Multifaceted Approaches to Enhancing Shoulder Health in Breast Cancer Patients undergoing Radiation Therapy: quantification of treatment effects and rib fracture prediction assessment

by

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Author’s Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Radiotherapy is a highly effective treatment for breast cancer, but it is also associated with several complications that can impact patients' quality of life and overall survival. This dissertation addressed the lack of research examining the influence of radiation therapy on shoulder health indicators during the treatment window. Additionally, it investigated the effectiveness of an intervention program focused on shoulder strength to compensate for potential shoulder health impairments. Finally, it assessed the feasibility of using quantitative ultrasound for more accessible evaluations of rib fragility fractures, which may arise as a long-term consequence of radiation therapy.

Study 1 and 2 shared an *in vivo* experimental collection. Shoulder health indicators of the affected limb of 27 breast cancer patients were tracked at baseline, midpoint, and endpoint assessments within the radiation therapy window. The activation of latissimus dorsi**,** teres major**,** pectoralis major**,** and serratus anterior, were quantified using a wearable electromyography (EMG) device during two shoulder flexion-extension, two shoulder abduction-adduction, and two shoulder external-internal rotation submaximal tasks. The kinematics of the shoulder complex were measured using an Inertial Measurement Unit (IMU) during six maximal range of motion trials involving flexion, abduction, and external rotation. Additionally, arm strength was evaluated using a hand-held dynamometer during flexion, extension, abduction, adduction, external rotation, and internal rotation maximal exertions. Finally, the arm circumference was determined using a measuring tape. Study 1 showed significant changes ($p<0.05$) in the latissimus dorsi and teres major muscles during all evaluated shoulder movement tasks. There was also a significant reduction ($p<0.05$) in shoulder abduction at the end of treatment compared to baseline. No changes were noted in pectoralis major and serratus anterior muscles, nor in arm strength. Radiation dose was negatively correlated with shoulder abduction range of motion. Study 2 evaluated and

compared a control group with a shoulder strength intervention group throughout the radiation treatment. The intervention group exhibited higher activation of teres major and serratus anterior compared with control group ($p < 0.05$) in external- internal rotation and flexion-extension movement tasks. This group also exhibited significantly greater ($p<0.05$) arm strength and negative correlations between radiation fractions and arm strength for all the evaluated movements. No significant differences were noted in pectoralis major and latissimus dorsi activation, nor shoulder complex range of motion between the groups.

Study 3 employed an *in-silico* approach to simulate oncological treatments and demonstrated that Quantitative Ultrasound Imaging of Bone (QUSIB) is sensitive to the structural changes induced by these therapies. Specifically, two sets of ribs were created to simulate the effects of 5 years of radiation and bisphosphonate treatments. Acoustic attenuation and backscatter coefficient parameters were examined to assess their ability to detect changes in trabecular structure. The results revealed significant correlations ($p<0.05$) between the observed and predicted values of Bone Volume Fraction (BV/TV)**.** Furthermore, significant differences ($p<0.05$) were observed in trabecular thickness between the base and simulated radiation and bisphosphonate models.

This dissertation provides valuable insights into the effects of radiation therapy on shoulder functionality. It aims to help patients minimize the potential side effects of this treatment and assist health providers in finding more accessible solutions for managing these long-term consequences.

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Chapter 1 - Introduction

1.1 Motivation

Breast cancer is widespread, but robust evaluations of the efficacy of treatment and post-treatment sequelae are limited (Hwang et al., 2008). Despite its advantages, several accompanying complications and consequences of radiotherapy could influence future patient quality of life and eventual survival (Hwang et al., 2008). The isolated influence of radiation therapy on the shoulder health indicators is presently unknown. Additionally, exercise is considered an intervention that may help mitigate the effects of oncological treatment. However, the impact of an intervention program focused on shoulder strength within the radiation therapy therapeutic window in breast cancer patients has yet to be investigated. Another potential consequence of radiation treatment that negatively impacts patients' quality of life, are the rib fragility fractures. These fractures are usually underestimated due to the lack of portability and accessibility of current approaches to assess bone quality.

The target variables of this thesis were based on a needs-based project from the University of Waterloo program 'CBB-CREATE'. In order to identify the implications of the application of radiotherapy in breast cancer, and to create a bridge between research and the health community, information was gathered among several professionals in the Kitchener-Waterloo area (Director of University of Waterloo 'Well-Fit' Center specialized in Cancer Rehabilitation; 'Well Fit' Fitness Staff; and Staff Professional Panel in charge of Radiation Therapy for Breast Cancer from Grand River Hospital). The health professionals consulted agreed that there was a need to study how shoulder health indicators change during the radiation therapy window, as well as to develop a more accessible and functional rib quality assessment.

1.2 Global Objective

To study how arm strength, shoulder muscle activation, shoulder complex range of motion, and the appearance of lymphedema change during the radiation window and to develop a more accessible and functional assessment of rib fragility fractures.

1.3 Outline

The three studies were conceptually linked (Figure 1), the scope was to improve assessment and documentation of the effects of radiation therapy on shoulder health indicators of breast cancer patients. Study 1 examined shoulder complex health indicators in breast cancer patients before radiation treatment and throughout a 6-week window, including the prescribed fractions of radiation therapy (which varied by each patient). Study 2 assessed the influence of exercise on arm function in breast cancer patients receiving radiation treatment. This study cohort was subdivided into 'Control' and 'Strength Training' groups. The 'Strength Training' group partook in an intervention training program focused on shoulder muscle strength. The functional indicators were compared to the 'Control' group, which experienced the current standard of care which did not include any specific intervention. Study 3 focused on improving the assessment of rib fragility fractures. Rib simulation models of five years of oncological treatment including both bisphosphonates and radiation treatment were performed, and a cohort of volunteers were assessed using quantitative ultrasound to predict rib quality.

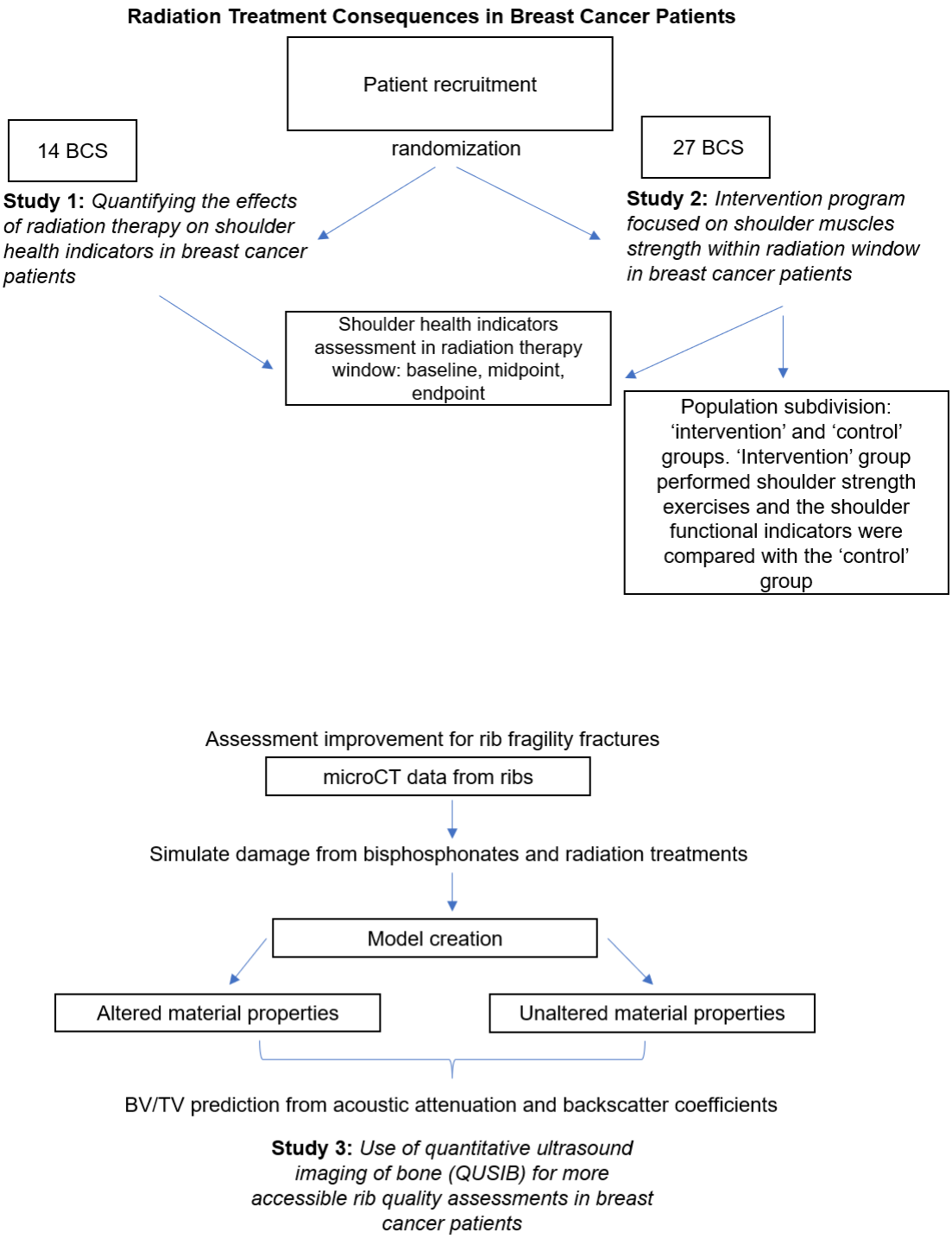


Figure 1. Flowchart describing the three integrated thesis studies. Data collection for studies 1 and 2 was concurrent. Shoulder functional indicators were used for studies 1 and 2.

Chapter 2 - Literature Review

2.1 Overview of Breast Cancer

2.1.1 Prevalence

Breast cancer is the most prevalent malignancy worldwide in women. There is an estimated incidence of more than 2.3 million per year and over 627.000 deaths (WHO, 2019; Sung et al., 2021). Within Canada, breast cancer is the most common cancer among women. It constitutes 25% of all new cancer cases each year for females and 13% of all cancer deaths in women per year (CCS, 2020). It is estimated that about 1 in 8 women in Canada will develop breast cancer at some point in their lives, and 1 in 31 women will die from it (CCS, 2020).

2.1.2 Diagnosis

2.1.2.1 Diagnostics and Pathophysiology

Breast cancer refers to the growth and proliferation of cells that originate in the breast tissue. The breast is composed of two main tissues: glandular and stromal (Table 1). Glandular tissues host the glands that produce milk (lobules) and the ducts (milk passages), whereas the stromal tissues contain both the fibrous and connective tissues of the breast. The cellular fluids and waste are removed from the breast through the lymphatic tissue-immune system tissue (Breast cancer information and resources, 2010). The tumors can develop within different areas of the breast. Most tumors result from benign changes in the breast, such as fibrocystic changes that lead to the accumulation of fluids, fibrosis, lumpiness, accumulation of breast thickness and tenderness (Sharma et al., 2010). Most breast cancers begin in the ducts or the lobules (Sharma et al., 2010).

Table 1. Type of breast cancer (Sharma et al., 2010).

Type of Cancer	Description
According to the site	
Non- invasive Breast Cancer	The cells are confined to the ducts, and do not invade the surrounding fatty and connective tissues.
Invasive Breast Cancer	The cells break through both duct and lobular wall and invade the fatty and connective tissues. Can be invasive without being metastatic.
Frequently occurring Breast Cancer	
Lobular carcinoma in situ	The cancer does not spread beyond the area which was originated. This type of cancer comprises an increase in the number of cells within the milk lobules of the breast.
Invasive lobular carcinoma	This cancer begins in the milk lobules of the breast, but it spreads to other regions of the body (metastasis).
Ductal carcinoma in situ	This is the most common type of non-invasive breast cancer. It is confined within the milk lobules of the breast.
Invasive ductal carcinoma	This cancer begins in the milk ducts of the breast, and it penetrates the wall of the duct, invading the fatty and other regions of the body. This is the most common type of cancer, accounting for 80% of the breast cancer diagnosis.
Less common occurring Breast Cancer	
Medullary carcinoma	Invasive cancer that forms a boundary between the tumor tissue and the normal tissue. It accounts for 5% of breast cancer diagnosis.
Multinous carcinoma	This rare type of cancer is formed by the mucus- producing cancer cells. This cancer has better prognosis compared to the other invasive carcinoma-types.
Tubular carcinoma	Special type of invasive carcinoma. This cancer has better prognosis compared to the other invasive carcinoma-types.
Inflammatory breast cancer	This is a rare (1% of breast cancer diagnoses) but fast-growing type of cancer. It is characterized by inflamed breast and dimples and/or thick ridges caused by the blocking lymph vessels or channels in the skin over the breast.
Paget's disease of the nipple	This is a rare (1% of breast cancer diagnoses) type of cancer that begins in the milk lobules, and it spreads to the skin of the nipples and the areola.
Phylloides tumor	Can be either benign or cancerous. These tumors develop in the connective tissues of the breast and may be treated with surgical removal.

2.1.3 Stages of breast cancer

The stages of cancer are defined by how advanced the cancer is. The stage helps to determine the most accurate treatment and prognosis. The stages can be described as non-invasive (in situ) or invasive and are often labelled in detail with numbers (0 from IV) (Sharma et al., 2010).

Table 2. Stages of breast cancer (Breast Cancer.org, 2010)

Stage	Description
In situ carcinoma	
0	The tumor is confined within a milk duct and it doesn't invade surrounding breast tissues.
Localized and regional invasive cancer	
I	The tumor is less than 2 cm in diameter and has not spread beyond the breast.
IIA	The tumor is 2 cm or less in diameter and it has spread to one to three lymph nodes in the armpit, microscopic amounts have spread to the lymph nodes near the breastbone on the same side as the tumor. Or the tumor is larger than 2 cm but smaller than 5 cm but has not spread beyond the breast.
IIB	The tumor is larger than 2 cm but smaller than 5 cm diameter, and it has spread to one to three lymph nodes in the armpit, microscopic amounts have spread to the lymph nodes near the breastbone on the same side as the tumor. Or the tumor is larger than 5 cms but has not spread beyond the breast.
IIIA	The tumor is 5cms or less in diameter, and it has spread to four to nine lymph nodes in the armpit or has enlarged at least one lymph node near the breastbone on the same side as the tumor. Or the tumor is larger than 5 cm and has spread to up to nine lymph nodes in the armpit or to lymph nodes near the breastbone.
IIIB	The tumor has spread out to the chest wall or skin and has caused breast inflammation.
IIIC	The tumor can be any size, and it has spread to 10 or more lymph nodes under or above the collar bone, or it has spread to lymph nodes in the armpit and has enlarged at least one lymph node near the breastbone on the same side of the tumor, or it has spread to four or more lymph nodes in the armpit, and microscopic amounts have spread to lymph nodes near the breastbone on the same side of the tumor.
Metastatic cancer	
IV	The tumor, regardless of the size, has spread to distant organs, such as lungs or bones.

2.2 Treatment

2.2.1 Therapy principles

Treatment for breast cancer depends on the presence of metastasis. The main goal of treatment for non-metastatic breast cancer is to remove the tumor from the breast and regional lymph nodes to prevent potential metastasis. The local therapy for these cancer types consists of surgical resection, sampling, or eradication of axillary lymph nodes with the combination of post-operative radiation therapy. The systemic therapy consists of endocrine treatment, and/or directed anti-body therapy, and/or chemotherapy applied either preoperatively, postoperatively or both (Waks & Winer, 2019). For metastatic breast cancer, the goal is to alleviate symptoms and prolong life. The same principles of systemic therapy are applied, and local therapy is only used for palliative purposes (Waks & Winer, 2019).

2.2.2 Systemic therapy for non-metastatic breast cancer

2.2.2.1 Endocrine therapy

Endocrine therapy neutralizes estrogen-promoted tumor growth. The standard administration includes the prescription of anti-estrogen oral medication for 5 years. Tamoxifen is the most common drug and is typically prescribed to either pre- or post- menopausal women. Aromatase inhibitors are also accurate in inhibiting the conversion of androgen into estrogen but can only be administered to post- menopausal women (Joshi & Press, 2018). The administration of tamoxifen for 5 years reduces the breast cancer recurrence rate by 50% in the first 5 years after diagnosis compared to no-endocrine therapy (Davies et al., 2011).

2.2.2.2 Chemotherapy regimen

Chemotherapy is often prescribed for patients diagnosed with stages I-III of breast cancer. This treatment is considered the only systemic treatment that demonstrates efficacy against breast cancer, and it is often prescribed with endocrine therapy (Waks & Winer, 2019). A meta-analysis including 100,000 women demonstrated that chemotherapy reduced 10-year breast cancer mortality by one-third, with major benefits during the first 5 years (Peto et al., 2012). Pre-operative chemotherapy decreases the size of the local tumor, facilitating breast-conservating surgery. Moreover, the application of this treatment before the surgery increases breast conservation rates and reduces local recurrence rates (Mauri et al., 2005). Chemotherapy regimens are often considered in early breast cancer, and the short and long-term effects related to the treatment toxicity are an important consideration for its prescription (Blum et al., 2017).

2.2.3 Local therapy for non-metastatic breast cancer

2.2.3.1 Surgery

Breast cancer surgery has evolved in the last decade, aiming to minimize its long-term effects. Nowadays, the most common approaches are either total mastectomy or an excision plus radiation (Fisher et al., 2002). Contradictions of conservative surgery include diffuse suspicious micro-calcifications on breast imaging, positive pathologic margins following lumpectomy, disease than cannot be addressed by excision, collagen-vascular diseases, and prior radiotherapy of the affected breast (National Comprehensive Cancer Network, 2018). There are two main options for breast cancer surgery: breast conservation surgery (only the tumor and an area of normal tissue are removed), or breast removal mastectomy (all breast tissue is removed). Breast conservation surgery options include lumpectomy, quadrantectomy, and wide excision (Sharma et al., 2010).

2.2.3.2 Lumpectomy

Surgical lumpectomy includes removing cancerous tissue and a small amount of healthy tissue, and it is a treatment for early-stage breast cancer. The lumpectomy can also be applied for diagnosis proposes. Radiation therapy usually follows cancer removal to prevent a recurrence of breast cancer and/or mastectomy surgery (Mayo Clinic, 2020).

2.2.3.3 Wide excision surgery and Quadrantectomy surgery

Wide excision surgery is a process similar to lumpectomy. In this procedure, the cancerous tissue is removed from the breast, but a larger amount of surrounding normal tissue is extracted (Sharma et al., 2010). Quadrantectomy surgery completely removes the affected breast quadrant that protects primary cancer, including the skin and fascia on top of the pectoralis major. In most cases, an axillary dissection is performed afterwards when the tumor is located in the breast tail. In other cases, the dissection is performed with an antero-posterior approach, crossing the axillary fossa in a downward direction (Veronesi et al., 1989).

2.2.3.4 Mastectomy

Mastectomy is a surgery in which all breast tissue including pectoral fascia is removed as a way to treat or to prevent breast cancer. Mastectomy can also be prescribed at the early stages of breast cancer, and the decision between mastectomy and lumpectomy can be challenging, as both procedures are equally effective when it comes to prevention for cancer recurrence. Mastectomy procedures have evolved in the last decade with newer techniques that allow the preservation of the breast skin, with limited scars. Mastectomy is often prescribed for ductal carcinoma in situ or non-invasive breast cancer, stages I and II, inflammatory breast cancer and stage III only after chemotherapy, locally recurrent breast cancer, and Paget' disease of the breast (Mayo Clinic, 2020). The procedure may include the removal of nearby lymph nodes to

determine if cancer has spread. If cancer is present following the analysis of the excised lymph nodes, radiation therapy can be prescribed to the axillary nodes.

Table 3. Types of mastectomy procedures (Mayo Clinic, 2020).

Types of Mastectomies	Description
Modified radical mastectomy	Removal of all breast tissue and most of the lymph nodes.
Total mastectomy	Removal of all breast tissue, including areola and nipple. Sentinel lymph node biopsy can be also performed at the end of the procedure.
Skin- sparing mastectomy	Removal of all breast tissue, nipple and areola, but not breast skin. Breast reconstruction and sentinel lymph node biopsy can be also performed at the end of the procedure.
Nipple-sparing mastectomy	Removal of all breast tissue, sparing the skin, nipple, and areola. Sentinel lymph node biopsy can be also performed, breast reconstruction is performed immediately afterwards.

2.2.3.5 Surgical management of lymph nodes

Lymph node surgical procedures are considered separately from the surgical therapy of the breast. It can be used for diagnostic purposes through the determination of the anatomical scope of the cancer or for therapeutic proposes through the removal of cancerous cells. The surgical decision is made based on the positive clinical involvement from the diagnosis and whether systemic therapy is being administered. Axillary lymph node dissection is the first treatment that the patient receives when axillary cancerous presence is noticed (National Comprehensive Cancer Network, 2018).

