to find in the body of literature related to esophageal cancer treatment. The present study will aim to measure theimpact of respiratory motion using diaphragm displacement on IGRT practices in esophageal radiotherapy and provide a foundation to build on for future management strategies.

Research Question

Due to different breathing patterns from CT Simulation to radiotherapy treatment, how does the measured displacement of the diaphragm impact the IGRT process during daily treatment?

Objectives

The primary objective of this study is to quantify the displacement of the diaphragm between the planning CT scan and the daily CBCT scan, where the independent variables are the standard match and the mask match, and the dependent variable is the displacement.

A secondary objective includes determining the relationship between the displacement of the diaphragm and the duration of IGRT (time required to perform IGRT), where the independent variable is the displacement, and the dependent variable is the time. In addition, determining relationships between the displacement of the diaphragm and other IGRT factors such as i) frequency of the radiation oncologist (RO) being called the unit; ii) manual matches being employed; iii) the daily CBCT being exported to the planning software for assessment; and iv) the initiation of a treatment re-scan and re-plan, where the independent variable is the displacement and the dependent variables are frequency of RO being called to the unit, manual matches, CBCT exports, and re-plans, respectively.

A third objective is to identify relationships between the displacement of the diaphragm and patient factors such as i) gender; ii) histology; iii) tumour location; and

iv) smoking status, where the independent variable is displacement and thedependent variables are gender, histology, tumour location and smoking status, respectively.

The fourth objective is to determine if there are any relationships between the duration of IGRT and patient factors such as i) gender; ii) histology; iii) tumour location; and iv) smoking status, where the independent variable is IGRT duration and the dependent variables are gender, histology, tumour location and smoking status, respectively.

Chapter 3. Methodology

Materials and Methods

Participants

This study used convenience sampling method where patients who received cancer treatment at the Stronach Regional Cancer Centre who met the eligibility criteria were assessed.

Inclusion Criteria

Patients were included in the study if they had a) histological confirmation of invasive primary squamous cell or adenocarcinoma of the esophagus, b) recommended treatment with high dose radiotherapy, c) registration in the IGRT software with a "refMAXINHALE" contour. Participants were either male or female and over the age of 18.

Exclusion Criteria

Patients were excluded if they had a) recommended treatment with low dose radiotherapy, b) contraindications to radiotherapy treatment, c) a treatment plan registered in the IGRT software without a "refMAXINHALE" contour, d) under the age of 18. There were no exclusions based on gender.

Study Design

Organizational data records, which identify the number of patients with a cancer diagnosis by disease site, have reported that approximately 30-40 esophageal cancer patients receive curative treatment including radiation at the Stronach Regional Cancer Centre annually. A convenience sampling approach was used for this study with the aim of recruiting 15 patients. This quality improvement initiative was a quantitative prospective study at the Stronach Regional Cancer Centre. Data was collected from May 2019 to March 2020.

The study received full ethical approval from Southlake Regional Health Centre Research Ethics Board (049-1920).

Measures

Sociodemographic and medical characteristics such as patients' gender, age, smoking status, co-morbidities, clinical tumour staging (TNM 7th edition), and histology were identified and recorded.

IGRT

To measure the IGRT assessments, Radiation therapists completed Part 1 of the IGRT Assessment chart after each daily treatment (see Appendix). Radiation therapists recorded the frequency of the RO attending the treatment, the frequency of using a manual match for treatment, the frequency of a CBCT being exported to the planning software (Pinnacle), and the frequency of an individual requiring a rescan. A member of the research team completed Part 2 at the end of the full course of treatment by retrospectively performing a Mask registration for diaphragm movement and recording the time stamps for IGRT duration.

Displacement. To measure the difference in the diaphragm placement between the plan and each daily fraction of radiation, study members retrospectively performed a Mask registration on the XVI software. Firstly, study staff recorded the lateral (X), vertical (Z) and longitudinal (Y) shifts after the standard vertebral body match (as per IGRT protocol) which corrects for setup error. Next, a study member performed a mask match using the refMAXINHALE contour and record the X, Y, Z shifts, which is representative of the baseline diaphragm shift. The difference between the X, Y and Z shifts represented the displacement of the diaphragm.

A mask registration is completed by creating a 5mm border around the refMAXINHALE contour for the computer algorithm to match all of the data points within the “mask”. This method was validated due to showing similar movements of the diaphragm and esophageal stent (for patients with a stent), which supports the literatures identification of the diaphragm as a strong surrogate for esophageal movement (Heethius et al. 2013).

Time. Time stamps from the IGRT software were recorded for two time points: ***1)*** the completion of the CBCT acquisition; and 2) the completion of the IGRT. The difference in these two times represented the time taken to perform the IGRT.

Statistical Analysis

Data from the IGRT Assessment chart was entered into the software R and the analysis was performed. Descriptive statistics were used to outline patient characteristics. Statistical Analysis was completed using a linear mixed effect model to determine any correlation between diaphragm displacement and IGRT duration or IGRT factors and diaphragm displacement and patient/medical characteristics.

Chapter 4. Results

Patient Characteristics

The sociodemographic and medical characteristics of the sample are shown in Table 1 and described here. Of the 19 patients undergoing esophageal radiotherapy during the study timeframe, from May 2019 to March 2020, three were excluded for missing the refMAXINHALE contour, and one was excluded for having a palliative course of treatment. The final sample size was 15 participants (n=15). Most of the participants were aged 71-80 years (n=9), with a small number or participants in the <60 years (n=3), 61-70 (n=1), and >80 years (n=2) age range. Most of the participants in the sample were male (n=10) and non-smokers (n=11). Most of the participants were married (n=9), retired (n=10) and had three or more co-morbidities at the time of diagnosis and radiation treatment (n=11).

Medical disease data indicated that the majority of participants had a diagnosis of adenocarcinoma (n=12) of the gastro-esophageal junction (GEJ) or lower esophagus, (n=12). TNM scores according to the 7th edition show that the majority of the sample had T3 disease (n=13), N2 disease (n=7) and no metastatic disease M0 (n=13). Two participants with M1a scores had disease in the celiac lymph nodes (Hong et al., 2014).

Table 1

Patient Characteristics

Covariate	
Age	N (%)
<60	3 (20)
61-70	1 (7)
71-80	9 (60)
>80	2 (13)
Gender	
Female	5 (33)
Male	10 (67)
Co-morbidities	
None	3 (20)
<3	1 (6)
3 or more	11 (73)
Histology	
Adeno	12 (80)
SCC	3 (20)
Location	
Distal/GEJ	12 (80)
Mid	3 (20)
Smoking	
No	11 (73)
Yes	4 (27)
T	
2	1 (7)
3	13 (93)
Missing	**1**
N	
0	2 (14)
1	4 (29)
2	7 (50)
3	1 (7)
Missing	**1**
M	
0	13 (87)
1a	2 (13)

Displacement of the Diaphragm

The mean displacement with minimum and maximum values for each plane is seen in Table 2. In the x plane, the mean diaphragm displacement was 0 (SD 0.2) cm, (min = -1.0cm, max = 0.7cm). In the y plane, the mean displacement was -0.9 (SD -0.6) cm, (min = -3.1cm, max = 0.7m). In the z plane the mean displacement was 0 (SD 0.3) cm, (min= -1.0cm, max = 2.2cm). The change in displacement over fractions can be seen in Figure 1 and show that there is a trend of greater displacement and greater variations in the y plane over time. There is no trend in the x or z planes.

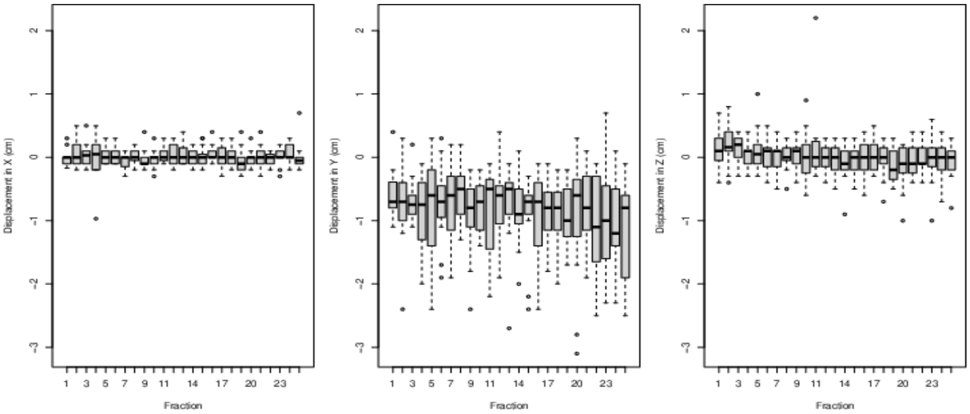
Table 2

Displacement of the Diaphragm n=375

Covariate	N (SD)
X (cm)	
Mean (sd)	0 (0.2)
Median (Min,Max)	0 (-1,0.7)
Missing	**10**
Y (cm)	
Mean (sd)	-0.9 (0.6)
Median (Min,Max)	-0.7 (-3.1,0.7)
Missing	**10**
Z (cm)	
Mean (sd)	0 (0.3)
Median (Min,Max)	0 (-1,2.2)
Missing	**10**

Figure 1

Displacement over Fractions



The displacement of the diaphragm over time (25 fractions) averaged amongst all 15 participants is seen for the x, y and z planes.

Associations Between Displacements and IGRT

IGRT Duration

The mean length of IGRT as well as summary statistics for the IGRT factors can be seen in Table 3 and listed here. The mean length of IGRT was 2 (SD 2.7) minutes, (minimum = 0.4min, maximum = 48.3min). Using generalized estimating equations (GEE) linear mixed model, there was no statistically significant association between the length of the IGRT process and the displacement in x (p=0.698), y (p=0.432) or z (p=0.251). Boxplot of these results are seen in Figure 2.