2.2.3.6 Radiation therapy

Radiation therapy includes the use of high-energy x-ray or gamma rays that target the tumor or the post-surgery tumor site. External beam radiation is the most common form of radiation treatment, in which the patient lies in supine position with two coplanar tangential photon beams targeting the whole breast (Hoskin, 2012). This standard approach can be expanded and the axillary nodes can be reached within the treatment volume (known as the ‘high

tangent' field) (Alço et al., 2010). If the aim of the therapy is also including the supraclavicular and/or axillary nodes, a third beam is incorporated placed in an anterior oblique direction (Hoebers et al., 2000; Lipps et al., 2017). It is very effective as it applies high doses of radiation that kill the cancerous cells that remain after surgery or recur after the tumor is removed. The application of adjunct radioactive catheters in the site (brachytherapy) or electron beam radiotherapy to the breast scar can also be implemented.

Radiation therapy is usually prescribed after the surgery. This reduces not only cancer mortality but also the risk of breast cancer recurrence by 70% (Clarke et al., 2005). Treatment is usually applied in a window of 6 weeks, five days a week, and 15 minutes per session (Rath, 2010; American Cancer Society, 2009). The administration can be done by hypofractionation or standard radiotherapy regimen. The international standard radiotherapy regimen for early breast cancer consists of 50 Gy in 25 fractions of 2.0 Gy over 5 weeks and is the most frequently used worldwide (Fisher et al., 1985; Van Dongen et al., 1992), whereas the hypofractionation regimen comprises 40 Gy in 15 fractions over 3 weeks (Williams et al., 2006; The START Trialists' Group, 2008).

2.2.3.6.1 Standard versus hypofractionation radiation regimens

Both normal and cancerous tissues react to radiotherapy fraction size (defined as 'fractionation sensitivity'). These responses are rated under a model that describes the degree of healthy tissue damage and the rate of tumor recurrence in a fraction size represented by the ratio of two constants 'α' and 'β' (Jones et al., 2001). The lower the ratio α to β (expressed in Gy), the greater the effect on both healthy and cancerous tissues of changes in fraction size. Healthy tissues of the breast and ribcage are very sensitive to the fraction size, with values α /β 5 Gy or less (Bentzen et al.,1999). Therefore, small changes in fraction size can cause meaningful

damage to these tissues by radiotherapy treatment. The trials A and B conducted by The START Trialists' Group (2008) in 2236 women 5 years after completing radiation therapy proposed a more effective radiotherapy regimen strategy with fewer, larger fractions with smaller doses (39 Gy in 13 fractions of 3.2 Gy versus 50 Gy in 25 fractions of 2.0 Gy). After 5 years the rate of local-regional tumor relapse was 3.6 % for those patients receiving the 50Gy regimen (95% CI 2.2-5.1) and 5.2% for the patients receiving the 39 Gy regimen (95% CI 3.5-6.9). The authors supported previous statements that were pointed out in the last decade based on the hypothesis that breast cancer cells are as sensitive as healthy breast tissue and rib cage to fraction size. Therefore, small fraction doses of 2 Gy would not offer any therapeutic advantage (Whelan et al., 2002; Yarnold et al., 2005).

2.3 Complications associated with Radiation Treatment

There are known long-term effects related to radiation treatment. Meta-analyses have shown that radiotherapy is an effective treatment for breast cancer patients that can lessen the risk for distant metastasis and increase the chances of long-term survival (Bergh et al., 2001). However, the expenses related to disability due to radiation effects to the bone and muscle are considerable, involving important economic costs.

2.3.1 Shoulder strength imbalances

Radiation therapy is believed to affect survival's shoulder muscle strength. A prospective study by Johansen et al., investigated the arm/shoulder strength decrements experienced by participants who received a combination of lumpectomies, axillary dissections, and radiotherapy treatments. 16% of persons had light/moderate and 7% moderate/severe decreases in shoulder strength (Johansen et al., 2000). Another prospective research performed by Blomqvist et al (2004), compared irradiated and non-irradiated limbs in patients who received both a

mastectomy and radiation therapy and reported significantly reduced shoulder strength in adduction (31.9 vs 35.2 Nm.), abduction (23.8 vs 26.4 Nm.), flexion (23.0 vs 27.9 Nm.), extension (11.6 vs 16.6 Nm.), and internal rotation (12.0 vs 15.6 Nm.) in the irradiated limbs. Lipps et al (2019) found that shoulder strength long-term deficits were only significant ($p<0.05$) in vertical adduction in patients receiving breast conserving surgery combined with radiotherapy. As the pectoralis major is the main shoulder vertical adductor, these findings suggest the compensatory mechanisms for breast cancer patients to stabilize the joint with muscles other than the pectoralis major (Lipps et al., 2019).

Documentation of shoulder strength employs various techniques, each with associated limitations. Shoulder strength has been assessed using isokinetic dynamometers (Blomqvist et al., 2004), hand-held dynamometers (Rietman et al., 2004; Johansson, Ingvar, Albertsson & Ekdahl, 2001; Harrington et al., & Groff, 2011; Brookham & Dickerson, 2015), and manual muscle testing (Kendall, 1993). Isokinetic dynamometers are considered the gold standard tool to assess muscle strength. However, these devices are not only expensive but also require a lab setting to perform the measurements. In contrast, hand-held dynamometers are accurate force measurement tools, easy to use, low cost, and are a convenient size to justify their use in a clinical setting (Stark et al.,2011).

2.3.2 Shoulder complex range of motion decrements

Shoulder complex range of motion decrements are linked to radiation treatment. Both, mastectomy and radiation therapy combined were associated with shoulder complex range of motion reductions ranging from 10° to 55°, as well as a decline of activity tolerance (Neto et al., 2018; Ryttov et al., 1988; Springer et al., 2010). After six months post-mastectomy, range of motion was restored in those patients who had surgery but did not have radiation therapy to the

axilla, compared to those who received both mastectomy and radiation treatments. Irradiated patients still had shoulder movement restrictions from 20° in mild cases to 50° in those patients with massive axillary spread who had been given a radiation boost to the axilla (Gunnar & Feuk, 2000). Another prospective study included the measurement of shoulder abduction and flexion before and one year after oncological treatment in 396 patients all of whom had surgery among other therapies including radiation therapy (70% of the patients). Mean shoulder abduction and flexion decreased 5.5° and 2.2°, respectively, for the affected side (Smoot et al., 2016).

Mastectomy surgery cause scar tissue in skin and fascia in the anterior wall of the chest. This scar tissue generates impediments in the normal gliding between the skin and the surrounding structures, including muscles and fascia. This scenario combined, with pain and posture selection and avoidance mediated by fear, leads to a resting shoulder-girdle malalignment and decreased shoulder complex range of motion (Neto et al., 2018). The fibrosis of the soft tissue (especially at the pectoralis major and minor) following radiation, likely exacerbates this problem (Neto et al., 2018).

Movement limitations in shoulder ROM increase the risk of upper extremity functional disability. According to the "Disabilities of the Arm Shoulder Hand (DASH)" scale, a score > 20/100 represents a significant loss of function. A combination of mastectomy, radiation, and chemotherapy led to upper extremity disabilities in breast cancer patients six months after treatment, reflected in patients with an average DASH score of 19.5 (slightly below the significant loss of function threshold) and decreases in shoulder complex ROM and shoulder strength (Harrington et al., 2001). These upper limb disabilities may manifest through difficulties in lifting and carrying objects, overhead movement such as combing hair or reaching to a shelve, and pushing and pulling objects such as a vacuum cleaner (Ebaugh et al., 2011). Shoulder

strength deficit also negatively impacts the ability to perform daily activities such as taking care of family or going back to work, resulting in financial and emotional burden not only for the survivor but also for their family and environment (Ebaugh et al., 2011).

2.3.3 Shoulder muscle activation imbalance

Radiation therapy for breast cancer may cause thickening of the connective tissue, thus restricting the movement within fascial planes. A combination of the limited ability of the tissue to expand in concert, muscle fibrosis, and ischemia produced by vascular network changes, limits the efficacy of the muscles to contract and activate (Oskrochi et al., 2015).

To date, several studies showed evidence of the existence of motor control impairments in breast cancer survivors. Galiano-Castillo (2011) confirmed a significantly higher upper trapezius activation ($p<0.05$) in breast cancer patients who received oncological treatment at 10 secs and 60 secs into the performance of a task consisting of drawing pencil marks in three circles in a counterclockwise direction with the affected (right) arm. The normalized root mean squares (RMS) values at 10 and 120 secs respectively were 0.86/0.82 in the affected side and 0.31/0.34 in the unaffected side for the breast cancer patients, compared to 0.66/0.71 in the right side and 0.28/0.32 in the left side for healthy controls. Moreover, the sternocleidomastoid muscle also evidenced a significant higher activation ($p<0.05$) in breast cancer patients who received oncological treatment at 10 and 120 secs respectively with RMS values of 0.29/0.42 in the affected side compared to 0.10/0.11 in the right side in healthy controls (Galiano- Castillo et al., 2011). Higher activation in the upper trapezius, rhomboids, and serratus, and decreased activation in pectoralis major (in the affected side) occurred in breast cancer patients with shoulder pain who were treated with wide local excision and radiation therapy (Shamley et al., 2012). Further, breast cancer survivors performing functional tasks activated the posterior

deltoid, supraspinatus, upper trapezius, and serratus anterior 5.1% more in the affected side ($p < 0.05$), whereas pectoralis major sternal decreased activation ($p < 0.0001$-0.0032) (Brookham et al., 2018). These patients received surgery, chemotherapy, and radiation therapy.

2.3.4 Arm lymphedema

Another important consequence of radiation treatment can be lymphedema in the affected arm. Lymphedema is characterized by regional swelling produced by the accumulation of protein-rich fluid in body tissues. Lymphedema relates to multiple symptoms such as pain, arm heaviness, tightness, and decreased shoulder range of motion. It also negatively impacts the performance of activities of daily living (Deutsch et al., 2008). Lymphedema can be cosmetically unappealing, psychologically distressing, and physically symptomatic. Edemas can lead to upper extremity infections and poor healing after trauma (Gross et al., 2018). The incidence of lymphedema in breast cancer patients after receiving oncological treatment is from 3 to 42 % (Hodgson et al., 2009), and the risk increases with axillary lymph node dissection and radiation therapy, especially axillary radiation (Shah, & Vicini, 2011). The development of lymphedema can be noticeable either immediately, months, or even years following treatment (Shah, & Vicini, 2011).

2.3.5 Intervention programs in breast cancer patients

Exercise is considered an intervention that may help mitigate the effects of oncological treatment. Several systematic reviews and meta-analyses support the use of the exercise in breast cancer patients as a path to improve body composition, life quality and to decrease fatigue (Courneya & Friedenreich, 1999; Hewitt, Mokbel, & Van Someren, 2005; Spence, et al., 2010). However, these studies did not assess whether the chosen exercises effectively

address specific goals for particular populations. Additionally, it remains unclear when the intervention program should be implemented during different phases of breast cancer treatment. Data on exercise intervention programs performed during radiotherapy window are scarce. A few studies used strengthening components in their intervention programs for breast cancer patients during radiation therapy (Steindorf et al., 2014; Kneis et al., 2018; Mustian et al., 2009). However, these interventions as many others noted in the literature were focused on aerobic capacity enhancement, resistance training, and fatigue improvement (Mock et al., 1997; Mock et al., 2001; Mock et al., 2005; Hee-Kim et al., 2013; Schmidt et al., 2006; Hwang et al., 2008; Kirshbaum, 2006). More research is needed to elucidate if strengthening exercises applied within the radiation therapy window can compensate for potential shoulder health indicators impairments.

2.3.6 Rib fragility fractures

2.3.6.1 Incidence

Oncological treatment in breast cancer patients may increase potential for rib fragility fractures. A common radiation dose per session in breast cancer ranges from 12 to 70 Gray (Gray) (Li et al., 2004), and doses greater than 6 Gy in adults are associated with osteonecrosis (Pierce et al., 1992). The causes of rib fractures are multiple, but higher radiation doses (above 50 Gy) are considered major contributors (Pierce et al., 1992). Radiation therapy does not aim at bones, but it may cause changes in the skeletal system. The changes in the bone depend on patient's age, absorbed dose, size of the radiation field, beam energy, and fractionation (Resnick & Kransdorf, 2004). In mature patients, radiation interferes with osteoblast production, leading to decreased matrix production. This phenomenon is called osteoradionecrosis, and it manifests clinically as osteopenia. Rib fragility fractures caused by radiation in breast cancer patients occur

approximately 12 months following radiation (Pierce et al., 1992). However, mechanical changes in the irradiated bone are perceptible earlier. Previous experiments performed in rats showed that increased absorption of the endosteal surface of the irradiated bone area started to be noticeable after 4 weeks of receiving a single dose of 50 Gy of radiation. The porotic changes in the bone become more noticeable at 12 weeks, with a significant decrease in bone strength. This progression reaches its maximum at 24 weeks (Sugimoto et al., 1991). Radiographic images captured within a 12-month window after radiation therapy revealed a heterogeneous bone with accumulation of bone deposits concentrated in certain areas, osteopenia, thick trabeculation, and disorganization of the trabecular architecture.

Rib fragility fractures in breast cancer patients are often misestimated. Rib fractures are commonly manifested in the anterolateral region of the 4^{th}, 5^{th}, and 6^{th} ribs (Mitchell et al., 1998). Moreover, there is an increased risk that the irradiated bone will develop infection and bone sarcomas in the irradiated field (Yi et al., 2009). The incidence of rib fractures in BCS ranges from 2% to 19% (Harris et al., 2016; Overgaard, 1988). Yet, these statistics likely underestimate the true scope as occurrence is often undetected by the patients or even by the health provider, also known as “silent fractures” (Guise, 2006). Although the health community is aware that cancer treatment induces bone loss (Taxel et al., 2012), bone quality assessments in the cancer population are inconsistently prescribed. During a follow-up study of 5.8 years, 66% of breast cancer patients and 53% of cancer-free women reported having a bone density assessment, and 112 incident cases of osteopenia and/or osteoporosis were identified (Ramin et al., 2018).

2.3.6.2 Breast cancer and osteoporosis

Osteoporosis increases the risk of bone loss and consequent fragility fractures in cancer patients. Rib fractures were reported as one of the most common co-morbidities experienced by BCS after receiving treatment in a 5-year prospective cohort study in Australia. Additionally, these rib fractures were most commonly seen in women who were postmenopausal and at a high risk of osteoporosis (Harris, 2016). Nearly 83% of the breast cancer population in Canada consists of females over 50 years old (CCS, 2020). This age group also has an increased risk of osteoporosis. According to the World Health Organization, 45% of women over 50 years old have either osteopenia or osteoporosis (Taxel et al., 2012). In Canada, at least one out of four women over 50 years old will have a fragility fracture related to osteoporosis at some point in their lifetimes (Lorrain et al., 2003). In addition, the risk of developing bone fragility fractures due to osteoporosis is even higher in the cancer population. Up to 80% of breast cancer patients experience bone loss (Runowicz et al., 2016). Despite these alarming statistics, approximately 77% of BCS with osteoporosis were undiagnosed by their health provider (Chen et al., 2005).

2.3.6.3 Screening and assessment of bone quality

The are a few options available for assessment and screening of bone quality. Early screening is a critical element in identifying patients at a high risk of developing bone fragility fractures (Hoff & Gagel, 2005). Still, bone density testing is performed in only 3% to 32% of cancer patients under high risk of bone loss (Guise, 2006). The standard approach to assess bone quality is a dual-energy X-ray absorptiometry (DXA) scan. This tool is accurate (~1-2% error), non-invasive (low radiation dose ~0.5 μSv), rapid, and requires no specific preparation. The DXA measurements are based on the molecular level of a 3-compartment model that comprises fat mass, non-bone lean mass, and bone mineral content (Bazzocchi et al.,2016). The physical

principle behind the DXA scan is the transmission of an x-ray through the body at a high and low energy level. The x-ray source generates a beam of x-rays, and it derives from a set of photon particles conducted within electromagnetic energy. The thickness and density of human tissues attenuate and decrease the beam of x-rays while the photon energy increases. Low-density materials such as soft tissues attenuate the x-ray beam less compared to high-density materials such as bone. The difference of attenuation coefficients at two different peaks of energy is measured by the device providing a specific value called R-value. The R-value is constant for bone and fat in all subjects, whereas it varies among the distinct soft tissues, and it also depends on each subject's soft tissue composition (Bazzocchi et al., 2016). Two-dimension bone mineral density calculation is accomplished through the calculation of a ratio of an area between bone mineral content and bone surface (Giampiero & Baloncelli, 2008).

Quantitative Ultrasound (QUS) is a novel, accessible, inexpensive, and portable tool for repeated measurements in peripheral bone sites. Multiple features of the cortical bone can be extracted using QUS, such as bone elasticity, microstructure, bone matrix constituents, and micro-damage accumulation components, providing a more comprehensive bone fragility evaluation (Raum et al., 2014). Ultrasound velocities from the calcaneus significantly correlated with femoral bone mineral density (from DXA scan), and thus, this device is predictive of osteoporosis status (Hans et al., 1996; Ng & Sundram, 1998; Gluer, 1997). The analysis of the ultrasound signal consists of the measurement of the speed of sound (SOS) and amplitude-dependent SOS (AD-SOS). A decrease in QUS parameters (both velocity and attenuation) was related to a decrease in BMD in populations with disorders or disturbances affecting bone health, as well as in healthy populations with fractures (it has been tested in phalanges, heel and tibia) (Laugier et al., 2004). QUS parameters depend on the bone composition and bone structure, and

the in vivo and in vitro QUS parameters can also detect collagen and organic matrix abnormalities (Laugier, 2004).

Quantitative Computer Tomography (QTC) is applied to assess the bone quality of the appendicular skeleton and the spine (Lang et al., 1998). These devices need calibration to convert their findings into units relevant to BMD. The QTC is very accurate in assessing cancellous bones as it can measure the volumetric density rather than an area-adjusted outcome (like DXA scan) (Lang et al, 1998). The main disadvantages of the QTC scan are the high exposure to radiation, difficulties with quality control, and high cost (Kanis, 2002).

Lastly, another method to assess bone quality is radiography. This method has a very low sensitivity, but it can help to improve diagnosis or in differential diagnosis. Radiographs are usually used in the identification of vertebral deformities produced by osteoporosis that are not of special clinical attention (Kanis, 2002).

2.4 Summary and the Dissertation Motivation

Overall, radiation therapy is effective in reducing both cancer mortality and the risk of breast cancer recurrence. However, many patients in North America decide not to undergo breast irradiation due to the potential short and long-term effects and its cost. Previous research reported the influence of oncological treatment (such as surgery, chemotherapy, radiation therapy, and hormone therapy) on shoulder functional health indicators. However, these studies did not focus on radiation therapy exclusively, and also were performed outside the radiation window. Radiation therapy may cause altered shoulder complex muscle strength and activation, joint range of motion restrictions, and arm lymphedema. However, the causative role of radiation therapy and its extent of influence on physical capacities and dysfunction are unclear. Further,

the extent of the incidence of type and dose of radiotherapy and the development of these shoulder complications is similarly unknown. Lastly, another potential consequence of radiation therapy application in breast cancer patients relates to the appearance of rib fragility fractures. While the DEXA scan is the current gold standard tool to assess bone quality and to predict bone fractures, its application is expensive and impractical for most research and clinical purposes. Therefore, a more accessible and practical tool must be developed to predict rib fragility fractures in breast cancer patients, thus warranting a feasibility study of ultrasonic detection.

Chapter 3 - Quantifying the influence of radiation therapy on functional shoulder health indicators in breast cancer patients: an exploratory study

3.1 Introduction

Oncological treatment for breast cancer patients comprises local and systemic options. Women with primary invasive breast cancer often receive both local and systemic treatment. Local treatments, such as surgery and radiation therapy, reduce the risk of cancer recurrence, prevent spread of the tumor, and also reduce mortality up to 70% (Clarke et al., 2005; Shapiro and Recht, 2001). The adjuvant radiotherapy treatment is usually prescribed five days a week, for a total of six weeks (Ringborg et al., 2001). Breast cancer is more likely to occur in the upper-outer quadrant, which is the quadrant with more breast area and dense area (Lipps et al., 2017). This quadrant is associated with an increased risk of dysfunction in the upper back, shoulder, and arm (Oza et al., 2017).

During radiation treatment, it is common to experience side effects that may affect the patient's well-being, either physically, psychologically, or psychosocially. The most common side-effects reported in a three-month follow-up of 134 breast cancer patients after receiving radiation therapy were fatigue, skin reactions, and pain (Wengstrom et al., 2000). These side-effects worsened as the treatment progressed. During the third month of follow-up, the majority of symptoms persisted. Fatigue was the most prevalent sign, being mild to moderate in 70% of the sample and severe to intolerable in 30% of the patients measured (Wengstrom et al., 2000). Another important side effect relates to a swollen arm. According to a questionnaire administered to breast cancer patients during and after the administration of radiation therapy, a swollen arm presented in 34% of 96 patients at the end of the treatment, 34% of 94 patients at

three weeks post-treatment, and 44% of 95 patients at six months post-treatment (Sjoval et al., 2010).