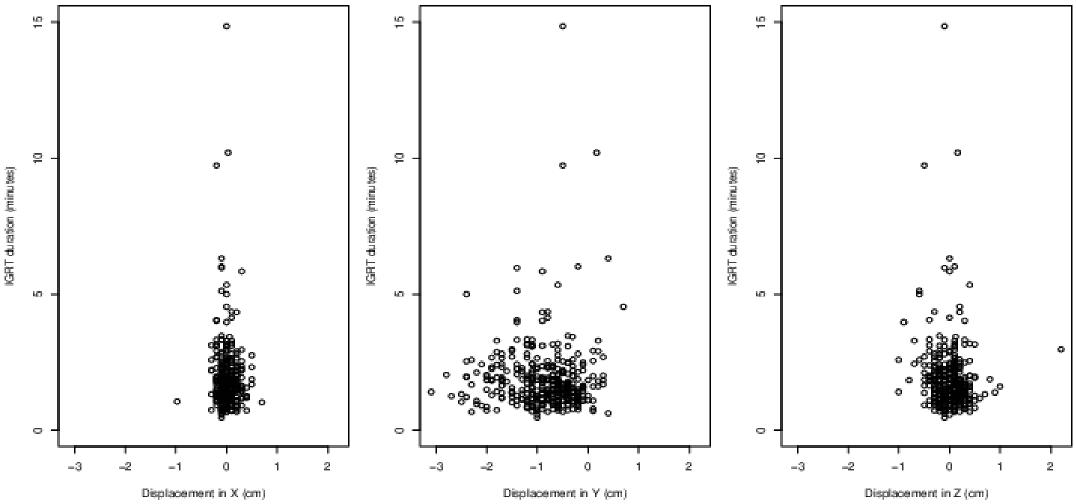
Table 3

Summary of IGRT Factors

Covariate	n=375
Length IGRT (min)	
Mean (sd)	2 (2.7)
Median (Min,Max)	1.6 (0.4,48.3)
Missing	**3**
RO called to unit	
No	292 (96%)
Yes	11 (4%)
Missing	**72**
Manual match	
No	278 (92%)
Yes	24 (8%)
Missing	**73**
CBCT exported to pinnacle	
No	294 (97%)
Yes	8 (3%)
Missing	**73**
Replan	
No	325 (99%)
Yes	2 (1%)
Missing	**48**

Figure 2

Associations Between Displacement and IGRT Duration



Displacement in each plane (x, y, z) is shown in association with the duration of the IGRT.

IGRT Factors

The frequency of IGRT factors being employed is seen above in Table 3. In total, there were 375 fractions assessed for IGRT (n=375). A portion of the fractions assessed in the IGRT charts were incomplete (n=73). A GEE linear mixed model was used to identify relationships between displacement and IGRT factors.

RO Called to the Unit. Most of the fractions were completed without the RO being called to the unit to assess the scan (n=292, 96%). As seen in Table 4, there was no statistically significant association between the RO being called to the unit and the displacement in x (p=0.796), y (p=0.834) or x (p=0.212).

Table 4

UVA for Associations Between Displacement and RO called to Unit

	Estimate	Standard Error	P value
Displacement in x (cm)	-0.642	2.483	0.796
Displacement in y (cm)	0.160	0.761	0.834
Displacement in z (cm)	-1.293	1.035	0.212

Manual Match. Most of the fractions were completed without the use of an off-protocol manual match (n=278, 92%). As seen in Table 5, there was a statistically significant relationship between the use of a manual match and a smaller displacement in x (p=0.033); however no statistically significant association between a manual match and the displacement in y (p=0.160) and z (p=0.314).

Table 5

UVA for Associations Between Displacement and Manual Match

	Estimate	Standard Error	P value
Displacement in x (cm)	-3.145	1.475	**0.033**
Displacement in y (cm)	-0.451	0.321	0.160
Displacement in z (cm)	-1.068	1.061	0.314

CBCT Exported to Pinnacle. The majority of fractions were completed without exporting the CBCT to Pinnacle (n=294, 97 %). As seen in Table 5, there was no statistically significant association between the CBCT being exported to pinnacle and the displacement in x (p=0.248), y (p=0.140) or z (p=0.180).

Table 6

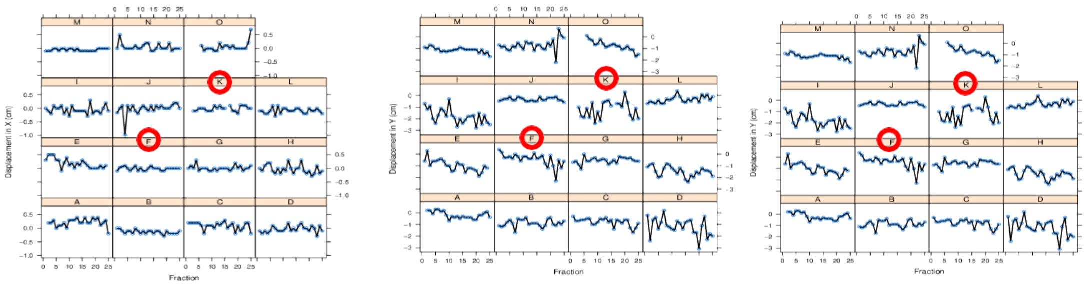
UVA for Associations Between Displacement and CBCT Export

	Estimate	Standard Error	P value
Displacement in x (cm)	2.377	2.056	0.248
Displacement in y (cm)	-1.032	0.700	0.140
Displacement in z (cm)	0.860	0.642	0.180

Replan. This study revealed that 2 of 15 (13%) patients required a replan rate of esophageal radiotherapy treatment plans (Participants F and K). The change in displacement over fraction by each participant is seen in Figure 3; it shows no trend in changes over fraction by participant in the x and z planes. However, it is clear there is a wide range of displacement of the diaphragm in the y plane for each of the aforementioned participants. Other participants whose plots show changes in displacement over time did not require a replan, therefore the displacement of the diaphragm did not correlate with the need for a replan.

Figure 3

Displacement over Fractions by Individual



Displacement in each plane (x, y, z) over an entire treatment course (25 fractions) for each of the 15 participants (A-O). Red circles appear around participants F and K to highlight participants who required a rescan.

Associations between Displacement and Patient Factors

Gender

Being male was associated with larger displacement in the x plane (p=0.019), while there was no statistically significant association between gender and displacement in y (p=0.918) and z (p=0.840). See Tables 7, 8 and 9.

Histology

There was no statistically significant relationship between the histology of the tumour and the displacement in x (p=0.226), y (p=0.279) and z (p=0.207). See Tables 7, 8 and 9.