Shoulder strength and range of motion are reduced in breast cancer patients following radiation therapy treatment. A longitudinal study revealed that 61% of 194 women presented decrements exceeding 20° in range of motion (especially in shoulder abduction), 20% in strength (mainly in shoulder abduction), and 200ml in arm volume. At least 10% of those impairments persisted up to 12 months (Kooststra et al., 2013). The study of Lipps et al (2019) compared nine patients receiving breast-conserving surgery to the breast and axilla (group 1), with nine patients receiving breast conserving surgery with radiation to the breast alone (group 2), and nine healthy controls. The healthy controls evidenced significantly greater differences in shoulder strength compared with the treatment groups (Table 4).

Table 4. Lipps et al (2019) study comparing breast cancer patients receiving breast-conserving surgery to the breast and axilla (group 1), with breast cancer patients receiving conserving surgery with radiation to the breast alone (group 2), and healthy controls.

Shoulder movement	Group 1	Group 2	Controls
Vertical adduction (Nm)	46.5	40.9	61.9
Vertical abduction (Nm)	43.6	40.5	45.9
Horizontal flexion (Nm)	43.7	33.9	40.3
Horizontal extension (Nm)	36.1	26.6	33.6
Internal rotation (Nm)	24.0	21.7	30.2
External rotation (Nm)	25.6	25.9	31.8

Another study also demonstrated that the shoulder strength reduced in adduction (31.9 vs 35.2 Nm.), abduction (23.8 vs 26.4 Nm.), flexion (23.0 vs 27.9 Nm.), extension (11.6 vs 16.6 Nm.), and internal rotation (12.0 vs 15.6 Nm.) in patients who received radiotherapy and modified radical mastectomy versus a control group who only received the mastectomy surgical procedure, measured 15 months after the end of the treatment (Blomqvist et al., 2004). In terms of shoulder range of motion, a mean decrease of 5.5° in shoulder abduction and 2.2° of shoulder flexion in the affected side (Smoot et al., 2016) occurred in breast cancer patients that had surgery and radiation therapy (applied in 70% of the patients). Moreover, Brookham et al (2018) found shoulder complex range of motion decrements in the affected side compared to the non-affected side in breast cancer patients after receiving several oncological treatments including surgery, radiation and/or chemotherapy. The humerothoracic ROM in the plane of elevation was 32.3° vs. 39.0°, $p = 0.0034$ during ROM-Reach tasks, and during ROM-Rotate tasks in the elevation angle was 9.7° vs. 12.0°, $p = 0.0121$; and 15.3° vs. 18.6°, $p = 0.0440$ (Brookham et al., 2018).

Following treatment, breast cancer survivors may use altered neuromuscular control to perform functional tasks. Higher activation in the upper trapezius, rhomboids, and serratus anterior, and lower activation in the sternal head of the pectoralis major occurred on the affected side in breast cancer patients with shoulder pain who were treated with wide local excision and radiation therapy (Shamley et al., 2012). Similarly, in breast cancer patients who received a combination of surgical and systemic treatments, higher activation occurred in the posterior deltoid, supraspinatus, upper trapezius, and serratus anterior on the affected side compared to the unaffected side (Brookham et al. 2018). However, the pectoralis major activity was lower in the same group of patients (Brookham et al. 2018). Serratus anterior was reported to be higher in

patients receiving oncological treatment including radiation therapy compared to the unaffected side or with healthy controls (Brookham et al 2016; Hage, 2014; Shamley et al., 2012). Similarity, latissimus dorsi activation increased ($p < 0.05$) in abduction, extension, flexion, internal rotation and scapular abduction in breast cancer survivors between 1 and 2 years since treatment ended compared with those within 1 year of treatment ending (Maciukiewicz et al., 2022). Radiation therapy is known to affect the pectoralis major muscle the most since it is in the direct field of treatment. The latissimus dorsi and teres major muscles work together with the pectoralis major to produce shoulder horizontal adduction. Therefore, if the pectoralis major muscle decreases its activation, the latissimus dorsi and teres major muscles may increase their activation to compensate and maintain shoulder functionality. However, this hypothesis is yet to be tested within the radiation therapy window.

Lastly, the incidence of lymphedema in BCS following oncological treatment is approximately 3 to 42 % (Hodgson et al., 2009), and the risk increases with axillary lymph node dissection and radiation therapy, especially axillary radiation (Shah, & Vicini, 2011). The development of lymphedema can be noticeable immediately, months, or even years following the treatment (Shah, & Vicini, 2011).

A small number of studies investigated the consequences of oncological treatment related to shoulder strength, muscle activation, shoulder range of motion, and the presence of arm lymphedema. However, no studies isolated the influence of radiation therapy on these measures. This research aims to investigate the shoulder complex range of motion, in addition to the shoulder muscle activity, shoulder strength, and arm lymphedema throughout radiation therapy. Understanding the changes in these measures during the radiation therapy window would allow

clinicians to develop targeted rehabilitation protocols aimed at overcoming changes in shoulder functionality following radiation treatment. Moreover, it would also help to assess the feasibility of the use of wearable devices in the clinic, permitting not only researchers to assess these variables without taking participants into biomechanics laboratories, but also patients to remain in the hospital setting providing more comfort and practicality.

3.2 Objective and Hypothesis

The objective of study 1 was to assess shoulder complex health indicators before the application of radiation and throughout the window of radiation treatment.

The following hypotheses were evaluated by study 1:

1. There would be significant changes in shoulder muscles activation at endpoint assessments compared to baseline and midpoint assessments

1.1 The activation of pectoralis major would be lower in endpoint assessments compared to baseline and midpoint assessments

1.2 The activation of latissimus dorsi, serratus anterior, and teres major would be higher in endpoint assessments compared to baseline and midpoint assessments

2. There would be lower shoulder muscle strength at endpoint assessments compared to baseline and midpoint assessments.
3. There would be lower shoulder complex range of motion at endpoint assessments compared to baseline and midpoint assessments.
4. There would be higher arm circumference at endpoint assessments compared to baseline and midpoint assessments.
5. Radiation dose and fractions would be negatively correlated with reductions in arm strength, activation, and shoulder complex range of motion.

3.3 Methods

3.3.1 Participants

Breast cancer patients receiving radiation therapy were selected for this study. Fourteen breast cancer patients participated in the present study (76.5 ± 15.1 kg, 165.5 ± 6.1cm) (Figure 2). A G*POWER 3.1 (Universitat Kiel, Germany) analysis for repeated measures ANOVA for 1 group, 3 measurements, an alpha of 0.05, a power of 0.8, and a medium effect size, revealed that 39 subjects were needed for the present study. However, due to COVID restrictions and difficulties in patient recruitment, only 14 participants were collected. Despite being underpower, the current sample size is comparable to that of previous studies that tracked similar variables in patients with breast cancer (Guirro, et al., 2019; Garcia- Jeronimo et al., 2023; Magnuson et al., 2023) Participants were recruited directly from the Grand River Hospital (Kitchener, ON) after ethics approval by the Office of Research Ethics at the University of Waterloo (ORE 42902), and Grand River Hospital. Potential participants were referred to the student investigator after the prescription of radiation treatment from Radiation Oncologist. All patients received IMRT (intensity modulated radiotherapy) treatment regimens. The average dose of radiation prescribed to the patients was 32.6 Gy, ranging from 26 Gy to 52.5 Gy, and the average fractions were 9.26, ranging from 5 to 20 (Table 6). The details of radiation treatment location are attached (Table 5). Recruitment criteria was based on the demographics of Waterloo/ Kitchener region to have a representative sample of women of the area. The inclusion criteria were women aged 25 to 75 years old who have been prescribed but have yet to start radiotherapy treatment for breast cancer, unilateral cancer diagnosis, and with mastectomy completed at least 3 weeks prior to participation.

Patients with the following breast surgery were allowed to participate in this study: full or partial mastectomy, modified radical, and lumpectomy. Patients receiving radiation to the breast alone, or radiation to the breast and axillary nodes, patients with cancer recurrence, and women who were diagnosed with metastatic cancer, were also recruited. Exclusion criteria was radical breast surgery, postmastectomy or augmented breast reconstruction, a recent history of rehabilitation after receiving mastectomy and taking medication that may affect the neuromuscular performance, patients who were experiencing shoulder pain/discomfort, and patients with muscle invasion of tumor. The surgical procedures and adjuvant treatment received by the patients of this cohort are detailed below (Table 4). Only female participants were recruited as women constitute the majority of breast cancer disease (less than 1% of breast cancers occur in men) (CCS, 2020). Participants were in the evaluation room for approximately 30 minutes, and there were three evaluation sessions. The initial assessments (i.e. baseline) were performed approximately one week before the start of the radiation treatment. The second assessments were completed at the midpoint of the treatments, and the third assessments on the last day of the therapy.

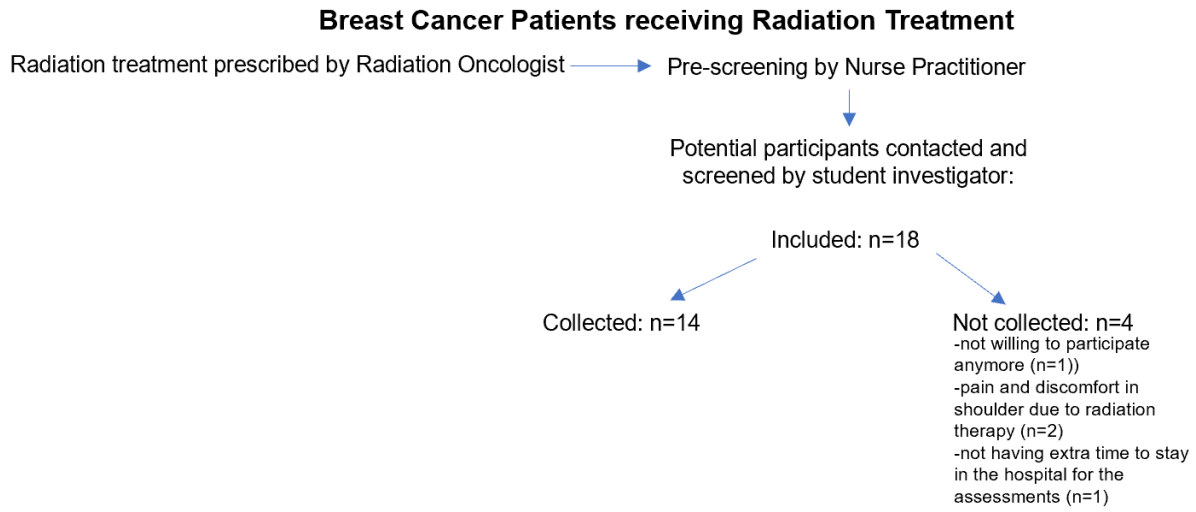


Figure 2. Diagram outlining recruitment and retention of participants in the study.

Table 5. Surgical procedures and adjuvant treatment received by participants.

Surgical procedures	Number of participants receiving surgery	Adjuvant treatment	Number of participants receiving treatment
Lumpectomy	11	Anastrazole	5
		Letrozole	3
		Tamoxifen	3
Mastectomy	3	Chemotherapy	1
		None	2

Table 6. Radiation dose and fractions treatment plans

Treatment plan		Boost?	
Radiation Dose	Radiation Fractions	Radiation Dose	Radiation Fractions
26	5		
26	5	5	10
26	10		
26	5		
26	5	5	10
26	5		
26	5	5	10
26	5	5	10
26	5	5	10
40	15		
26	5	5	10
26	5	5	12.5
26	5		
42.5	16	10	4

Table 7. Radiation treatment location for all patients

Radiation treatment location details	Number of participants
Right breast with boost to surgical cavity	2
Right breast with boost to seroma	1
Right breast	3
Left breast	3
Right breast with boost to tumor bed	1
Left chest wall	1
Left breast with boost to tumor bed	2
Right chest wall and axilla	1

3.3.2 Hand-held dynamometer Instrumentation

Strength was recorded with an ‘Ergo Fet’ hand-held dynamometer (Hoggan Health Industries, Inc, West Jodan, UT). The dynamometer was placed about four fingers above the elbow joint at the midline point to test shoulder flexion, extension, abduction, and adduction (Figure 3), and four fingers above the wrist joint at the midline to test shoulder external and internal rotators. During strength measurements, the participants were instructed to produce maximum force in the desired direction for five seconds, while the examiner maintained static resistance. A standard cue of “ready, set, go” was used at the beginning of each trial. Experimental details of the assessments are found in session 3.3.6.1

Figure 3. Shoulder strength test using hand-held dynamometer

3.3.3 Surface Electromyography

Muscle activity evaluation of pectoralis major (sternal insertion), latissimus dorsi, serratus anterior, and teres major was measured using four skin-mounted Shimmer patches (Shimmer Sensing, Dublin, LE, Ireland) (Figure 4; Table 8). Ground-reference electrodes were placed at the acromion and clavicle. In order to keep consistency of the electrode placement throughout the three evaluation sessions, a picture of the location of the electrodes was taken during the first session. Both trials and MVC were sampled at 1500Hz, raw EMG signals were band-pass filtered from 10-500Hz and differentially amplified (Common Mode Rejection Ratio (CMRR) >100dB at 60Hz, input impedance 100MΩ). The skin overlying the muscle target area was cleansed with abrasive gel and a wet cloth. This cleansing intended to ensure that the signal recorded with the wearable sensor is without interference from dead skin cells. After the patch placement on each muscle, the participants were asked to perform muscle-specific maximal voluntary contractions (MVCs) against the researcher arm (Table 8). These maximal contractions were important for subsequent normalization of the raw EMG signals to the maximum in post-processing steps.

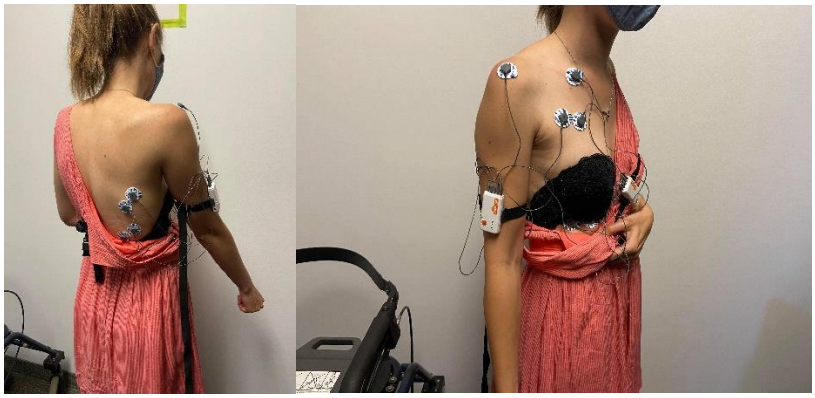


Figure 4. Shimmer wearable sEMG with patches adhered to the skin.

Table 8. Electrode placement and MVC postures (Cram & Kasman, 2010).

Muscle	Electrode Placement	MVC Posture
Pectoralis major (sternal head)	Medial to the axillary fold with the arm medially rotated, horizontally on the chest wall, over the muscle mass 2 cm out from the axillary fold	Subject stands upright, elbow and shoulder are flexed to 90º, participant exerts upwards and inwards
Teres Major	Along the lateral scapula, 2-3cm above the inferior angle.	Subject stands upright, with elbow flexed and hand resting at gluteus maximum region, participant resists shoulder flexion.
Latissimus Dorsi	Approximately 4 cm below the inferior angle of the scapula, half the distance between the spine and the lateral edge of the torso, oriented slightly oblique at approximately 25°	Subject stands upright, with elbow fully extended, arm in adduction and internal rotation position. Participant resists shoulder abduction and flexion.
Serratus Anterior	Over the seventh rib, one electrode posterior and the other anterior to a point in the midaxillary line.	Subject presses fist against opposite palm while maintaining 90º of shoulder flexion and 125º of shoulder abduction.

3.3.4 Tri-axial accelerometer Instrumentation

Inertial motion capture was used to estimate shoulder complex range of motion through an embedded 3-axis accelerometer (±200 g) and 3-axis gyroscope (±2000 deg/s) inertial motion units (IMUs) (Shimmer Sensing, Dublin, LE, Ireland) (Rodrigues et al., 2019) (Figure 5). The sensor was placed at the anterior side of the wrist, across the joint midline. For shoulder flexion and abduction trials, the entire upper limb was considered a rigid link segment; therefore, the elbow must be kept fully extended while the movement is being captured. For shoulder external rotation, the forearm was considered a rigid link segment. The IMU was secured on the body with elastic and Velcro straps. The mounting orientation of the IMU remained consistent across

all participants. Orientation estimates was derived from the combined acceleration and angular velocity data.

Figure 5. Shimmer Tri-axial accelerometers placed on subject's wrist and chest.

3.3.5 Video recordings

A supporting motion capture method was used in case the IMU failed during data recording. Video recordings of each movement were performed using a smart phone camera.

3.3.6 Experimental protocol

Following, is an overview of the protocol chapter. The measurements were performed on the patient's affected arm. The comparison of each target was made between the affected limbs within the assessments. No comparisons were made between the affected and unaffected limbs (see sections 3.3.6.1 to 3.3.6.4). Participants filled out informed consent at the beginning of the session. Information regarding surgical procedures and adjuvant treatment received by each participant as well as radiation dose and fractions, were provided by the Nurse Practitioner upon

participants' authorization. Arm circumference measurements occur first, followed by the placement of Shimmer skin patches for the sEMG testing in conjunction with the strength assessments. Two trials of maximal voluntary contractions of shoulder flexion, extension, abduction, adduction, external and internal rotation were collected, followed by a single trial of muscle-specific MVCs. Subsequently, muscle activity was recorded while the participant performed the same strength evaluation tasks but holding a strength-scaled (30%) dumbbell (Figure 7). Lastly, the IMU was placed for the shoulder complex range of motion evaluation. All the shoulder functional indicators were used for Study 2 for testing the efficacy of the intervention shoulder strength program and is outlined in section 4.3.3 (page 83).

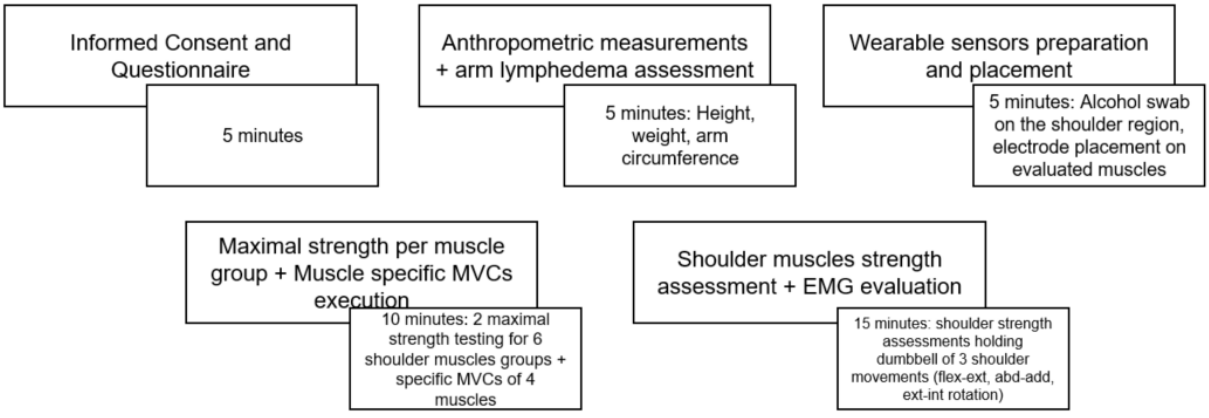


Figure 6. Overview of the components evaluated at each section of data collection.

A  B. 