Tumour Location

Tumours in the mid esophagus had smaller displacement in x compared to the distal esophagus/GEJ (p=0.013). There were no statistically significant associations between tumour location and displacement in y (p=0.529) and z (p=0.073). See Tables 7, 8 and 9.

Smoking

There was a statistically significant association between smoking and smaller displacement in y (p<0.001) and z (p<0.001), however no association in displacement in x (p=0.065). See Tables 7, 8 and 9.

Table 7

UVA for Associations Between Patient Factors and Displacement in X (cm)

	Estimate	**Standard Error**	**P value**
Male (Ref = Female)	0.086	0.037	**0.019**
Histology = SCC (Ref = adeno)	0.072	0.060	0.226
Location = MID (Ref = DISTAL/GEJ)	-0.079	0.032	**0.013**
Smoking = Yes (Ref = No)	-0.059	0.032	0.065

Table 8

UVA for Associations Between Patient Factors Displacement in Y (cm)

	Estimate	Standard Error	P value
Male (Ref = Female)	0.025	0.241	0.918
Histology = SCC (Ref = adeno)	-0.182	0.169	0.279
Location = MID (Ref = DISTAL/GEJ)	-0.193	0.306	0.529
Smoking = Yes (Ref = No)	-0.545	0.147	**<0.001**

Table 9

UVA for Associations Between Patient Factors and Displacement in Z (cm)

	Estimate	Standard Error	P value
Male (Ref = Female)	0.024	0.117	0.840
Histology = SCC (Ref = adeno)	-0.125	0.099	0.207
Location = MID (Ref = DISTAL/GEJ)	-0.199	0.111	0.073
Smoking = Yes (Ref = No)	-0.267	0.068	**<0.001**

Associations between Patient Factors and IGRT Duration

Associations between IGRT duration and patient factors can be seen in Table 7 and are described here. There was no statistically significant relationship between IGRT duration and gender (p=0.105); histology (p=0.617); tumour location (p=0.767); or smoking (p=0.981).

Table 10

UVA for Associations Between Patient Factors and IGRT Duration (min)

	Estimate	Standard Error	P value
Male (Ref = Female)	-0.689	0.425	0.105
Histology = SCC (Ref = adeno)	0.182	0.365	0.617
Location = MID (Ref = DISTAL/GEJ)	0.114	0.384	0.767
Smoking = Yes (Ref = No)	0.008	0.359	0.981

Summary

The most significant displacement of the diaphragm is seen in the y plane. There was no statistically significant relationship between the displacement and the duration of IGRT. The only statistically significant relationship between the displacement and IGRT factors was the association between a smaller displacement in x and a manual match ($p=0.033$). Being male was statistically significant for a smaller displacement in x ($p=0.019$), and tumours in the mid-esophagus had significantly smaller displacements in x than lower/GEJ tumours ($p=0.013$). Smoking was associated with a smaller displacement in both y ($p<0.001$) and z ($p<0.001$). There were no statistically significant associations between patient factors and the duration of IGRT.

Chapter 5. Discussion

The primary objective of this study was to quantify the displacement of the diaphragm between a breath-hold CT Simulation and the daily CBCT in free-breathing. The results of this study have quantified the displacement of the diaphragm, noting the most significant displacement in the y plane, with smaller, but consistent displacements in x and z.

The second objective looked to identify any relationship between the displacement and the duration of IGRT or any other IGRT factors. Contrary to anticipated results, there was no statistically significant relationship between the displacement and the duration of IGRT. Surprisingly, the only association between displacement and other IGRT factors was a statistically significant relationship between smaller displacements in x and the use of a manual match. We anticipated larger displacements in each plane would be associated with IGRT factors, so this finding is the opposite of our hypothesis. Other IGRT factors did not correlate to the displacement of the diaphragm in any plane.

The third objective sought to identify relationships between patient factors and the displacement. Statistically significant associations were found between males and larger displacements in x; lower/GEJ tumours and larger displacements in x; and smokers and smaller displacements in y and z, suggesting that these are important patient characteristics to consider when prioritizing a reduction or elimination of respiratory-induced motion.

The fourth objective addressed the relationship between patient factors and IGRT duration, for which there was no statistically significant association, meaning that other future studies will be needed to identify the factors associated with longer IGRT duration.

Displacement of the Diaphragm

The results of our study are consistent with the literature which does acknowledge significant displacement of the diaphragm during free-breathing esophageal radiotherapy. As in the studies by Zhao et al. (2007) and Yoshiko et al. (2018), our study also determined the largest displacement to be in the y plane (superior-inferior direction), compared to x (right-left) and z (anterior-posterior). This is important to note, as the greatest reduction in displacement with strategies to minimize respiratory motion is also in the y plane (Zhao et al., 2007). While the significant displacement in the y plane did not correlate with the duration of IGRT or any other IGRT factors, it did correlate with participants who were non-smokers.

Perhaps the most important finding from the present study related to displacement of the diaphragm is that significant y displacement is independent of the IGRT process or patient specific factors; instead, it affirms the potential to reduce the PTV margins when respiratory motion is minimized, which in turn limits radiation exposure to healthy tissues (Ghani & Ng, 2018).

IGRT

While Arabloo et al. (2016) reported respiratory motion as one of the deviations that can require extra time to manage during IGRT, this study did not identify a positive correlation between the displacement of the diaphragm and the duration of IGRT. According to Arabloo et al. (2016), other possible deviations that can be identified and need to be addressed during IGRT are set-up errors, weight loss, and systematic changes to tumour volumes or other internal organs. In addition, other unpredictable factors such as technical difficulties or patient pain/movement throughout the IGRT process could also contribute to the length of the IGRT assessment.