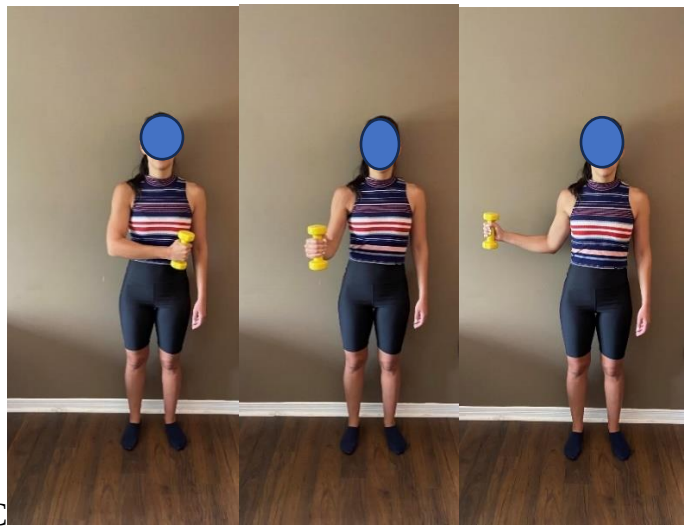
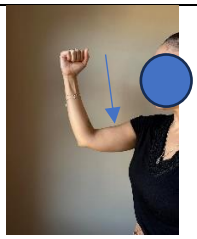
C 

Figure 7. Muscles activation evaluation tasks at 30% of maximal voluntary force. A: Shoulder flexion/extension. B: Shoulder abduction/ adduction. C: Shoulder external/ internal rotation

3.3.6.1 Maximal Strength Assessment

Participants were asked to slowly ramp to a maximum, hold the exertion for 3 seconds, and then slowly ramp down. Verbal encouragement was provided. There was a 30-second pause between the trials and one minute between each testing position. The measurements were completed as shown in Table 9 (Blomqvist et al., 2004).

Table 9. Body segments position for shoulder strength assessment.

Flexion	Standing in upright position, shoulder at 45° of flexion and 0° of abduction.	
Extension	Upright position, shoulder at 10° of extension and 0° of abduction.	
Abduction	Standing in upright position, shoulder at 45° of abduction	
Adduction	Standing in upright position, shoulder at 90° of flexion and 0° of abduction.	
External and internal rotation	Standing in upright position, shoulder at 90° of abduction, and elbow at 90° of flexion.	

3.3.6.2 Muscle activation

Firstly, the participants were asked to perform the maximal strength assessments and muscle activation was also recorded. Subsequently, the MVCs measurement took place. For every muscle MVC, the participants were asked to push as hard as they could. They were verbally encouraged throughout the trial. Participants were asked to slowly ramp to a maximum, hold the contraction for 3 seconds, and then slowly ramp down. The patient stood in upright position for performing all MVCs as described in Table 6. Thirty seconds of rest were provided in between. The MVC protocol was the same for all the assessment across treatment. After the execution of MVCs, the participants were instructed to perform analogous submaximal assessment tasks: shoulder flexion, extension, abduction, adduction, external, and internal rotation while holding a dumb-bell, representing 30% of the maximum voluntary force (Figure 7). This 30% was calculated according to the hand-held dynamometer output of the patient's performance on each strength task (this test assumed the patient was performing at their maximum capacity).

3.3.6.3 Range of motion

The patient remained in standing position, ensuring that the trunk was straight throughout the data collection. Calibration movements consisted of 3 repetitions of each of the following movements: dynamic 90 degrees of shoulder flexion, dynamic 90 degrees of shoulder abduction, trunk leaning to both right and left sides, trunk leaning to right side with pro/supination of the wrist, trunk forward flexion until reaching the toes, hold 90 degrees of shoulder flexion for 3 seconds, and hold 90 degrees of shoulder abduction for 3 seconds (Figure 8). After calibration was completed, the participant was instructed to perform the following movements: shoulder flexion, abduction, and external rotation. The baseline posture for shoulder flexion was

anatomical position, and patients were instructed to flex their shoulder as much as possible. For shoulder external rotation, the baseline posture was standing with the elbow bent at a 90-degree angle and the forearm against the trunk, and patients were instructed to rotate their arm outward as much as possible until the hand was pointing away from their body. Finally, for shoulder abduction, the baseline posture was anatomical position, and patients were instructed to abduct their shoulder as much as possible.

Figure 8. Calibration movements for tri-axial accelerometer

3.3.6.4 Arm circumference

A lymphedema assessment was performed with a measuring tape through arm circumference measurement of the affected arm. The site assessed was the estimated midpoint of the upper arm (Chen, Tsai, Hung, & Tsauo, 2008) (Figure 9). The participant's hand rested on a pillow, and the circumference was measured using tape.

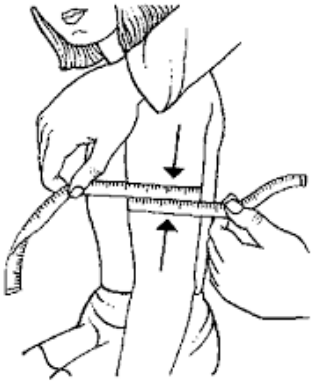


Figure 9. Arm lymphedema assessment using measuring tape placed at the midpoint of the upper arm.

3.4 Data analysis

3.4.1 Peak force data

The peak force data was obtained from the selected shoulder strength motions. Peak force data was obtained from each isometric strength trial. These parameters represent the isometric strength in each evaluated shoulder strength motion (flexion, extension, abduction, adduction, external rotation, and internal rotation). Two isometric measurements of each muscle group were taken, and the average was used for further analysis. Force was reported in N. The torque generated by the muscle was not calculated in this study because the moment arm of the joint was not tracked. Instead, the study focused on measuring the force exerted at the greatest moment arm of each specific movement. This approach was selected based on previous research assessing arm strength in breast cancer patients (Harrington et al., 2011; Merchant et al., 2008). The study did not aim to calculate the torque at different joint angles.

3.4.2 Muscle activation data

The muscle activation data were obtained and analyzed from each movement task and normalized to the correspondent muscle specific MVC. Raw EMG signals were processed using Matlab 2022b (Mathworks, USA). The signal of each muscle was corrected for resting bias by subtracting the mean of the raw trial from each time point. To reduce heart rate contamination from all trials, a high-pass, second-order, dual-pass Butterworth filter with a cut-off frequency of 30Hz was applied (Drake & Callaghan, 2006). The signal was filtered using a second-order, single-pass Butterworth filter with a cut-off frequency of 2.5Hz after full-wave rectification. For each participant, the average value of the EMG amplitude was extracted from a time window between 3.5 and 5.5 seconds for each muscle MVC and all subsequent submaximal trials were normalized to this value. Averaged normalized EMGs were extracted from each repetition of each performed trial for analysis. Average amplitude EMG has been used in previous research assessing muscle activation in breast cancer patients (Maciukiewicz et al., 2022; Lulic- Kuryllo et al., 2023).

3.4.3 Range of motion data- tri-axial accelerometer orientation

The shoulder complex range of motion data was obtained and analyzed from an IMU and recorded on each selected shoulder movement task. The IMU data was recorded at 128 Hz and saved into the device internal storage. Angular acceleration (rad/s) and velocity (m/s) were low pass filtered at 15Hz.

Madgwick and Mahony algorithms were used to estimate the orientation of the IMU from raw sensor data and to reduce the integration drift (El-Gohary & McNames., 2012). These algorithms were used in previous studies, and it estimates the orientation derived from combined acceleration and angular velocity data (Goodwin et al., 2021). They use the angular velocity signal to estimate the orientation during periods with significant body acceleration and use the acceleration signal to update or correct the orientation during periods in which the measured acceleration is closed to the acceleration of gravity (Goodwin et al., 2021).

The humero-thoracic rotations (Y-X-Y') (Wu et al., 2005) were described as follows:

E1: Glenohumeral plane of elevation (being 0 deg pure abduction, and 90 deg pure flexion).

E3: internal rotation (positive) and external rotation (negative).

E2: elevation (negative).

The segment and local coordinate system for the upper arm (Wu et al., 2005) (Figure 10) were defined as:

- Positive y axis: Line between humeral head and elbow joint center (midpoint between lateral and medial epycondyles) pointing upwards.
- Positive x axis: Cross product of y axis and temporary z axis (line formed between lateral and medial epicondyle), pointing forwards.
- Positive z axis: Cross product of y and x axes, pointing to the right.

The body segmental anatomical frames from IMU data were obtained using the 'functional alignment' calibration method. In this method, participants completed different known

movements to estimate ‘Y’ and ‘temporary Z’ anatomical axes in an IMU-fixed frame of reference (Vitali & Perkins., 2020):

- Z temporary anatomical axis: Was determined by dynamic flexion movement until 90 deg of shoulder flexion.
- Y anatomical axis: Was determined by leaning the trunk to the side.

The orientation of the upper extremity with respect to the world reference frame was estimated using the orientation of the IMU and the orientation of the anatomical axes relative to the IMU-fixed reference frame.

Averaged ROM values were taken across two trials of each movement. Coding and calculations were performed through Matlab^{TM} 2022b (Mathworks Inc., USA).

For the video recordings (2D), the data was analyzed using Kinovea software (a free 2D motion analysis software under the GPLv2 license), with the ‘track angles’ feature. 2D data was used in 5 subjects, 8 assessments. The video recordings were used as a backup method in case the IMU failed to work. During the data processing process, some IMU files could not be used due to multiple reasons, including file corruption, noisy signals, and device failure to track the data. In these cases, backup 2D data was used. The videos were recorded from different planes to track shoulder movements: sagittal plane for flexion, transverse plane for external rotation, and front plane for abduction.

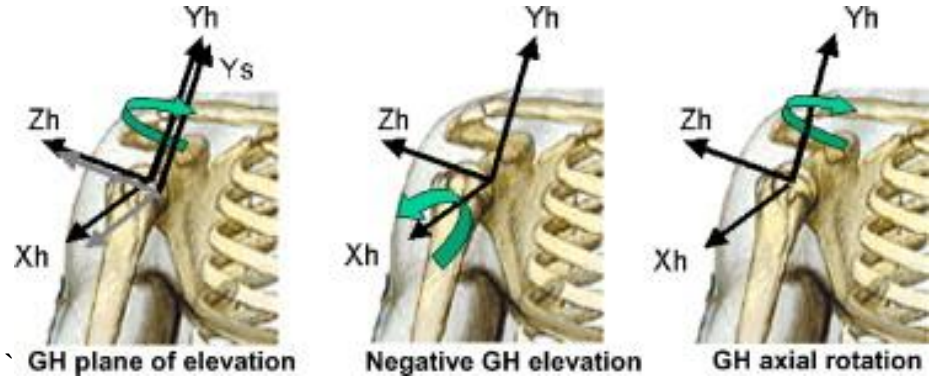


Figure 10. Humerus coordinate system definition and glenohumeral joint motions (Wu et al., 2005)

3.4.4 Arm circumference data

Arm circumference data (cm) was obtained from each measuring tape assessment. These parameters evaluated the presence of arm lymphedema due to the application of radiation therapy. Three measurements of the site were collected and averaged for further analysis.

3.5 Statistical analysis

Statistical analysis was performed using JASP (Version 0.18.1.0; JASP Team, 2023), a free and open-source statistical software package. Repeated measures ANOVA were used to identify differences in shoulder muscles activation, arm strength, and range of motion between baseline-midpoint-endpoint levels. Statistical significance was set to $p < 0.05$. Post hoc Tukey-Kramer HSD identified significant differences between levels. The normality of the data was assessed using Shapiro- Wilk test and found to be non-parametric. However, the distribution of skewness was approximately symmetric, and the sample size met the criteria for the central limit theorem. As a result, ANOVA remained a viable option for producing reliable results. A multiple linear regression model was performed for each dependent measurement accounting for radiation dose and radiation fractions as predictor variables. Correlation coefficients and p values were

extracted for linear relationships between each predictor and outcome variable. Only successful models with $p<0.05$ were included for interpretation.

Table 10. Summary of outcomes measurements for study 1.

Assessment	Dependent measurements	Covariates
Arm strength assessment	Shoulder flexion peak force Shoulder extension peak force Shoulder abduction peak force Shoulder adduction peak force Shoulder external rotation peak force Shoulder internal rotation peak force	Radiation dose Radiation fractions
Shoulder muscle activation assessment	Pectoralis major mean activation Teres major mean activation Latissimus dorsi mean activation Serratus anterior mean activation	
Shoulder range of motion assessment	Shoulder flexion Shoulder abduction Shoulder external rotation	
Arm lymphedema assessment	Arm circumference	

3.6 Results

Shoulder muscle activation patterns and shoulder abduction range of motion changed across radiation treatment. There were decreases in latissimus dorsi activation from baseline to midpoint in the three evaluated movements, and from baseline to endpoint in flexion-extension and abduction-adduction movements. Teres major activation decreased from baseline to endpoint in flexion-extension and external- internal rotation movements. Shoulder abduction range of motion decreased from baseline to endpoint. Radiation dose was negatively correlated with shoulder abduction (Table 11).

Table 11. Summary of differences between assessments. The data of muscles strength, activation, and shoulder complex range of motion is presented per task: flexion-extension (Flex-Ext), abduction-adduction (Abd-Add), and external-internal rotation (ER-IR). The outcomes of the comparisons are presented between baseline and endpoint assessments (B-E), between baseline and midpoint assessments (B-M), and between midpoint and endpoint assessments (M-E). The arm circumference data is presented for baseline, midpoint, and endpoint assessments. Significant decrease is represented by the arrow ⇩ whereas absence of significant changes is represented by the symbol ⊘

		Evaluated movements								
		Flex- Ext			Abd- Add			ER-IR		
		B-E	B-M	M-E	B-E	B-M	M-E	B-E	B-M	M-E
Muscle Activation	Latissimus Dorsi	⇩	⇩	⊘	⇩	⇩	⊘	⊘	⇩	⊘
	Teres Major	⇩	⊘	⊘	⊘	⊘	⊘	⇩	⊘	⊘
	Pectoralis Major	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘
	Serratus Anterior	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘
Arm Strength		⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘
Range of motion		⊘	⊘	⊘	⇩	⊘	⊘	⊘	⊘	⊘
Arm Circumference		⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘	⊘

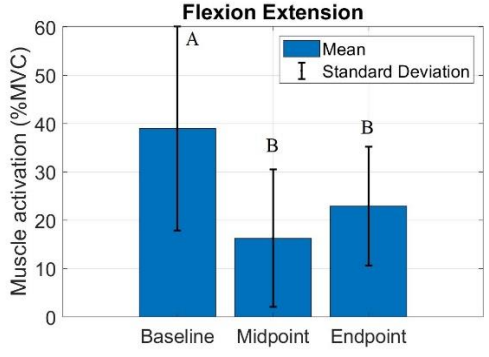
3.6.1 sEMG

3.6.1.1 Changes of shoulder muscles activation across baseline, midpoint, and endpoint assessments

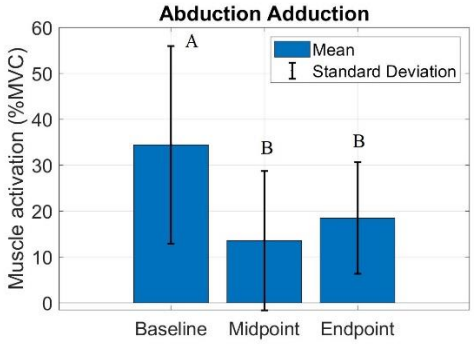
3.6.1.1.1 Latissimus Dorsi

Latissimus dorsi activation decreased progressively across radiation treatment. There was a significant difference in latissimus dorsi activation between baseline and midpoint ($p = 0.04$) and between baseline and endpoint ($p = 0.03$) for flexion- extension movement tasks. There was also a significant difference between baseline and endpoint ($p = 0.03$) and between baseline and midpoint ($p = 0.007$) for abduction-adduction movement tasks. Finally, there was a significant difference between baseline and midpoint ($p = 0.01$) for external-internal rotation movement tasks (Table 12) (Figure 11).

A.



B.



C.

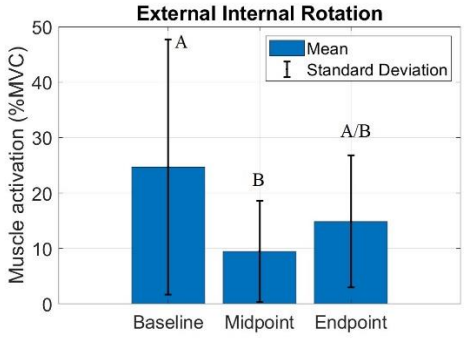


Figure 11. Plots representing the mean latissimus dorsi activation and the standard deviation for flexion-extension (A), abduction-adduction (B) and external- internal rotation (C) movement tasks in baseline, midpoint, and endpoint scenarios. Data points not sharing the same letter are significantly different ($p < 0.05$)

3.6.1.1.2 Teres Major

Teres major activation decreased across radiation treatment. There was a significant difference in teres major activation between baseline and endpoint ($p = 0.04$) for flexion-extension movement tasks. There was also a significant difference between baseline and endpoint ($p = 0.03$) for external-internal rotation movement tasks. No significant difference was found for abduction-adduction movement tasks (Table 12) (Figure 12).

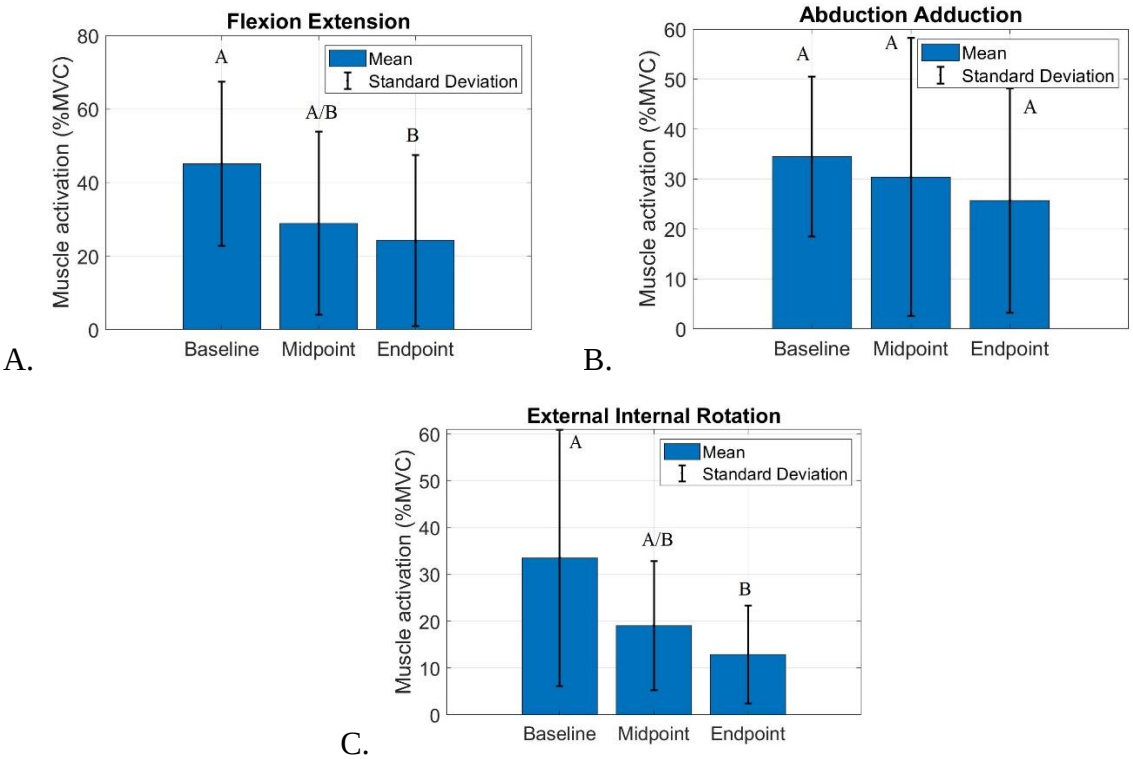


Figure 12. Plots representing the mean teres major activation and the standard deviation for flexion-extension (A), abduction-adduction (B) and external- internal rotation (C) movement tasks in baseline, midpoint, and endpoint scenarios. Data points not sharing the same letter are significantly different ($p < 0.05$)

3.6.1.1.3 Pectoralis Major

Pectoralis major activation remained unchangeable during radiation treatment. There were not significant differences in pectoralis major activation between baseline, midpoint, and endpoint for any of the evaluated movement tasks ($p > 0.05$) (Table 12) (Figure 13).

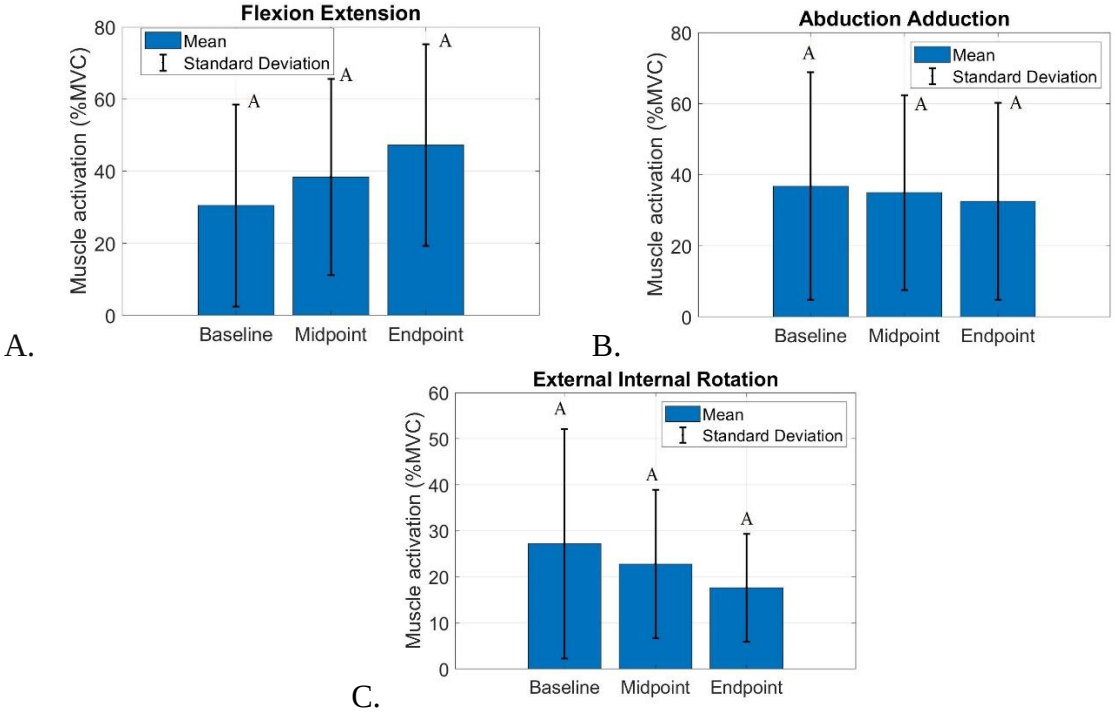
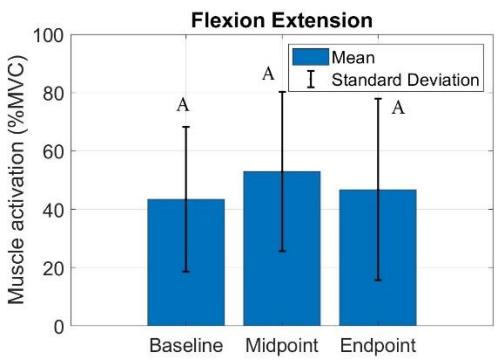


Figure 13. Plots representing the mean pectoralis major activation and the standard deviation for flexion-extension (A), abduction-adduction (B) and external- internal rotation (C) movement tasks in baseline, midpoint, and endpoint scenarios. Data points not sharing the same letter are significantly different ($p < 0.05$)

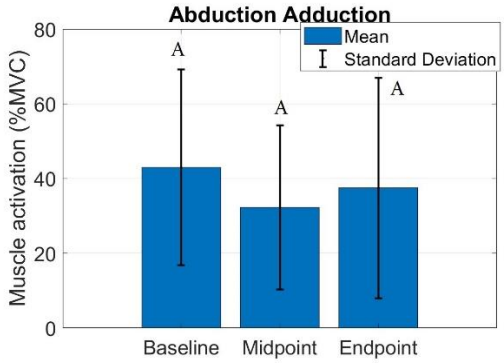
3.6.1.1.4 Serratus Anterior

Serratus anterior activation did not change during radiation treatment. There were not significant differences in serratus anterior activation between baseline, midpoint, and endpoint for any of the evaluated movement tasks ($p > 0.05$) (Table 12) (Figure 14).

A.



B.



C.

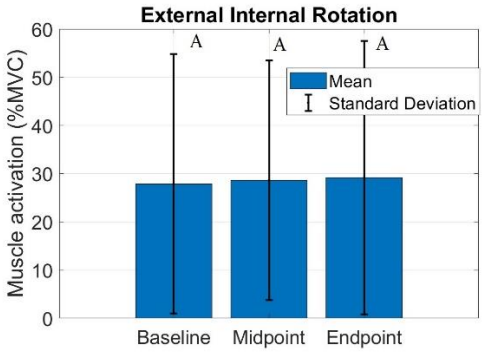


Figure 14. Plots representing the mean serratus anterior activation and the standard deviation for flexion-extension (A), abduction-adduction (B) and external- internal rotation (C) movement tasks in baseline, midpoint, and endpoint scenarios. Data points not sharing the same letter are significantly different ($p < 0.05$)

Table 12. Repeated measures ANOVA results for latissimus dorsi, teres major, serratus anterior, and pectoralis major activation normalized to %MVC per muscle in the three movement evaluation tasks (A) and Tukey-Kramer HSD Post Hoc results for significant findings (B).

A.

		p value		p value		p value
Latissimus dorsi	Flex_Ext	0.04 (a)	Abd_Add	0.01 (b)	ER_IR	0.02 (c)
Teres Major	Flex_Ext	0.04 (d)	Abd_Add	0.667	ER_IR	0.037 (e)
Pectoralis Major	Flex_Ext	0.394	Abd_Add	0.891	ER_IR	0.336
Serratus Anterior	Flex_Ext	0.727	Abd_Add	0.489	ER_IR	0.993

B.

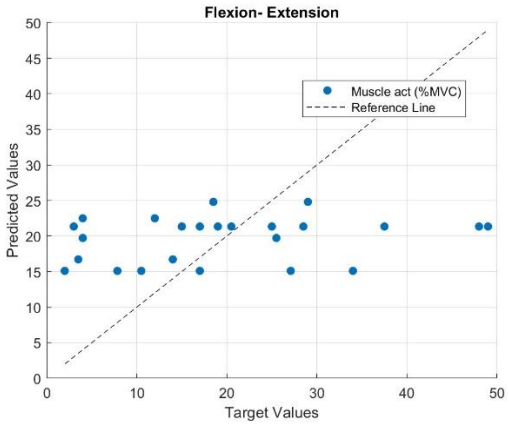
	p value	levels	Cohen's d
(a)	0.04	baseline-midpoint	1.391
	0.03	baseline-endpoint	0.984
(b)	0.007	baseline-midpoint	1.245
	0.03	baseline-endpoint	0.953
(c)	0.018	baseline-midpoint	0.958
(d)	0.04	baseline-endpoint	0.888
(e)	0.039	baseline-endpoint	1.103

3.6.1.2 Radiation dose and radiation fractions as covariant for shoulder muscles activation in baseline, midpoint, and endpoint assessments

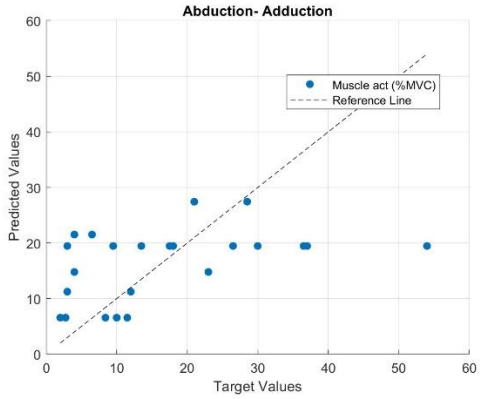
A multiple linear regression was used to test if radiation dose and fractions significantly predicted muscles activation. A regression model was statistically significant in endpoint assessments of flexion-extension movement tasks for pectoralis major activation (r = 0.698, r ^ 2 = 0.488, p = 0.049). It was noted that radiation fractions positively predicted pectoralis major activation with a strength of p = 0.05. Another regression model was statistically significant in endpoint assessments of abduction-adduction movement tasks for pectoralis major activation (r = 0.786, r ^ 2 = 0.618, p = 0.013). However, none of the predictor variables were individually significant (p > 0.05) (Table 13) (Figure 15).

Figure 15. Multiple linear regression scatter plot for target radiation dose and fractions versus predicted values of latissimus dorsi (a-b-c), teres major (d-e-f), pectoralis major (g-h-i), and serratus anterior (j-k-l) activation at flexion- extension, abduction-adduction, and external- internal rotation movement tasks.

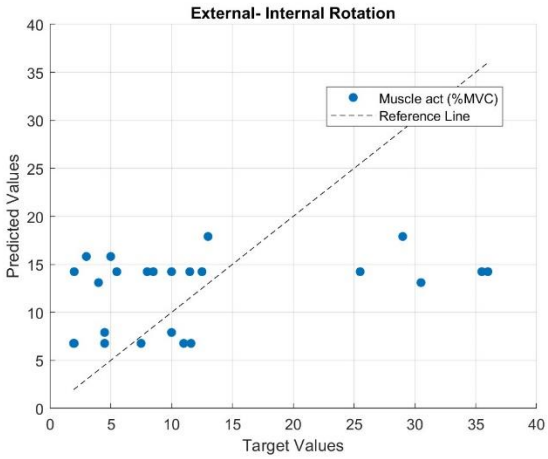
a.



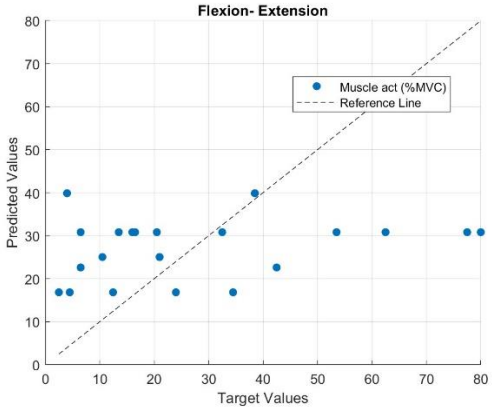
b.



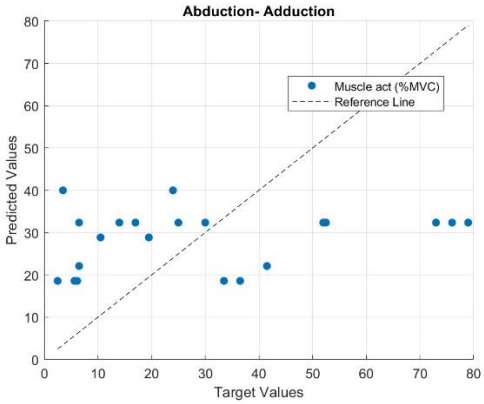
c.


External- Internal Rotation
Muscle act (%MVC)
Reference Line
Predicted Values
Target Values

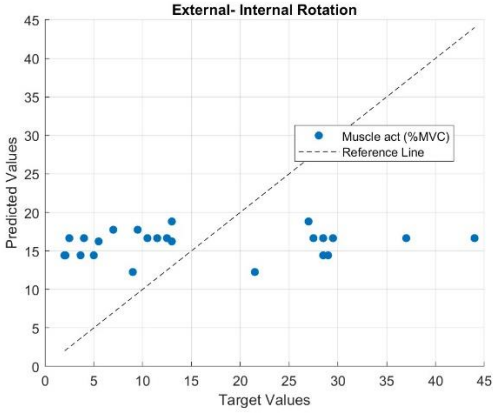
d.


Flexion- Extension
Muscle act (%MVC)
Reference Line
Predicted Values
Target Values

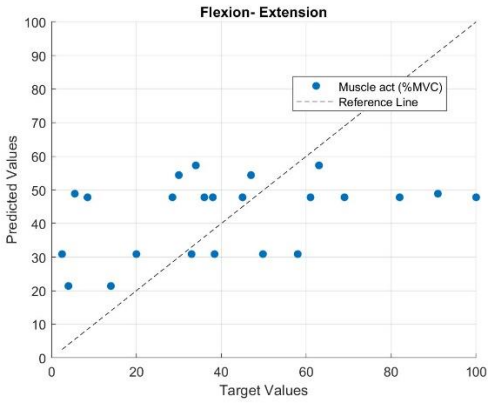
e.


Abduction- Adduction
Muscle act (%MVC)
Reference Line
Predicted Values
Target Values

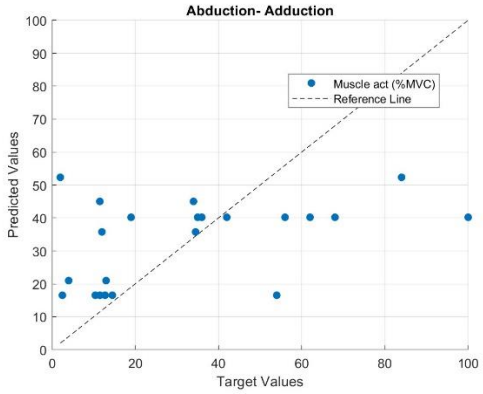
f.


External- Internal Rotation
Muscle act (%MVC)
Reference Line
Predicted Values
Target Values

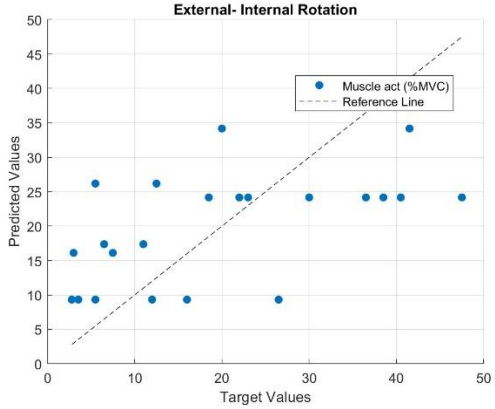
g.


Flexion- Extension
Muscle act (%MVC)
Reference Line
Predicted Values
Target Values

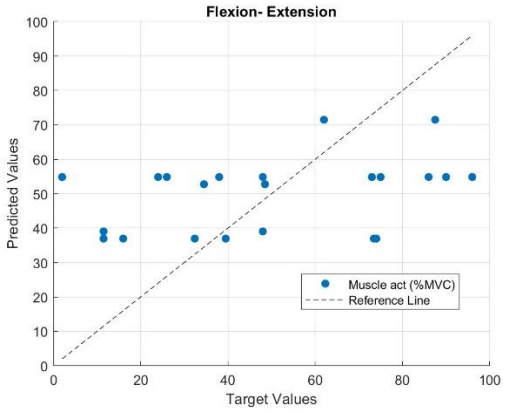
h.


Abduction- Adduction
Muscle act (%MVC)
Reference Line
Predicted Values
Target Values

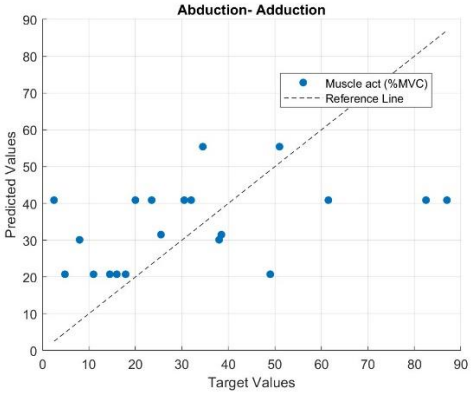
i.


External- Internal Rotation
Muscle act (%MVC)
Reference Line
Predicted Values
Target Values

j.


Flexion- Extension
Muscle act (%MVC)
Reference Line
Predicted Values
Target Values

k.


Abduction- Adduction
Muscle act (%MVC)
Reference Line
Predicted Values
Target Values

l.

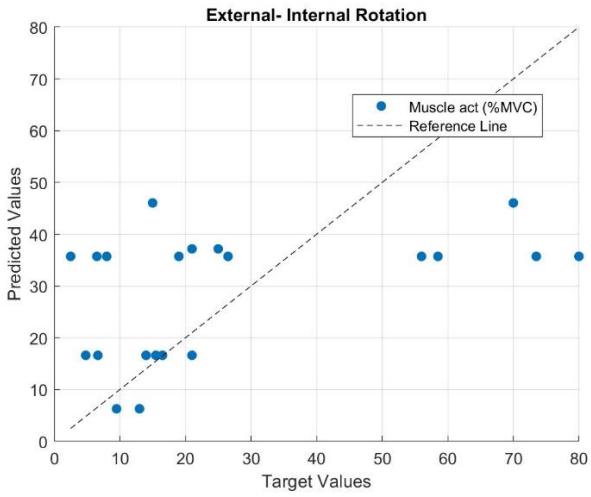

External- Internal Rotation
Muscle act (%MVC)
Reference Line
Predicted Values
Target Values
0
10
20
30
40
50
60
70
80

Table 13. Multiple linear regression analysis results for latissimus dorsi, teres major, serratus anterior, and pectoralis major muscles for the three movement evaluation tasks, in midpoint and endpoint scenarios. Flex_Ext = Shoulder Flexion- Extension movement task, Abd_Add = Shoulder Abduction – Adduction movement task, ER_IR = Shoulder External- Internal Rotation movement tasks, Rad_F = radiation fractions, Rad_D = radiation dose, CI = Confidence Interval, t = t value (Coefficient estimate/ st error): negative sign (–) stands for negative correlation, positive sign (+) stands for positive correlation

Latissimus Dorsi

Flex_Ext						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.114	0.337	0.942	0.425	0.651	0.408

Abd_Add						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.430	0.655	0.399	0.592	0.769	0.144

ER_IR						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.619	0.786	0.114	0.397	0.630	0.462

Teres Major

Flex_Ext						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.2338	0.483	0.793	0.524	0.723	0.277

Abd_Add						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.220	0.469	0.819	0.494	0.702	0.327

ER_IR						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.075	0.273	0.975	0.258	0.507	0.734

Pectoralis Major

Flex_Ext						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.283	0.531	0.687	0.698	0.835	0.049
	Coefficients			Coefficients		
	t	p value	St error	t	p value	St error
Rad_F	-3.354	6.545	2.188	2.268	0.050	1.675
Rad_D	-0.864	0.410	3.849	-0.207	0.841	2.947
	95 % CI			95 % CI		
	lower	upper		lower	upper	
Rad_F	-3.354	6.545		0.009	7.589	
Rad_D	-12.032	5.380		-7.276	7.589	

Abd_Add						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.327	0.571	0.602	0.786	0.886	0.013
	Coefficients			Coefficients		
	t	p value	St error	t	p value	St error
Rad_F	1.033	0.329	2.167	1.133	0.286	1.432
Rad_D	-0.780	0.456	3.811	1.878	0.093	2.518
	95 % CI			95 % CI		
	lower	upper		lower	upper	
Rad_F	-2.664	7.139		-1.616	4.860	
Rad_D	-11.593	5.650		-0.966	10.426	

ER_IR						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.592	0.769	0.143	0.603	0.776	0.131

Serratus Anterior

Flex_Ext						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.600	0.774	0.168	0.187	0.432	0.868

Abd_Add						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.548	0.740	0.240	0.349	0.590	0.595

ER_IR						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.490	0.7	0.334	0.560	0.748	0.223

3.6.2 Arm strength

3.6.2.1 Changes of arm strength across baseline, midpoint, and endpoint assessments

Arm strength remained unchangeable during radiation treatment. There were not significant differences in arm strength between baseline, midpoint, and endpoint for any of the evaluated movement tasks ($p > 0.05$) (Table 14) (Figure 16).