Though standard IGRT protocols are in place to help reduce the significance of inter-user variability, the literature does describe inter-user variability in soft-tissue positioning (Hirose et al., 2020). Therefore, it is reasonable to assume that some variations in interpretations of IGRT would be observed between different therapists from day to day, and between different ROs who may be called to assess. This could also contribute to differences in IGRT duration. Contrary to the hypotheses of this study, there were also no strong correlations between diaphragm displacement and the other IGRT factors. As previously discussed, it is possible that scenarios where these factors were used were related to other contributing factors such as patient pain and anatomical or target changes, independent of the diaphragm.

Patient Factors

One of the most interesting findings is the association between smokers and smaller displacements in the y and z planes. This finding is consistent with the identification of a direct, negative impact of smoking on respiratory function (Tantisuwat & Thabeeratitham, 2014). Tantisuwat and Thabeeratitham (2014) noted that smoking had a direct and negative impact on respiratory function; smokers had significantly less chest expansion, spirometry and respiratory muscle strength than their non-smoking counterparts. Considering this, it is not surprising to note that participants in our study who were smokers, had smaller diaphragm displacements, which could be consistent with smaller chest expansion, spirometry and respiratory muscle strength noted for smokers in the literature. This finding suggests that the impact of respiratory motion is smaller in smokers than it would be in non-smokers, and the need to minimize the effects of respiratory motion is more apparent for non-smokers.

Clinical Implications

The results of this study indicated that there is no immediate solution to improve the displacement of the diaphragm or the IGRT process during esophageal radiotherapy. Further studies are required in order to identify a positive solution and ultimately change the standard practice for this population. It will be important to evaluate the specific challenges associated with longer IGRT in future studies, as it is not definitively clear that IGRT challenges and replans were prompted by the displacements.

Notably, with a 13% replan rate in the present study, the workload and resources required for each of these cases is doubled. This represents an impact on workload and resources, which may be scarce. The patient must undergo a new planning CT scan, new contours by both the RO and the treatment planner, perform new quality assurance procedures. There is also an impact on the patient who must undergo an additional procedure involving more exposure to radiation. This process would be initiated by the RO and discussed with the patient. Considering the suspected improvement in the patient's treatment, these benefits would be expected to outweigh the small additional radiation exposure to the patient. It will also be important to evaluate the other specific circumstances surrounding replans and challenges in the IGRT assessment in order to determine if other management strategies can be used to enhance this important process in esophageal radiotherapy.

Limitations

The impact of respiratory motion on esophageal movement has been widely studied and identified in the literature (Yashamita et al. 2010; Yoshiko et al. 2018; Zhao et al., 2007). Many potential management strategies have also been widely examined in other disease sites, such as 4DCT in lung cancer and DIBH in breast cancer and lymphoma. However, these strategies have yet to be employed for improvements to the IGRT process or dosimetry for esophageal radiotherapy.

Initially, this study was to have two parts. The second part of the study would have been a comparison of the same factors with patients undergoing DIBH for CT Simulation and treatment, and would have been the first study to measure and compare the differences in both IGRT and the dosimetry (dose to targets and OARs) between the standard of care and this respiratory motion reduction strategy. However, due to the time constraints and the significant limitations on research studies throughout the course of the Covid-19 pandemic, we were unable to recruit participants for part two of this study. Though the literature regarding respiratory motion in esophageal radiotherapy is well documented, the researchers in this study focused attention on looking for relationships between the displacement and IGRT duration, as well as other IGRT factors, which has not been addressed in this nature in the literature.

External validity of this study is somewhat limited due to the small sample size. However, given that 15 patients yielded 375 fractions total, this was a reasonable sample size. Moreover, the number of incomplete fractions in the IGRT assessment chart also limits the internal validity of the study. Using the mask match for assessing the baseline shift of the diaphragm improves the internal validity of the study, as this process was validated due to similar movements of the diaphragm and esophageal stent placement, which is consistent with the literature that identifies the diaphragm as a strong surrogate for esophageal placement (Heethius et al. 2013).

Recommendations for Future Research

Aims for future studies should focus on identifying the impact of respiratory motion management strategies such as 4DCBCT or respiratory gating on the IGRT process. It is worth exploring the use of a 4DCBCT with a match to the CTV as outlined by Voncken et al. (2019) who revealed improved target positioning during IGRT and a potential reduction in PTV margin size with a 4DCBCT CTV match. In addition, a more effective approach in future studies may be to explore treatment techniques to actively reduce respiratory motion. A study using DIBH could be used to compare displacement, other IGRT factors as well as dosimetry.

To date, studies on DIBH in esophageal cancer have investigated dosimetric comparisons from the treatment planning perspective (Dieters et al, n.d.; Yin, Liu & Zhai (2012),; Gong et al, (2013); Zhao et al., (2018). The DIBH technique for esophageal radiotherapy has yet to be studied to determine the feasibility of this technique throughout a full course of treatment. As Ghani and Ng (2018) mentioned in their study, many lung patients can have a hard time completing multiple breath holds over the course of each daily treatment, and esophagus patients could face similar challenges due to their many comorbidities and more severe treatment side effects from concurrent chemo-radiation. A study that focuses on the feasibility of this technique is necessary to understand whether respiratory motion reduction strategies like a DIBH can be used for this population, or whether the best approach will be using respiratory motion management (4DCBCT, respiratory gating) instead.

The study centre has received REB approval to begin a prospective cohort study comparing the dosimetric effects and feasibility of a DIBH technique for esophageal radiation patients throughout their full course of radiation treatment. In addition to dosimetric comparisons, this study will build on the investigations of the present study to assess the impact on the IGRT process when respiratory motion is controlled.