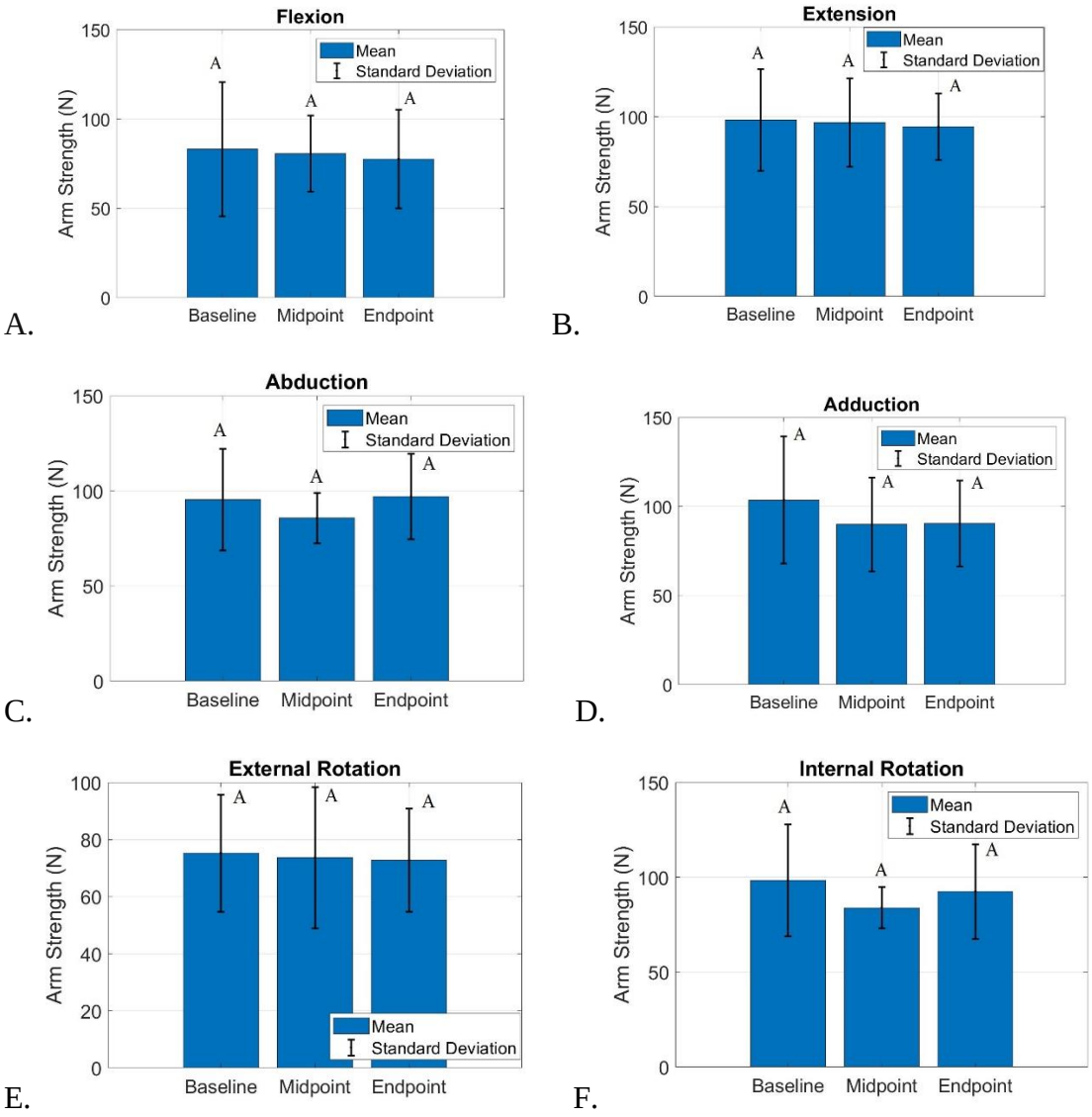


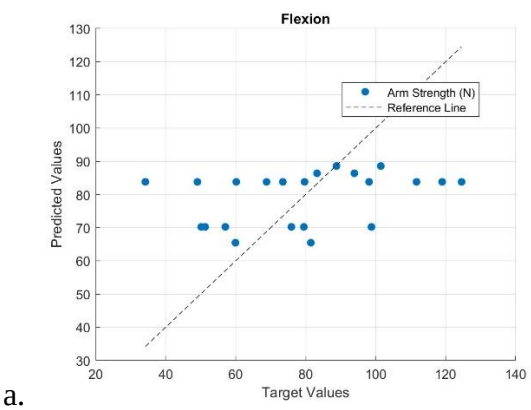
Figure 16. Plots representing the mean arm strength and the standard deviation for flexion (A) extension (B), abduction (C), adduction (D), external rotation (E), and internal rotation (F) movement tasks in baseline, midpoint, and endpoint scenarios. Data points not sharing the same letter are significantly different ($p < 0.05$)

Table 14. Repeated measures ANOVA results for arm strength in the three movement evaluation tasks. Flex = Flexion, Ext = Extension, Abduction = Abd, Adduction = Add, External Rotation = ER, Internal Rotation = IR.

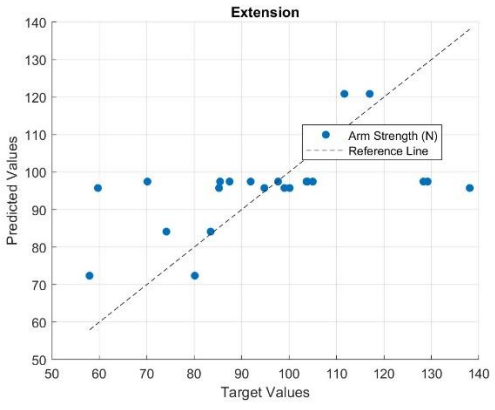
	p value
Flex	0.845
Ext	0.89
Abd	0.253
Add	0.224
ER	0.938
IR	0.217

3.6.2.2 Radiation dose and radiation fractions as covariant for arm strength in baseline, midpoint, and endpoint assessments

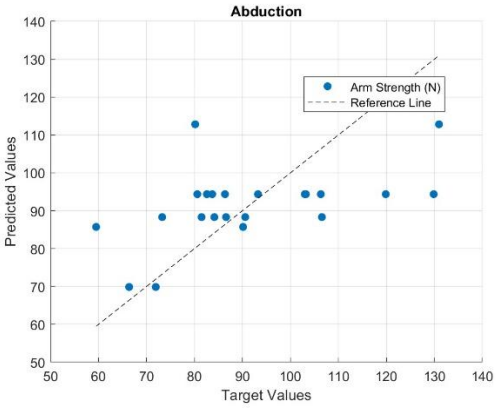
A multiple linear regression was used to test if radiation dose and fractions significantly predicted arm strength. A regression model was statistically significant in endpoint assessments of shoulder abduction strength ($r = 0.721$, $r \wedge 2 = 0.519$, $p = 0.05$). It was noted that radiation fractions negatively predicted shoulder abduction strength with a strength of $p = 0.05$. Additionally, radiation dose positively predicted shoulder abduction strength with a strength of $p = 0.01$ (Table 15) (Figure 17).



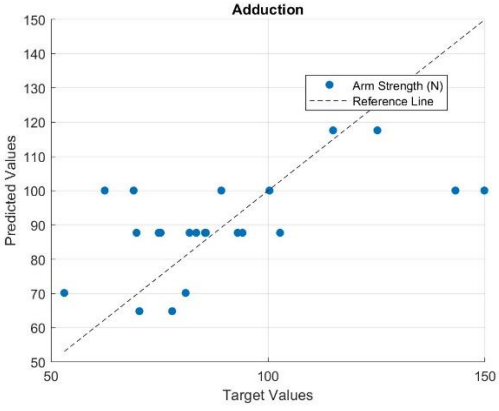
a.



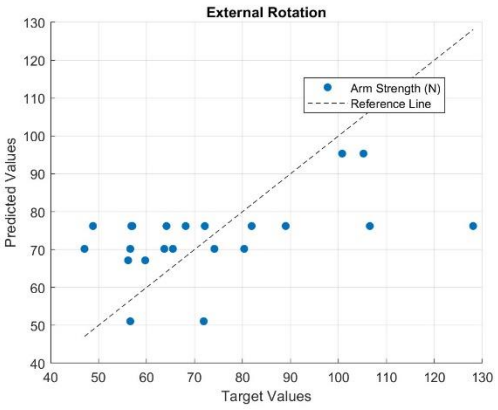
b.



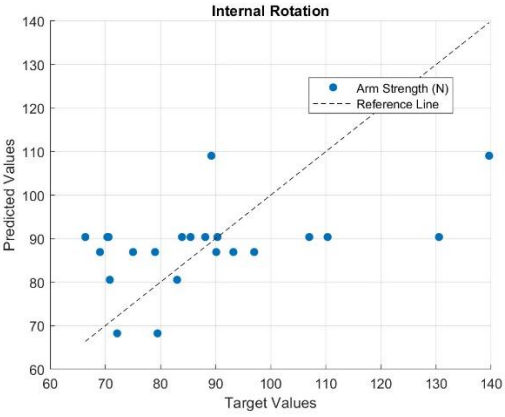
c.



d.



e.



f.

Figure 17. Multiple linear regression scatter plot for target radiation dose and fractions versus predicted values of arm strength at flexion (a), extension (b), abduction (c), adduction (d), external (e), and internal rotation (f) movement tasks.

Table 15. Multiple linear regression analysis results for arm strength for the three movement evaluation tasks, in midpoint and endpoint scenarios. Flex_Ext = Shoulder Flexion- Extension movement task, Abd_Add = Shoulder Abduction – Adduction movement task, ER_IR = Shoulder External- Internal Rotation movement tasks, Rad_F = radiation fractions, Rad_D = radiation dose, CI = Confidence Interval, t = t value (Coefficient estimate/ st error): negative sign (–) stands for negative correlation, positive sign (+) stands for positive correlation

Arm Strength

Flexion						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.576	0.758	0.2	0.198	0.444	0.852

Extension						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.655	0.809	0.106	0.591	0.768	0.179

Abduction						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.387	0.622	0.523	0.721	0.849	0.05
				Coefficients		
				t	**p value**	**St error**
Rad_F				-2.226	0.05	2.340
Rad_D				2.924	0.019	1.386
				95 % CI		
				lower	**upper**	
Rad_F				-10.605	0.188	
Rad_D				0.857	7.247	

Adduction						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.579	0.760	0.195	0.584	0.764	0.188

External Rotation						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.577	0.759	0.198	0.423	0.650	0.454

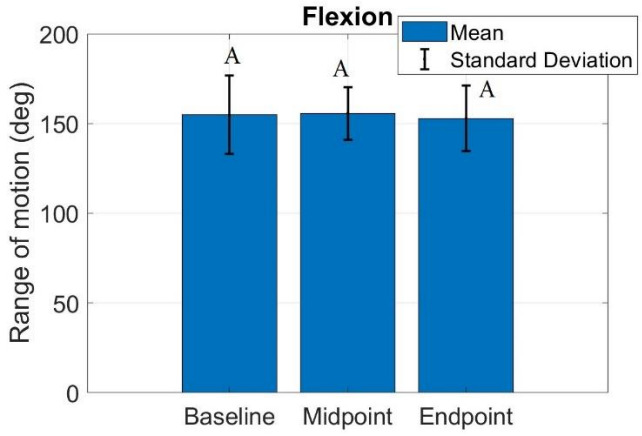
Internal Rotation						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.345	0.587	0.603	0.668	0.817	0.094

3.6.3 Shoulder complex range of motion

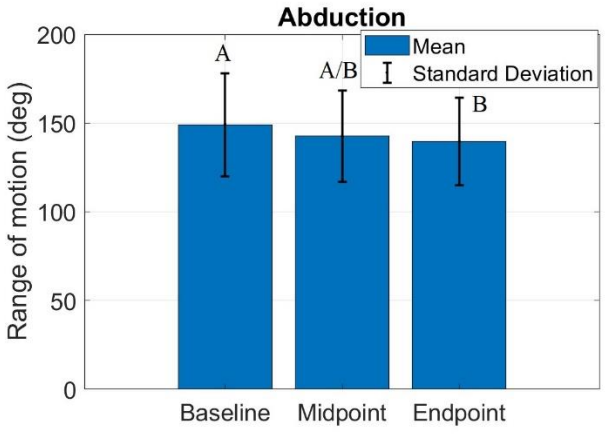
3.6.3.1 Changes of shoulder complex range of motion across baseline, midpoint, and endpoint assessments

Shoulder abduction range of motion decreased across radiation treatment. There was a significant difference in shoulder abduction range of motion between baseline and endpoint ($p = 0.04$). No significant differences were found in shoulder flexion and external rotation range of motion (Table 16) (Figure 18).

A.



B.



C.

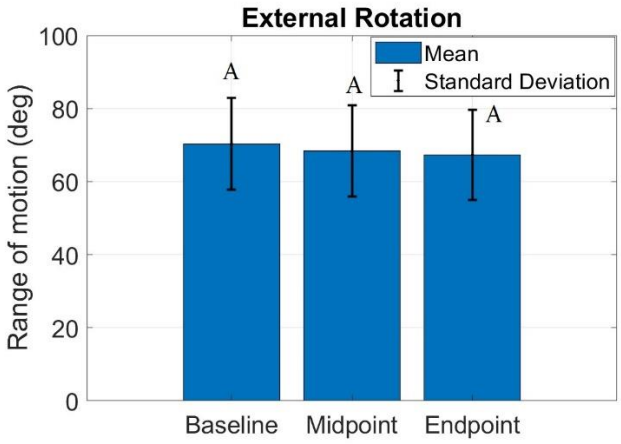


Figure 18. Plots representing the mean shoulder range of motion and the standard deviation for flexion (A), abduction (B) and external rotation (C) in baseline, midpoint, and endpoint scenarios. Data points not sharing the same letter are significantly different ($p < 0.05$)

Table 16. Repeated measures ANOVA results for shoulder complex range of motion in flexion, abduction, and external rotation between baseline, midpoint, and endpoint scenarios (A) and Tukey-Kramer HSD Post Hoc results for significant findings (B).

A.

	p value
Flexion	0.646
	p value
Abduction	0.04 (a)
	p value
E rotation	0.273

B.

	p value	levels	Cohen's d
(a)	0.02	baseline- endpoint	0.354

3.6.3.2 Radiation dose and radiation fractions as covariant for shoulder complex range of motion in baseline, midpoint, and endpoint assessments

A multiple linear regression was used to test if radiation dose and fractions significantly predicted shoulder complex range of motion. A regression model was statistically significant in endpoint assessments of shoulder abduction ($r = 0.683$, $r \wedge 2 = 0.466$, $p = 0.03$). It was noted that

radiation fractions positively predicted shoulder abduction with a strength of p = 0.01. Additionally, radiation dose negatively predicted shoulder abduction with a strength of p = 0.01 (Table 17) (Figure 19).

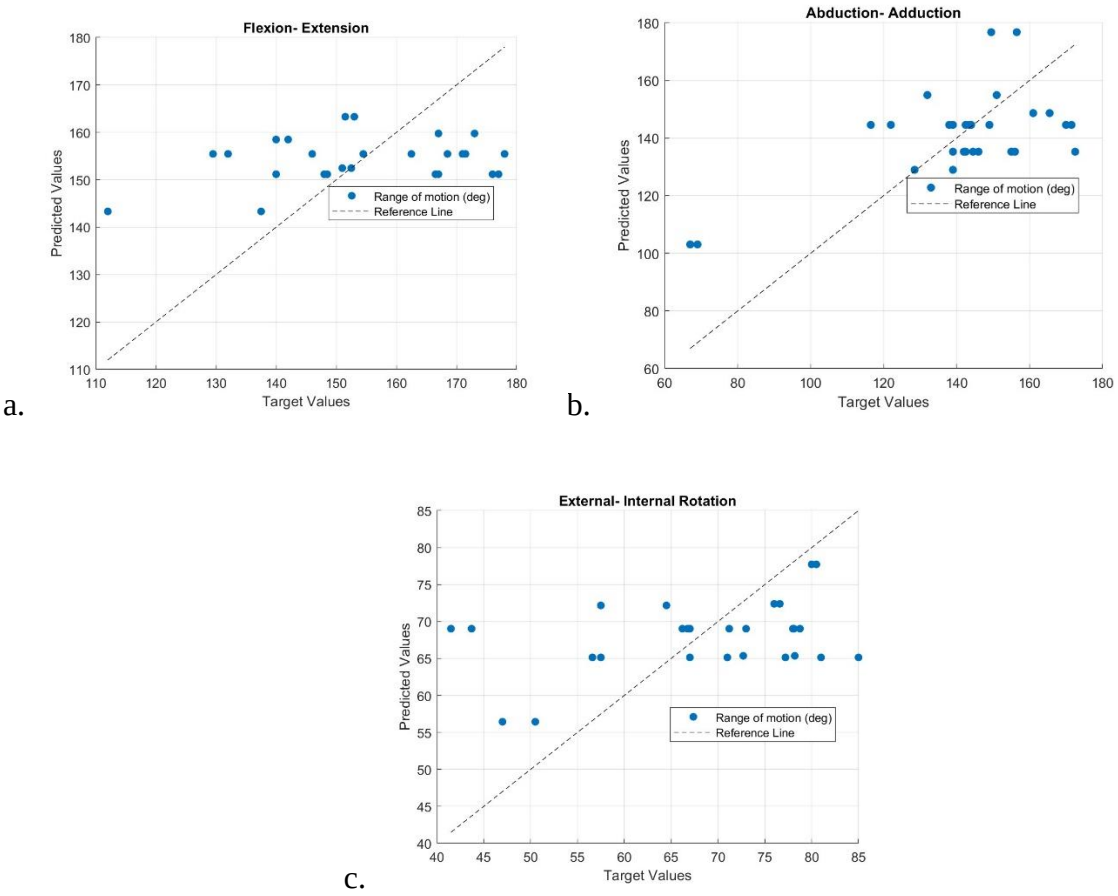


Figure 19. Multiple linear regression scatter plot for target radiation dose and fractions versus predicted values of shoulder complex range of motion at flexion- extension (a), abduction-adduction (b), and external- internal rotation (c) movement tasks.

Table 17. Multiple linear regression analysis results for shoulder complex range of motion for the three movement evaluation tasks, in midpoint and endpoint scenarios. Flex_Ext = Shoulder Flexion- Extension movement task, Abd_Add = Shoulder Abduction – Adduction movement task, ER_IR = Shoulder External- Internal Rotation movement tasks, Rad_F = radiation fractions, Rad_D = radiation dose, CI = Confidence Interval, t = t value (Coefficient estimate/ st error): negative sign (–) stands for negative correlation, positive sign (+) stands for positive correlation

Shoulder complex range of motion

Flex_Ext						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.188	0.433	0.821	0.378	0.614	0.429

Abd_Add						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.585	0.764	0.106	0.683	0.826	0.032
	Coefficients			Coefficients		
	t	p value	St error	t	p value	St error
Rad_F	2.390	0.036	1.638	3.092	0.01	1.417
Rad_D	-2.109	0.059	2.864	-2.756	0.019	2.478
	95 % CI			95 % CI		
	lower	upper		lower	upper	
Rad_F	0.309	7.519		1.263	7.503	
Rad_D	-12.345	0.262		-12.286	-1.377	

ER_IR						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.486	0.697	0.228	0.323	0.568	0.546

3.6.4 Arm Circumference

There was no significant difference in arm circumference between baseline, midpoint, and endpoint ($p = 0.348$). The average arm circumference was 32.5cm in baseline, 32.7 cm in midpoint and 32.4 cm in endpoint (Figure 20).

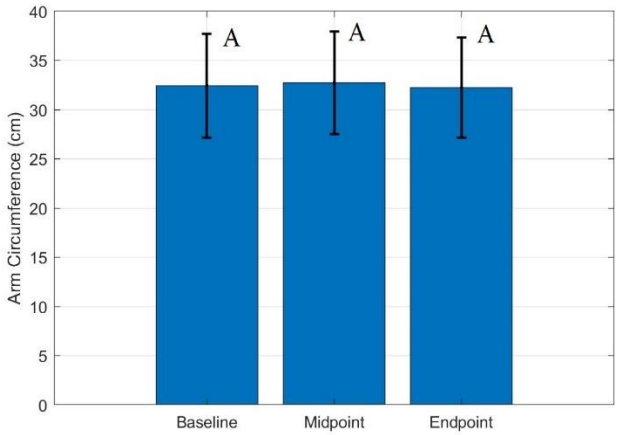


Figure 20. Plots representing the averaged arm circumference and the standard deviation in baseline, midpoint, and endpoint scenarios.

3.7 Discussion

During the treatment window, radiation therapy had a limited impact on shoulder health indicators. Specifically, the activation of the teres major muscle decreased during flexion-extension and internal-external rotation movements, while the latissimus dorsi muscle activation decreased across all movement tasks. Additionally, shoulder abduction was restricted, and negative correlations were observed between shoulder abduction and radiation dose. However, no other significant changes or regressions in shoulder health indicators were noted. These observed changes may be related to inflammation resulting from the treatment, and it's possible that the effects of radiation on shoulder health indicators may take longer to become noticeable.

3.7.1 Shoulder muscles activation

There were differences in teres major and latissimus dorsi activation in the three evaluated tasks. The first hypothesis was that there would be significant changes in shoulder muscles activation at endpoint assessments compared to baseline and midpoint assessments. More specifically, it was hypothesized that the activation of pectoralis major would be lower in endpoint assessments compared to baseline and midpoint assessments, whereas the activation of latissimus dorsi, serratus anterior, and teres major would be higher in endpoint assessments compared to baseline and midpoint assessments. This hypothesis was partially accepted, as differences in teres major and latissimus dorsi activation occurred in all movement tasks. However, the activation of these muscles was lower in the evaluated tasks at midpoint and endpoint assessments compared with baseline, instead of higher as stated in the hypothesis. The decrease in latissimus dorsi and teres major activation reflects that the inflammation produced by

the treatment appears to have affected the muscle tissue and that other muscles may have compensated thereby enabling task performance.

Reductions in shoulder muscles activation in breast cancer patients following oncological treatment are supported by previous research. Yang and Kwon (2018) demonstrated lower muscle electrical activity patterns in 9.1 % of patients three months after surgery, in 3.3% at six months, and 12.9% at 24 months in pectoralis major, upper trapezius, and middle deltoid muscles of 274 breast cancer survivors. Similarity, Shamley et al (2007) noted muscle activation reductions in upper trapezius and rhomboids in breast cancer patients who received oncological treatment 6 months to 6 years prior during a scapular plane elevation movement in the affected side compared to the non-affected side. Except for the pectoralis major, these two studies match with the present study in showing lower electrical activity of muscles that are not in the direct field of surgery or radiotherapy. This might indicate that secondary muscles changes occur with radiation treatment. Further, levels of pain and functional inability were associated with reductions in rhomboids and upper trapezius activation (Shamley et al., 2007). The current study did not sample all possible muscles that contribute to shoulder capability. Further research may explore the activation of additional secondary muscles to obtain a better understanding of the neuromuscular control and compensatory strategies occurring during the radiation treatment window.