Beyond this, there are other breathing patterns and strategies addressed in the literature that a larger, multi-institutional study could provide an opportunity to investigate such as the differences between an abdominal DIBH and a thoracic DIBH, or an exhalation breath hold (Dieters et al., n.d.). As discussed above, being that there was a relationship between smoking and displacement, future studies may be required to determine which patients are better suited to respiratory motion management strategies such as 4DCBCT and respiratory gating, versus those who are more suited to respiratory motion reduction/elimination strategies like a DIBH or exhalation breath hold. Lengthier time frames and more significant resources at multiple institutions would allow for an in-depth investigation into these options for esophageal radiotherapy patients.

Given the results of the current study, future research should focus specifically on the y plane (superior inferior plane) where the greatest improvements can be made and the significant time required for data collection in all three planes. Since the results of this study did not show a correlation between displacement and IGRT duration/factors, other factors that are unique to this subset of populations that may be impacting IGRT should be monitored, such as stent or feeding tube placement during the course of radiation therapy, or weight fluctuations (Arabloo et al., 2016). Future studies will also require more robust participation and completion of study materials.

Conclusion

There is significant impact of respiratory motion in the superior-inferior direction for esophageal radiotherapy. While it was anticipated that this motion and subsequent displacement of the diaphragm between the planning CT scan and the daily CBCT was negatively impacting the IGRT process, the present study did not find any significant associations between displacement and IGRT. While there were interesting findings to build upon, including the reduced displacements in the y direction for smokers and a 13% replan rate, the true factors associated with displacement and IGRT challenges in our centre have yet to be identified.

Future research in this centre will focus on exploring respiratory motion management and reduction strategies and expand beyond the small sample size at the study centre. Esophageal patients undergo a tremendous amount of treatment and subsequent side effects, and it is imperative that we have the tools in place to help radiation therapist ensure their esophageal patients receive treatment that is precise, accurate and timely to improve not only patient outcomes but overall patient experience.

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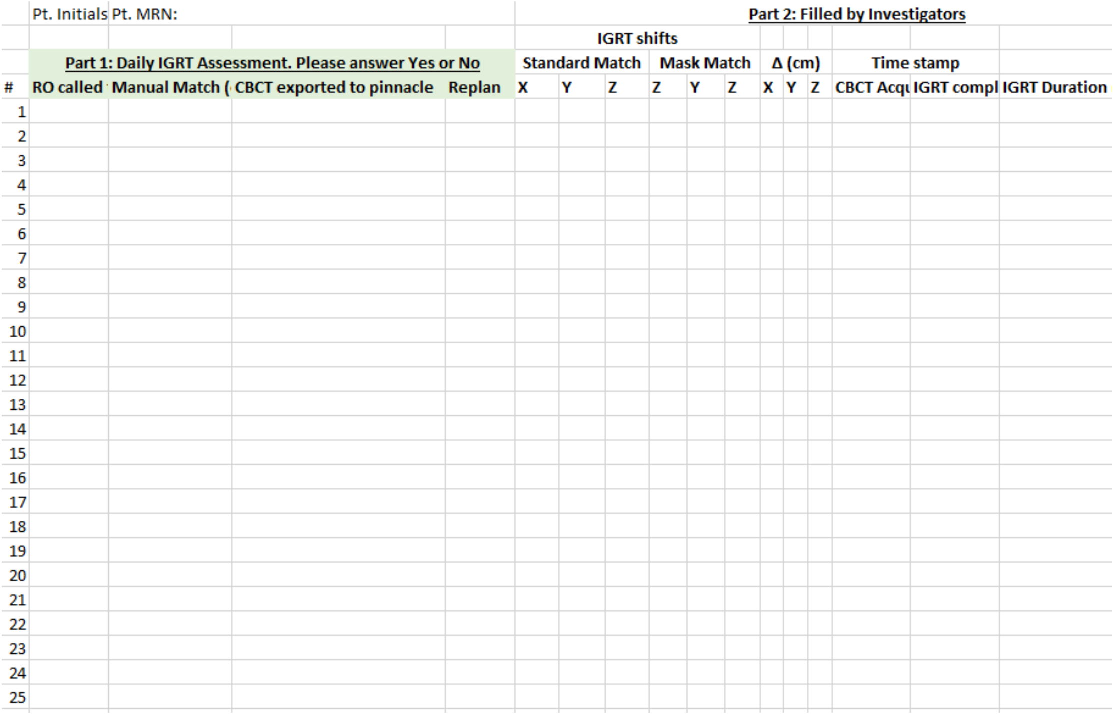
Appendix A: IGRT Assessment Chart



	Pt. Initials	Pt. MRN:			Part 2: Filled by Investigators											
					IGRT shifts											
	Part 1: Daily IGRT Assessment. Please answer Yes or No				Standard Match			Mask Match			Δ (cm)			Time stamp		
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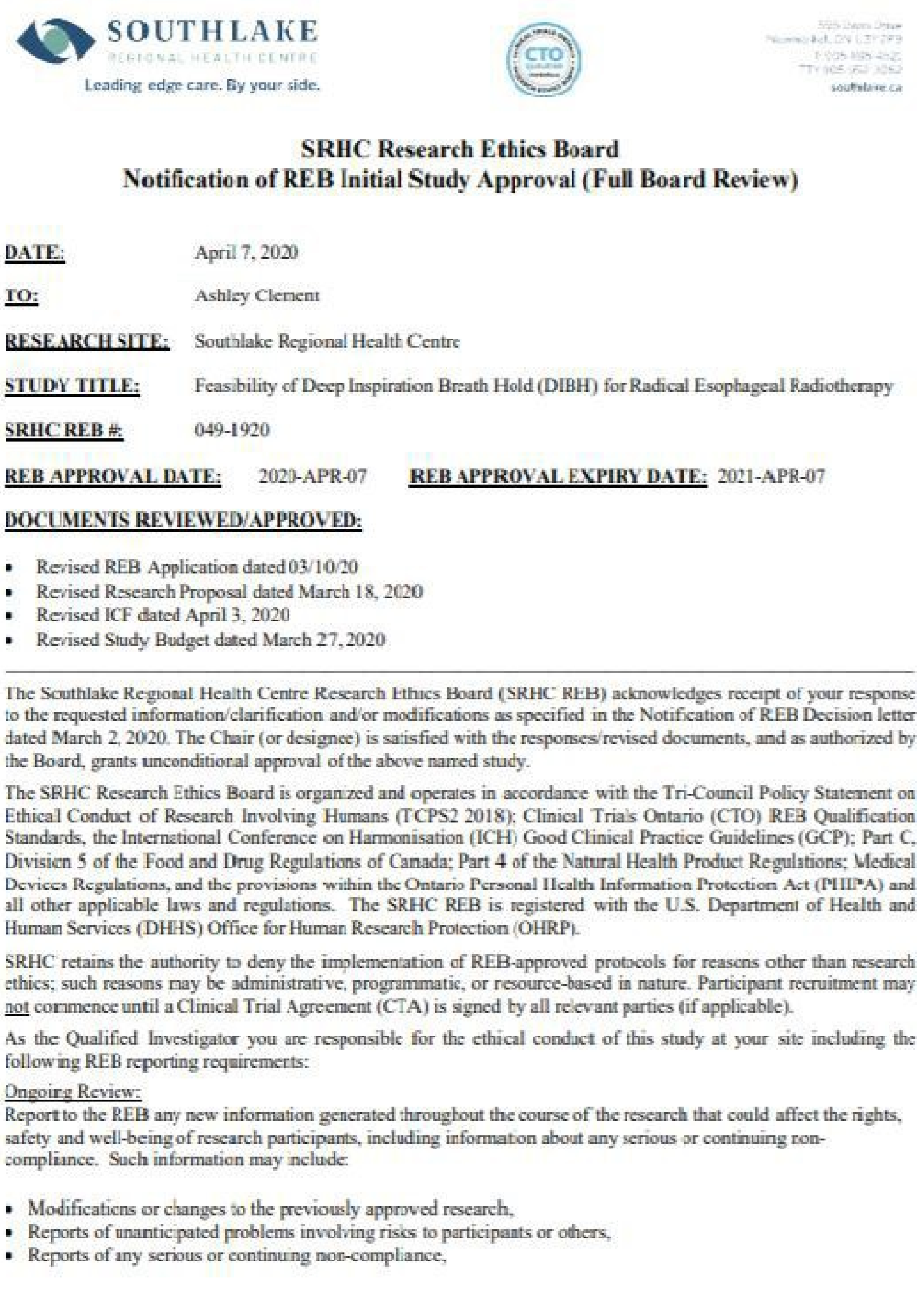
Appendix B: Ethics



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SRHC Research Ethics Board
Notification of REB Initial Study Approval (Full Board Review)

DATE: April 7, 2020

TO: Ashley Clement

RESEARCH SITE: Southlake Regional Health Centre

STUDY TITLE: Feasibility of Deep Inspiration Breath Hold (DIBH) for Radical Esophageal Radiotherapy

SRHC REB #: 049-1920

REB APPROVAL DATE: 2020-APR-07 **REB APPROVAL EXPIRY DATE:** 2021-APR-07

DOCUMENTS REVIEWED/APPROVED:

- Revised REB Application dated 03/10/20
- Revised Research Proposal dated March 18, 2020
- Revised ICF dated April 3, 2020
- Revised Study Budget dated March 27, 2020

The Southlake Regional Health Centre Research Ethics Board (SRHC REB) acknowledges receipt of your response to the requested information/clarification and/or modifications as specified in the Notification of REB Decision letter dated March 2, 2020. The Chair (or designee) is satisfied with the responses/revised documents, and as authorized by the Board, grants unconditional approval of the above named study.