Cancer population elicited high activation levels of latissimus dorsi in several earlier studies, in contrast to the current results. Previous research demonstrated that the activation of latissimus dorsi was higher or was unaffected in breast cancer patients receiving oncological treatment including radiation therapy compared with unaffected side or with healthy controls. Latissimus dorsi activation was increased in breast cancer survivors compared to heathy

population for external rotation type exertions (23.7 ± 19.6 versus 7.4 ± 8.3 %MVF) and for internal rotation type exertions (26.5 ± 23.8 versus 9.6 ± 12.3 %MVF) (Brookham et al., 2016). Latissimus dorsi activation in several activities including ROM-reach, ROM-rotation, ADL, and work-related tasks was bilaterally similar ($p > 0.05$) in affected versus non-affected sides in breast cancer survivors (Brookham et al., 2018). Latissimus dorsi activation increased ($p < 0.05$) in abduction, extension, flexion, internal rotation and scapular abduction in breast cancer survivors between 1 and 2 years since treatment ended compared with those within 1 year of treatment ending (Maciukiewicz et al., 2022). Our findings do not match these previous studies. However, besides radiation, other factors could be interfering in the shoulder muscles activation in breast cancer patients such as the use of chemotherapy, the type of breast surgery received, time since surgery, exercise, and pain (Yang and Kwon, 2018). Additionally, the discrepancies between the findings of the present study and previous research may be due to the moment where these assessments took place. The muscle tissue responds differently to radiation treatment in subacute phases compared to chronic phases. The study by Seo et al (2019) reported increases in pectoralis major size during 2 months after radiation therapy and a continuous volume reduction from 2 to 48 months post-treatment. Inflammation can cause early temporal changes in the muscle tissue after radiation therapy caused by several factors inducing potential vasculitis, tissue injury, and denervation (Silliman et al., 1999; Kamath et al., 2008; McMahon et al., 2010). In the current study, the muscle edema caused by the radiation therapy in this acute phase could have affected the muscle activation. If following-up the activation of these muscles later in time, we might find similarities with the literature. Moreover, in this present study, only arm strength was tracked and not muscle-specific force. Multiple muscles cooperate to perform each shoulder action. It is possible that some muscles were decreasing in strength while others were

compensating to maintain it. This could be another reason why significant changes in arm strength were not noted.

Radiation fibrosis, radiation location, and muscle size can also produce decreases in muscle activation and muscle capacity in breast cancer patients. Radiation fibrosis syndrome is a disability following radiation treatment that can affect any tissue type (Hojan et al., 2013). While indwelling EMG studies proved decreases in muscle activation years after radiation therapy in cancer survivors (Stubblefield, 2011), there is a lack of research on early affection of radiation on shoulder health indicators, including muscle activation. The radiation affection in the capacity of the muscles differs depending on the treatment regimens. A simulation model established that radiation to the whole breast alone produced a decrease in latissimus dorsi volume from 10.7 ± 3.6 % to 9.4 ± 7.5% while receiving radiation doses of 48 Gy (Lipps et al., 2017). The current study matches this description since most of the participants received radiation to the right and left breast alone. Moreover, the participants were required to repeat the same tasks in midpoint and endpoint assessments, thus no differences were expected if there were no disease effects. Hence, it is possible that this radiation location and dose diminishes the capacity of the muscle, and thus, its activation. Lastly, muscle size can also lower muscle activation. Decreases in muscle size caused decreases in muscle activation previously (Gyedu et al., 2009; Shamley et al., 2007). Therefore, smaller muscles can have smaller activations and vice versa. Additionally, muscle size is related to muscle volume, being muscle volume the total space that a muscle occupies and muscle size the cross-sectional area of the muscle (Trappe et al., 2007). If radiation causes decreases in muscle volume (Lipps et al., 2017), it is possible that the muscle size is also affected. Future research may take muscle size into account when studying the affection of radiation in shoulder health indicators.

The present study showed no difference in pectoralis major and serratus anterior activation across the treatment. These findings do not align with previous research. It was demonstrated that activation of pectoralis major and serratus anterior was higher or was unaffected in breast cancer patients receiving oncological treatment including radiation therapy compared with unaffected side or with healthy controls (Brookham et al 2016; Hage, 2014; Shamley et al., 2012). As previously stated, the early consequences of radiation in breast cancer patients (during treatment and up until one-year post treatment) as well as the underlying muscle adaptation mechanisms of it, are unknown. It is possible that it takes longer for pectoralis major and serratus anterior to show radiation-induced changes in muscle activation due to iatrogenic disruption. Further research should focus on effects that exist immediately following the treatment to understand better how muscles adapt to radiation therapy in early stages. Another explanation for a lack of changes in pectoralis major and serratus anterior activation in the current study could be related to potential presence of skin adhesions on the anterior chest wall. Skin adhesions are often produced by the combination of surgical procedures and radiation therapy along the field of treatment (Lauridsen et al., 2008). Additionally skin reactions in the radiated area are particularly worse within the first two weeks of starting radiation treatment. These reactions include skin irritation, dryness, peeling, rash, tenderness, burning, and swelling (Canadian Cancer Society, 2023). The presence of these skin reactions and adhesions could have weakened the EMG signal of pectoralis major and serratus anterior muscles leading to an underestimation of the real muscle activation.

3.7.2 Arm strength

The present study identified no differences in arm strength across the treatment. It was hypothesized that there would be lower arm strength at the endpoint assessments compared to

earlier assessments. This hypothesis was not accepted for any of the evaluated movement tasks. Lipps et al (2019) compared control versus breast cancer patients who received radiation to the breast alone and reported greater strength deficit in shoulder vertical adduction (61.9 versus 45.5 N respectively) and shoulder internal rotation (30.2 versus 21.7 N respectively) in a time window of 18 to 40 months after treatment. Additionally, Blomqvist et al (2004) compared breast cancer patients after receiving mastectomy and breast cancer patients after receiving radiation and determined shoulder adduction as the second impacted shoulder movement (31.9 Nm versus 35.2 Nm) only after shoulder extension (11.6 versus 16.6 Nm) in a time window of 15 months post-treatment. In the current study, despite a decreasing trend in arm strength between baseline and endpoint for flexion-extension, abduction-adduction, and external- internal rotation movement tasks, these differences were not statistically significant. The arm strength was assessed within the treatment window, while the other studies evaluated it at 15 to 40 months post-treatment. This indicates that changes in arm strength may not be immediate consequences of radiation therapy.

There was no correspondence between the lower muscle activation noticed in latissimus dorsi and teres major and arm strength. Muscle activation decrements are often linked to strength declines. Reductions in handgrip strength were associated with reductions in forearm muscles activation in 102 breast cancer survivors who underwent surgery, chemotherapy, and radiotherapy (Fuentes- Abolafio et al., 2023). Both latissimus dorsi and teres major extend flexed arm, adduct, and internally rotate the arm (Moore et al., 2014). Their reduced activation was expected to be accompanied by a decrease in arm strength in at least shoulder extension, adduction, and internal rotation movement tasks. However, the testing approach to assess arm strength used in the current study was maximal isometric contraction. Even though this method

is considered reliable, it indicates the capacity to produce force in one condition, often intentionally isolating a single muscle group and/or joint and neglecting the involvement of other muscles or movements (Verschuren et al., 2008). It is possible that the latissimus dorsi and teres major muscles were not fully engaged while performing these tests. Functional strength tests consist of multi- joint movements that not only assess strength but also coordination and endurance (Larin et al., 1994). Further studies should check if functional strength testing methods could engage more muscles and provide a more comprehensive representation of the functionality of the shoulder joint within the treatment window.

3.7.3 Shoulder complex range of motion

Shoulder abduction range of motion was reduced alongside radiation treatment. It was hypothesized that there would be lower shoulder complex range of motion at the endpoint assessments compared to baseline and midpoint assessments. This hypothesis was accepted for shoulder abduction between baseline and endpoint assessments. Previous research showed declines of shoulder flexion by 2°, and 5.5° in shoulder abduction in patients following radiation therapy and surgery (Smoot et al., 2016). Another study stated shoulder external rotation decrements by 3° in affected versus non-affected in breast cancer patients receiving oncological treatment including radiation therapy (Brookham et al., 2018). The present study agrees with previous research in terms of shoulder flexion and shoulder external rotation, but the decline in shoulder abduction was notably more, reaching the 11° of range of motion impairment. These observed shoulder abduction impairments can have long-lasting effects on patients, affecting their quality of life by interfering with essential daily activities such as showering, combing hair,

putting on clothes, and reaching objects on cupboards (Shamley et al., 2012) Additionally, it can also impact their ability to return to work (Shamley et al., 2012).

Finally, the current study tracked shoulder movements such as flexion, abduction, and external rotation because they are involved in many activities of daily living and are most affected in breast cancer patients after receiving oncological treatment (Smoot et al., 2016; Brookham et al., 2018; Maciukiewicz et al., 2022). Future research could consider tracking other shoulder movements not studied in the present research, such as internal rotation, adduction, and extension, to better understand the implications of radiation therapy over the whole shoulder complex in breast cancer patients.

3.7.4 Arm Circumference

Arm circumference did not change across radiation treatment. It was hypothesized that there would be a bigger arm circumference at endpoint assessments compared to baseline and midpoint assessments. The hypothesis was not accepted as no differences in arm circumference existed.

Arm lymphedema is associated with oncological treatment in breast cancer survivors. In average, 40% of breast cancer survivors experience arm lymphedema as a secondary effect of breast cancer treatment (Shaitelman et al., 2017). Comprehensive surgery including the excision of the lymph nodes and extended radiation regimens such regional lymph node radiation, are considered the main contributors of arm lymphedema (Chandra et al., 2014). The absence of significant presence of arm lymphedema in the present study could be relate to potential development of arm lymphedema not occurring until months or even years after treatment (Shah & Vicini, 2011). Additionally, the patients of the current study received either mastectomy or

lumpectomy as surgical procedures, and only one participant received radiation to the axilla. Therefore, according to the literature, these patients were at low risk of developing lymphedema.

Lymphedema grading systems were used and defined in previous cohort studies (Bar et al .,2010; Gerber et al., 1992) . Severe, moderate, and mild arm lymphedema were described as differences in arm circumference greater than 3 cm, 2.1 to 3 cm, and 0.5 to 2 cm respectively between affected and un-affected sides (Bar et al., 2010). In the current study, we did not assess the un-affected arm. Further research could measure arm circumference and compare affected versus non-affected arms to have a better understanding of the development of this condition during the treatment window.

3.7.5 Associations between radiation dose and fractions and shoulder health indicators

Radiation dose was negatively correlated with shoulder abduction range of motion and arm strength in abduction movements. The second hypothesis, states that higher doses and fractions of radiation would cause higher reductions in shoulder muscles activation, arm strength and shoulder complex range of motion. This hypothesis was only accepted for shoulder abduction and arm strength in abduction movements. This finding is related to the significant decrease in shoulder abduction at endpoint compared to baseline. The higher the radiation dose, the higher the shoulder abduction range of motion restriction. Moreover, radiation dose also impacted arm strength in abduction movements. Restricted range of motion can be caused as compensations for strength deficits.

The lack of correlations between radiation dose and fractions and the rest of the shoulder health indicators could be explained by the absence of a good spread of predictor variable. The

radiation dose and fractions values were not varied enough. This might have led to a noisy linear relationship on the regression plots.

Additionally, all patients received IMRT treatment regimen. The goal of this regimen is to deliver the correct dose of radiation to the target and minimize radiation outside of the target. This helps reduce the risk of damaging nearby healthy tissue (Aref et al., 2000). Patients undergoing standard radiation therapy treatment plans were at 1.7 higher risk of developing changes in the breast appearance compared to those undergoing IMRT plans (Donovan et al., 2007). The prescription of IMRT plans in the patients of the current study could be another reason for the lack of correlations between radiation dose and fractions, as this regimen is more targeted and safer.

Moreover, the variability of patients' responses to radiation treatment could have affected this relationship too. While many patients experience radiation-induced fibrosis, the incidence rate of this condition ranges from 60% to 80% of the population (Paulino, 2004) Finally, there are potential influences of confounding factors beyond radiation dose and fractions (such as age, pre-existing conditions, and muscle resilience to treatment (Bazan et al., 2021).

3.8 Limitations

A few limitations should be considered when interpreting these findings. Regarding the methods, the hand-held dynamometer measurement is known to present inter and intra-variabilities in the measurements (Toemen et al., 2011). This limitation was managed by designating the same person within each patient' assessments to keep consistent measurements. Additionally, the IMU hardware occasionally presented some technical difficulties during data recording. However, as a

precaution, shoulder range of motion data was also recorded by video-camara and analyzed through Kinovea as a back-up method in case the main IMU method failed.

This study presented a relatively small sample size. With a bigger sample size, more differences in shoulder health indicators between treatment assessments may have been quantified. However, the current sample size is realistic from what can be done considering the COVID limitations, and also similar to the ones evaluated in previous research in the field (Guirro, et al., 2019; Garcia- Jeronimo et al., 2023; Magnuson et al., 2023), and significant results in the measured variables were captured.

3.9 Conclusions

- **Study purpose:** To examine the impact of radiation therapy on shoulder complex joint in breast cancer patients.
- **Main findings:**
    - Repeated measures ANOVA showed that progression through the radiation therapy window was associated with reduced muscle activation of latissimus dorsi in the three movement tasks, and teres major in flexion-extension and external-internal rotation movement tasks. Additionally, the shoulder abduction range of motion decreased during the radiation therapy window. No other significant changes in shoulder health indicators were noted.
    - Multiple linear regression showed significant negative regressions between radiation dose and shoulder abduction. No other significant regression model emerged.
    - The reductions in muscle activation may indicate that the inflammation produced by the treatment appears to have affected the muscle tissue and that other muscles may have compensated thereby enabling task performance. The reduction in shoulder range of motion could potentially affect the quality of life and work ability of patients. These reductions appeared after initial treatment.
    - Despite being more tumor-targeted, radiation dose prescribed within the IMRT regimen is still related to shoulder range of motion restrictions.

- **Recommendations:**
    - Shoulder disability prevention programs should target the recruitment of latissimus dorsi and teres major muscles and shoulder abduction mobility exercises.
    - Future research should explore the quality of life and work ability of patients during radiation therapy.

Chapter 4 - Intervention program focused on shoulder muscles strength within the radiation window in breast cancer patients

4.1 Introduction

Radiation therapy in breast cancer relates to multiple complications affecting patients' quality of life. Radiotherapy after mastectomy is one of the most effective treatments for breast cancer, reducing the risk of breast cancer recurrence up to 2/3 (National Comprehensive Cancer Network, 2018; Clarke et al., 2005). The benefits of this therapy are well-documented throughout the literature. However, there are multiple complications with radiation treatment that may affect the patient's quality of life and possible survival. Amongst all the complications associated with radiation therapy, shoulder strength decrements are an important contributor (Hwang et al., 2008).

Exercise is considered an intervention that may help mitigate the effects of oncological treatment, but more clarity is necessary. Several systematic reviews and meta-analyses support the use of the exercise in breast cancer patients as a path to improve body composition, life quality and to decrease fatigue (Courneya & Friedenreich, 1999; Hewitt, Mokbel, & Van Someren, 2005; Spence, et al., 2010). However, these studies did not evaluate if the chosen exercises target specific desired outcomes (e.g.: improve general cardio-vascular capacity or shoulder range of motion), and the desired population (e.g.: patients undergoing chemotherapy or reporting cancer-related fatigue). Further, it is unclear when the intervention program should be administered with respect to different phases of breast cancer treatment (e.g. throughout treatment, after treatment), or if development of specific descriptions to accomplish particular outcomes is more appropriate (Campbell et al.,

2011). Most of the intervention programs for breast cancer patients focus on improving the quality of life through the enhancement of aerobic capacity and fatigue resistance, with half of the studies conduced during adjuvant treatment (Campbell et al., 2011).

Data on exercise intervention programs performed during radiotherapy window are scarce. Most of the literature regarding these types of intervention programs focused on aerobic capacity enhancement, resistance training, and fatigue improvement (Mock et al., 1997; Mock et al., 2001; Mock et al., 2005; Hee-Kim et al., 2013; Schmidt et al., 2006; Hwang et al., 2008; Kirshbaum, 2006). To our knowledge, despite aiming for general resistance-improvement and not muscle strength, only three studies have used strengthening components in their intervention programs for breast cancer patients during radiation therapy. Steindorf et al (2014) included a 12-week resistance training program in 77 stage 0-III breast cancer participants while receiving radiation therapy, compared to 78 control breast cancer participants who received a muscle-relaxation program. The intervention was administered twice a week in a 60 minute session, under the supervision of trained physiotherapists. The program comprised of eight machine-based resistance exercises with a volume of 3 sets, 8-12 repetitions, 60%-80% of 1 RM (repetition maximum), while the control group performed muscle-relaxation exercises without any strengthening component. The exercise group had greater improvements in general fatigue, and pain, compared to the control group. Kneis et al (2018) studied the effects of an intervention program using a combination of stationary bicycle within 60% to 75% of maximum heart rate, with exercises with a vibrating dumbbell which aimed to enhance shoulder mobility and upper limb strength in 22 breast cancer patients while receiving radiation treatment. The exercise group performed the program for 3 times per week during 6 weeks of radiotherapy, and results were compared to 22 breast

cancer patient-controls. The training group had higher shoulder ROM (11 deg of shoulder abduction; 95% CI 5 to 20, and 5 deg of external rotation; 95% CI 0 to 10), as well as hand grip strength (1.6 Kg; 95% CI -0.6 to 3.1) compared to the control group (Kneis et al., 2018). Finally, Mustian et al (2009) proposed a 4-week home-based progressive resistance exercise intervention for 38 breast and prostate cancer patients during radiation therapy compared to controls. The program included a moderately intense walking prescription (between 60%-70% of heart rate). The second component was low to moderately intense resistance band exercises targeting the maintenance of muscle strength in the upper body. Both components were performed 7 days a week for the entire duration of the intervention. Strength was evaluated using a handgrip dynamometer. The exercise group had an improvement in daily steps walked, daily minutes of resistance training, and number of resistance exercise days post-intervention compared to controls. Regarding upper extremity strength, the exercise group demonstrated small declines in strength from baseline (26.02 Kg) to post-intervention (25.49 Kg) (Cohen's d= -0.07), but small improvements after 3 months post-intervention (26.89 Kg) (Cohen's d= 0.11). The control group on the other hand exhibited declines from baseline (24.92 Kg))to post-intervention (24.12 Kg) (Cohen's d= -0.10) as well as a decline after 3 months post-intervention (23.87 Kg) (Cohen's d= -0.06) (Mustian et al., 2009).

The effects of an intervention program focused on shoulder strength alongside shoulder functional indicators assessments before, during, and after a radiation therapy therapeutic window in breast cancer patients have yet to be investigated. Although multiple factors can affect the shoulder function in breast cancer patients, the current research focuses solely on the implications of radiation treatment. Specifically, an intervention program that focused on shoulder flexors, extensors, adductors, abductors, internal and external rotators, administered

during radiation treatment, was evaluated as a potential compensation for shoulder capacity decrements.

4.2 Objective and Hypotheses

The objective for Study 2 was to determine if an intervention program focusing on the training of shoulder muscles could compensate for shoulder health indicators imbalances.

The following hypotheses are presented for study 2:

1. Control group would have lower arm strength and higher arm circumference at endpoint assessments compared to exercise group.
2. Control group would have lower shoulder complex range of motion at endpoint assessments compared to exercise group.
3. Shoulder muscle activations would be affected in control group at endpoint assessments compared to exercise group
    a. Pectoralis major activation would be higher in control group
    b. Latissimus dorsi, teres major, and serratus anterior activation would be lower in control group.
4. Radiation dose and fractions would be negatively correlated with arm strength, activation, and shoulder complex range of motion in controls.
5. The exercise group is expected to show no significant negative correlation between radiation dose and fractions and arm strength, activation, and shoulder complex range of motion

4.3 Methods

4.3.1 Participants

Twenty- seven patients participated in the present study (Figure 21), thirteen in the exercise group (68.9 ± 13.7 kg, 160.9 ± 4.9cm) and fourteen in the control group (76.5 ± 15.1 kg, 165.5 ± 6.1 cm). A G*POWER 3.1 (Universitat Kiel, Germany) analysis for Mixed model ANOVA for 2 groups, 3 measurements, an alpha of 0.05, a power of 0.8, and a medium effect size, revealed that 40 subjects were needed for the present study. However, due to COVID restrictions and difficulties in patient recruitment, only 27 participants were collected. Despite being underpowered, the current sample size approximates previous studies that conducted intervention programs for patients with breast cancer: Hagstrom et al., 2017 had 19 participants in a resistance training group and 14 participants in the control group; Stan et al., 2016 had 14 participants in a yoga group and 9 in a strengthening exercise group; and Galiano-Castillo et al., 2011 compared 15 breast cancer survivors versus 15 matched controls. The participants from the control group are the same participants from study 1 (7 comparators and 7 observational). A mixed model ANOVA was performed between comparator and observational groups comparing all the measured variables. No differences were noted between the groups. Therefore, both groups were compiled into a 'control' group. Participants were recruited directly from the Grand River Hospital (Kitchener, ON) after ethics approval by the Office of Research Ethics at the University of Waterloo (ORE 42901), and Grand River Hospital. Potential participants were referred to the student investigator after the prescription of radiation treatment from Radiation Oncologist. All patients received IMRT (intensity modulated radiotherapy) treatment regimens. The average dose of radiation prescribed to the patients in the exercise group was 45.4 Gy, ranging from 40 Gy to 60 Gy. The average fractions were 18, ranging from 10 to 30. Whereas in the control group, the average prescribed dose of radiation was 32.6 Gy, ranging from 26 Gy to

52.5 Gy, and the average fractions were 9.26, ranging from 5 to 20 (Table 19). Recruitment criteria was based on the demographics of Waterloo/ Kitchener region to have a representative sample of women of the area. The inclusion and exclusion criteria were the same as study 1 (Chapter III, section 3.3.1, page). The surgical procedures and adjuvant treatment received by the patients of this cohort are detailed below (Table 15). The details of the radiation location prescribed are also attached (Table 16). A questionnaire describing the average amount of hours per week of daily activities divided into strenuous, moderate, and mild, is presented for both groups (Table 17) (time dedicated to exercises for exercise group is not included). Only female participants were recruited as women constitute the majority of breast cancer disease (less than 1% of breast cancers occur in men) (CCS, 2020). The shoulder functional indicators assessments from Study 1 were used in the Study 2 analysis.