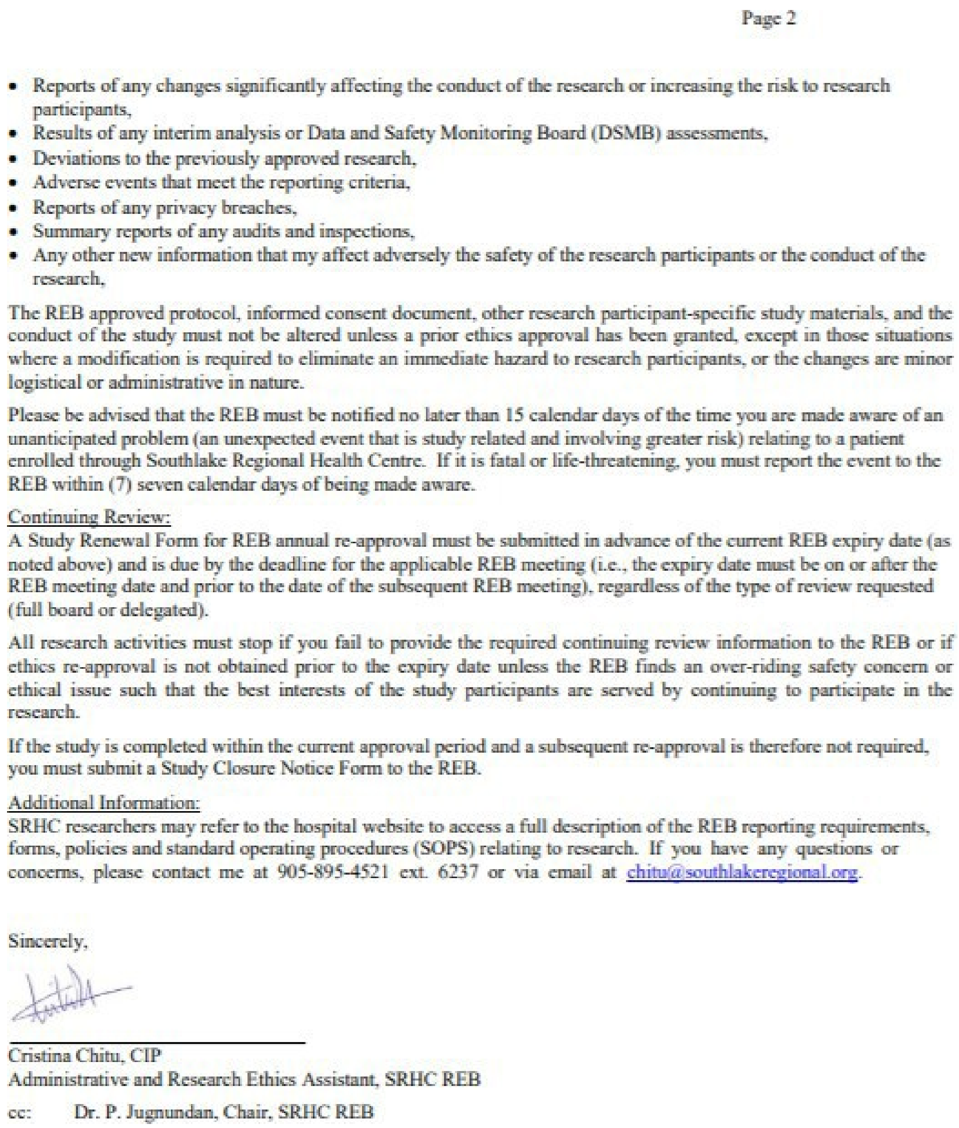
The SRHC Research Ethics Board is organized and operates in accordance with the Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans (TCPS2 2018); Clinical Trials Ontario (CTO) REB Qualification Standards, the International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines (GCP); Part C, Division 5 of the Food and Drug Regulations of Canada; Part 4 of the Natural Health Product Regulations; Medical Devices Regulations, and the provisions within the Ontario Personal Health Information Protection Act (PHIPA) and all other applicable laws and regulations. The SRHC REB is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

SRHC retains the authority to deny the implementation of REB-approved protocols for reasons other than research ethics; such reasons may be administrative, programmatic, or resource-based in nature. Participant recruitment may not commence until a Clinical Trial Agreement (CTA) is signed by all relevant parties (if applicable).

As the Qualified Investigator you are responsible for the ethical conduct of this study at your site including the following REB reporting requirements:

Ongoing Review:
Report to the REB any new information generated throughout the course of the research that could affect the rights, safety and well-being of research participants, including information about any serious or continuing non-compliance. Such information may include:

- Modifications or changes to the previously approved research,
- Reports of unanticipated problems involving risks to participants or others,
- Reports of any serious or continuing non-compliance,



- Reports of any changes significantly affecting the conduct of the research or increasing the risk to research participants,
- Results of any interim analysis or Data and Safety Monitoring Board (DSMB) assessments,
- Deviations to the previously approved research,
- Adverse events that meet the reporting criteria,
- Reports of any privacy breaches,
- Summary reports of any audits and inspections,
- Any other new information that my affect adversely the safety of the research participants or the conduct of the research,

The REB approved protocol, informed consent document, other research participant-specific study materials, and the conduct of the study must not be altered unless a prior ethics approval has been granted, except in those situations where a modification is required to eliminate an immediate hazard to research participants, or the changes are minor logistical or administrative in nature.

Please be advised that the REB must be notified no later than 15 calendar days of the time you are made aware of an unanticipated problem (an unexpected event that is study related and involving greater risk) relating to a patient enrolled through Southlake Regional Health Centre. If it is fatal or life-threatening, you must report the event to the REB within (7) seven calendar days of being made aware.

Continuing Review:
A Study Renewal Form for REB annual re-approval must be submitted in advance of the current REB expiry date (as noted above) and is due by the deadline for the applicable REB meeting (i.e., the expiry date must be on or after the REB meeting date and prior to the date of the subsequent REB meeting), regardless of the type of review requested (full board or delegated).

All research activities must stop if you fail to provide the required continuing review information to the REB or if ethics re-approval is not obtained prior to the expiry date unless the REB finds an over-riding safety concern or ethical issue such that the best interests of the study participants are served by continuing to participate in the research.

If the study is completed within the current approval period and a subsequent re-approval is therefore not required, you must submit a Study Closure Notice Form to the REB.

Additional Information:
SRHC researchers may refer to the hospital website to access a full description of the REB reporting requirements, forms, policies and standard operating procedures (SOPS) relating to research. If you have any questions or concerns, please contact me at 905-895-4521 ext. 6237 or via email at chitu@southlakeregional.org.

Sincerely,

Cristina Chitu, CIP
Administrative and Research Ethics Assistant, SRHC REB

cc: Dr. P. Jugnundan, Chair, SRHC REB