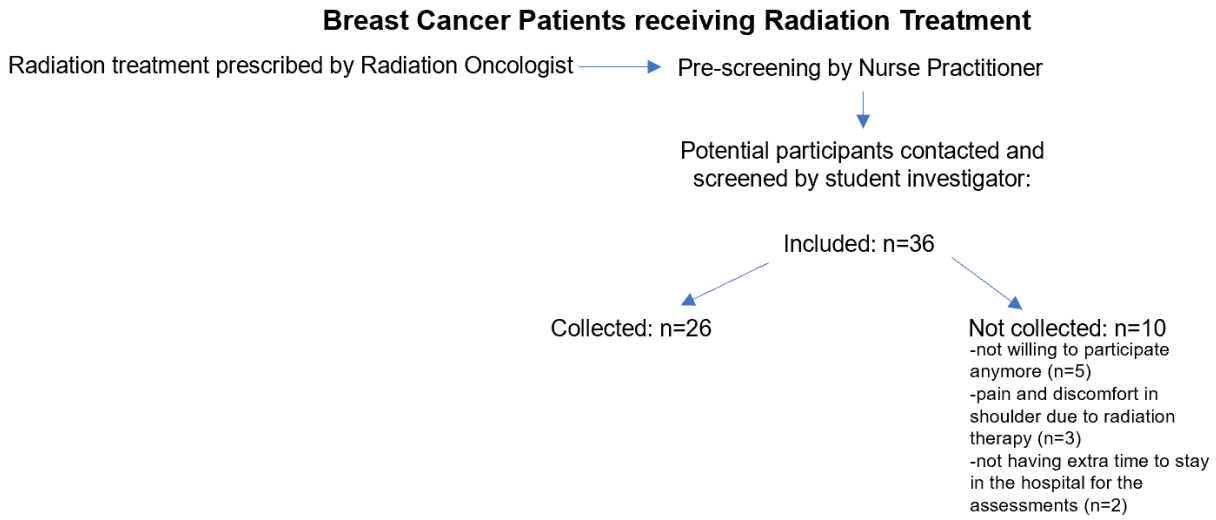


Figure 21. Diagram outlining recruitment and retention of participants in the study.

Table 18. Surgical procedures and adjuvant treatment received by participants.

Exercise Group			
Surgical procedures	Number of participants receiving surgery	Adjuvant treatment	Number of participants receiving treatment
Lumpectomy	11	Anastrazole	3
		Letrozole	2
		Tamoxifen	2
Mastectomy	2	Chemotherapy	2
		None	4

Control Group			
Surgical procedures	Number of participants receiving surgery	Adjuvant treatment	Number of participants receiving treatment
Lumpectomy	11	Anastrazole	5
		Letrozole	3
		Tamoxifen	3
Mastectomy	3	Chemotherapy	1
		None	2

Table 19. Radiation dose and fractions treatment plans

Control Group			
Treatment plan		Boost?	
Radiation Dose	Radiation Fractions	Radiation Dose	Radiation Fractions
26	5		
26	5	5	10
26	10		
26	5		
26	5	5	10
26	5		
26	5	5	10
26	5	5	10
26	5	5	10
40	15		
26	5	5	10
26	5	5	12.5
26	5		
42.5	16	10	4

Exercise Group			
Treatment plan		Boost?	
Radiation Dose	Radiation Fractions	Radiation Dose	Radiation Fractions
42.5	16		
42.5	16	16	4
40	15		
50	25		
26	5	10	5
42.5	16	10	4
26	10	10	12.5
26	10	5	12.5
40	15		
40	15		
40	15		
50.4	28		
50	25	10	5

Table 20. Radiation treatment location for all patients

Radiation treatment location details	Number of participants for exercise group	Number of participants for control group
Right breast with boost to surgical cavity	1	2
Right breast with boost to seroma	1	1
Right breast	1	3
Left breast	2	3
Right breast with boost to tumor bed	1	1
Left chest wall	2	1
Right breast and regional lymphatic nodes	1	1
Left breast with boost to seroma	2	
Left breast with boost to tumor bed		2
Left breast with boost to surgical cavity	1	
Left chest wall, axilla, and supraclavicular	1	

Table 21. .Questionnaire with average amount of hours of daily life activities for control and exercise groups divided into strenuous, moderate, and mild activities.

	Control: Average hours per week	Exercise: Average hours per week
a) Strenuous exercise (heart beats rapidly) (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	10	7.5
b) Moderate exercise (not exhausting) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	15	18
c) Mild/light exercise (minimal effort) (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-moiling, easy walking)	10	17

4.3.2 Trial design

The data collection for study 2 occurred concurrently with study 1. Informed consent form and general health information questionnaire are attached (Appendix).

This study was a six-week intervention program. It compared shoulder strengthening exercises with a control group receiving usual care referral in the radiation therapy window in breast cancer patients (Table 22). A computer-generated randomization sequence was used, and participants were randomized in a 1:1 allocation ratio to: 1) Exercise Group, or 2) Control Group. Participants in the Intervention Group arm attended a 30-minute online class, three times per week for 6 weeks. The Control Group arm was prescribed with a usual care plan for breast cancer patients' rehabilitation. It consisted of 30 minutes of aerobic exercises three times per week. The randomization sequence was created and maintained using REDCap and was kept by the investigator at the University of Waterloo. Participants were not blind to group allocation because they knew what group they were assigned to. However, they were blinded to the study hypotheses; they were informed that two different types of exercise were being compared.

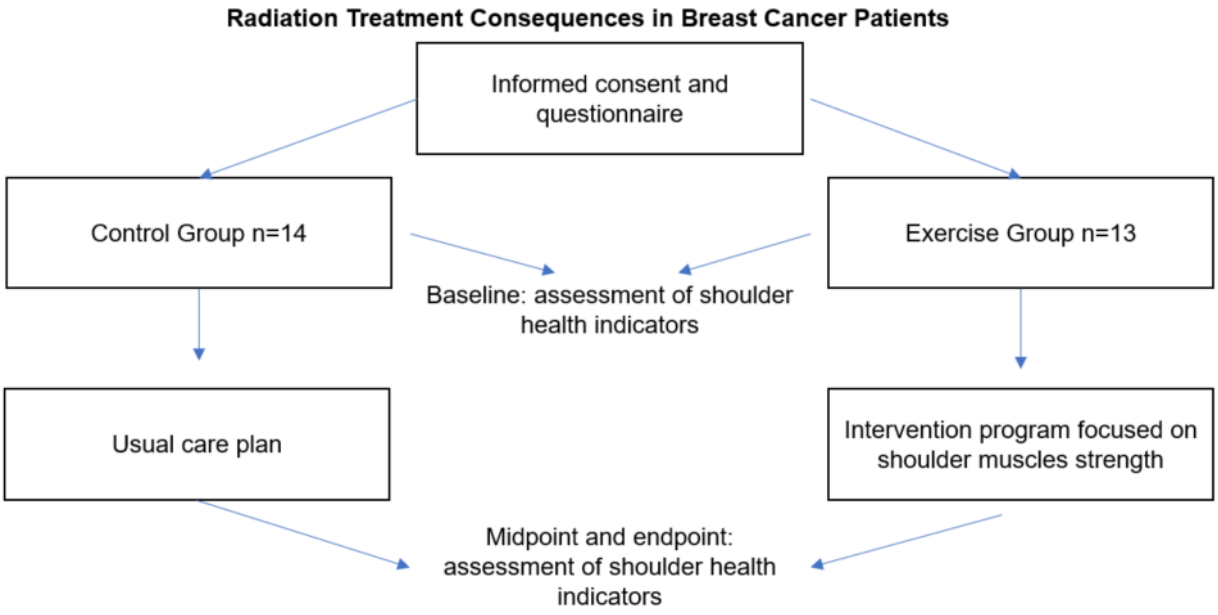


Figure 22. Study 2 flowchart. Comparison of exercise group receiving intervention versus control group across radiation treatment. Quantification of shoulder health indicators at baseline, midpoint, and endpoint for both groups.

4.3.3 Intervention Program Description

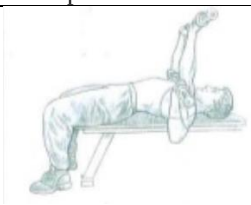
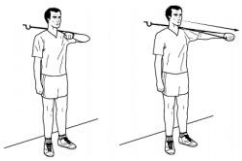
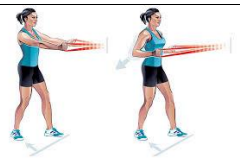
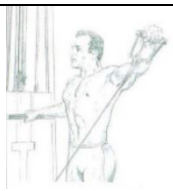
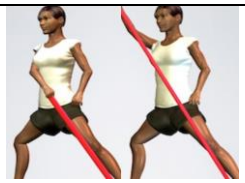
4.3.3.1 Setting and Supervision

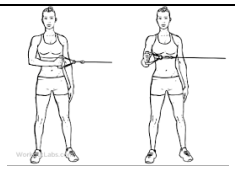
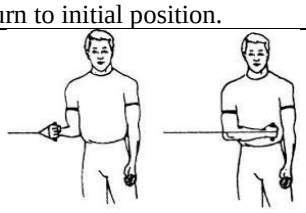
The intervention program was conducted over an online platform, 'Zoom'. Classes were accommodated according to the researcher and participant. Patients chose either morning or afternoon classes. To attend the meeting, the participants needed a laptop with camera and internet accessibility or a smart phone. In some cases, more than one participant joined the zoom meeting at the same time. In order to protect each individual's privacy, the host (student investigator) used the 'Focus mode' feature, in which only she was allowed to see everyone's video, and also each participant was able to see the host's video. Zoom classes were not recorded. In case of emergency during the class, there was a remote programming emergency protocol (Appendix C) that could be developed for two scenarios: patient not being home alone, and patient being home alone. No emergencies occurred in any of the classes.

4.3.3.2 Goal and Exercise Modes

Online sessions were used to instruct the exercises listed below (Table 19). The training program included strength exercises focused on shoulders flexors, extensors, external rotators, internal rotators, adductors and abductors. The selection criteria for the exercises were based on previous strength programs for breast cancer patients (De Backer et al., 2007; Young Kang et al., 2010; Richmond et al., 2018). The exercises involved the use of TheraBands (TheraBand, Akron, USA) and dumbbells and were provided to the participants during the baseline assessment session. In case of experiencing struggles while performing the proposed exercises, a simpler variation of each exercise was offered to each participant. The Control Group did not receive exercise instruction sessions.

Table 22. Intervention Training Program Exercises description.

Exercise	Initial position	Action	Description
Bilateral vertical row with dumbbell	Standing position, trunk bent 45° forward, elbows completely extended, and weight held with both hands with the overhand grip.	Lift the weight straight up until elbows are fully flexed.	
Simpler version: unilateral vertical row, perform sets and repetitions on one side and repeat it to the other side.			
Bench press with dumbbell	Lying supine on training bench or similar, holding one dumbbell with each hand in overhand grip. Shoulder flexed 100° and elbows completely flexed.	Completely extend elbows while protracting scapula.	
Simpler version: perform the exercise repeating the same action but changing the position to seated.			
Elbow extensions with dumbbell	Lunge position, trunk bent forward 45°, forward knee flexed 20°. Opposite hand on top of thigh. Shoulder extended 20°, elbow flexed 90°.	Completely extend elbow.	
Simpler version: Perform the exercise in standing position. Completely extend elbow from a 90° of elbow flexion with shoulder in neutral position.			
Forward punch with elastic band	Standing position, elastic band held with both hands and placed behind the back. Shoulders flexed 100° and elbow completely flexed.	Completely extend elbows with scapula fully protracted.	
Simpler version: Perform the exercise from shoulder in neutral position and elbow flexed 90°.			
Horizontal row with elastic band	Standing position, elastic band held with both hands and placed forward. Shoulder and elbow completely extended.	Completely flex elbow and extend shoulder 20°.	
Simpler version: Perform the exercise until shoulder reach neutral position.			
Outward elevation with one hand with elastic band	Seated in chair, fasten elastic band under foot and hold the other end of the band with one hand.	Move shoulder to 100° of flexion and 20° of abduction, while maintaining the elbow completely extended and the scapula protracted.	
Simpler version: Perform the exercise until 45° of shoulder flexion.			
Sword pulling with elastic band	Standing position, fasten elastic band without any slack under one foot, and hold the other end of the band with opposite side hand.	Stretch band performing a semi-circle movement until 150° of shoulder abduction while maintaining the	

		elbow completely extended.	
Simpler version: perform the exercise until 90° of shoulder abduction.			
Shoulder external rotation at side	Standing position, grab elastic band with slight resistance, with arm across body and elbow bent 90°.	With an open hand grip and keeping the upper arm steady, rotate the hand outwards until is lined up with the side of the body. Return to initial position.	
Simpler version: Perform the exercise rotating hand outwards until 45° and return to initial position.			
Shoulder internal rotation at side	Standing position, grab the end of the band securely attached at waist-height.	Grab the other end of the band with tension, and pull the band away from the wall, rotating forearm inward.	
Simpler version: Perform the exercise rotating hand inwards until 45° and return to initial position.			

4.3.3.3 Frequency and Duration

Participants from both Exercise and Control Groups were asked to perform the exercises three times per week, 30 minutes each session for six weeks.

4.3.3.4 Intensity

The maximal intensity of each exercise was quantified during the first evaluation session. For those exercises including loads, an estimation of 1RM (Repetition maximum) was accomplished through a multiple repetition test procedure. The patient was instructed to perform 10 repetitions of the exercise with a certain load and was asked to rate their exertion. The starting load was 1 kg for the vertical row, and 2kg for the bench press and pull over. The goal was to perform the 10 repetitions without feeling any fatigue or pain. In case of feeling fatigue or pain, the test was over, and the maximal number of repetitions correctly performed were used in a formula to calculate the RM: 1RM= load (Kg) / (1.0278-0.0278 x reps). This RM estimation test did not last more than 5 minutes.

The maximal intensity for those exercises including TheraBands was estimated with the Borg rate of perceived exertion. The participant was instructed to perform 10 repetitions of the exercise with a medium resistance band (black) and was instructed to rate their exertion. If the exertion perceived was rated from 0-3 (very light activity) or from 4-6 (moderate activity), the maximal intensity was set with a band with greater resistance (silver). If the exertion perceived was rated from 7-10 (vigorous to very hard activity), the maximal intensity was set with a band with lower resistance (blue) (Table 24) .

4.3.3.5 Volume

The initial volume per exercise was 3 sets of 8 repetitions. The patient was instructed to increase the number of repetitions each week for the first 3 weeks of the training program: 3x8 the first week, 3x10 the second week, and 3x15 the third week. The participant then used a Borg rate of perceived exertion to evaluate each exercise with the new number of repetitions each week. If the exertion perceived was rated from 0-3 (very light activity) or from 4-6 (moderate activity), the intensity was set with a band with greater resistance (silver) for the TheraBand exercises, and with an increase of 0.5kg for the dumbbell exercises. If the exertion perceived was rated from 7-10 (vigorous to very hard activity), the intensity was set with a band with lower resistance (black) for the TheraBand exercises, and with a decrease of 0.5kg for the dumbbell exercises.

During the midpoint assessment, arm strength was assessed, and feedback of the strength progression was communicated to the patient. An increase of exercise intensity was established (0.5 kg for dumbbells exercises and higher resistance for TheraBand exercises). The initial volume per exercise with the new volume was 3 sets of 8 repetitions.

Table 23. Participants' strength was tested on week 1 (before the starting of the intervention program), week 5 and week 7. The baseline evaluation was conducted to estimate the initial maximal volume, whereas the midpoint evaluation determined the volume for the rest of the intervention program.

Week 1	Pre-radiation: Baseline assessment	Initial max volume estimation Strength baseline assessment
Week 2	Program starts	Intensity: 3 x 8 reps
Week 3		Intensity: 3 x 10 reps
Week 4		Intensity: 3 x 15 reps
Week 5	Midpoint assessment	Volume re-calculation Strength assessment feedback Intensity: 3 x 8 reps
Week 6		Intensity: 3 x 10 reps
Week 7	Endpoint assessment	Intensity: 3 x 15 reps

Table 24. TheraBand resistance and intensity description.

Level of exercises	Intensity/ %RM	TheraBands
High	70-80%	Silver
Moderate	60-70%	Black
Low	50-60%	Blue

4.3.3.6 Time

Participants from the Exercise Group were asked to attend the classes 3 times per week, 30 minutes each session, for 6 weeks.

4.3.3.7 Control

The Control Group was prescribed aerobic exercises to be performed 3 times per week, 30 minutes each day. Examples of aerobic exercise included: walking, running, bike riding, and

dancing. These exercises replicate a “usual care” referral for breast cancer rehabilitation (Olsson et al., 2019).

4.3.3.8 Weekly leisure-time activity tracker questionnaire

At the end of each week of the radiation therapy window, patients were instructed to fill-in a quick questionnaire regarding the physical activity performed that week. The questionnaire was sent over email to the student investigator once the treatment was over. Reminders to fill-in the questionnaire were sent to participants by email or text (Appendix B).

4.3.4 Instrumentation

Study 2 shared the same hand-held dynamometer, surface electromyography and tri-axial accelerometer instrumentation as Study 1 (Chapter III, sections 3.3.2, 3.3.3, and 3.3.4 pages 34-36).

4.4 Data analysis

4.4.1 Shoulder functional indicators data

Peak force, muscle activation, range of motion, and arm circumference data were obtained from the protocols described in Study 1 (Chapter III, sections 3.3.2, 3.3.3, and 3.3.4 pages 34-36). The shoulder complex range of motion analysis was done with orientation data from IMUs. In some specific cases that technical difficulties aroused during data recording, 2D data was used (4 subjects, 5 assessments).

4.5 Statistical analysis

Statistical analysis was performed using JASP (Version 0.18.1.0; JASP Team, 2023), a free and open-source statistical software package. A mixed model ANOVA was used to identify differences in shoulder muscles activation, arm strength, and range of motion between baseline-midpoint-endpoint levels. Statistical significance was set to $p < 0.05$. Post hoc Tukey- Kramer HSD identified significant differences between levels. The normality of the data was assessed using Shapiro- Wilk test and found to be non-parametric. However, the distribution of skewness was approximately symmetric, and the sample size met the criteria for the central limit theorem. As a result, ANOVA remained a viable option for producing reliable results. A multiple linear regression model was performed for each dependent measurement accounting for radiation dose and radiation fractions as confounding factors. Correlation coefficients and p values were extracted. Only successful models with $p<0.05$ were included for interpretation.

Table 25. Summary of outcome measures for study 2.

Input	Dependent variables	Co-variants
Arm strength assessment	Shoulder flexion peak force Shoulder extension peak force Shoulder abduction peak force Shoulder adduction peak force Shoulder external rotation peak force Shoulder internal rotation peak force	Radiation dose Radiation fractions
Shoulder muscle activation assessment	Pectoralis major mean activation Teres major mean activation Latissimus dorsi mean activation Serratus anterior mean activation	
Shoulder range of motion assessment	Shoulder flexion Shoulder abduction Shoulder external rotation	
Arm lymphedema assessment	Arm circumference	

4.6 Results

Shoulder muscles activation and arm strength were influenced by exercise*time interactions. Activation of latissimus dorsi in flexion-extension movements, activation of teres major in external- internal rotation movements, and arm strength in abduction movements were influenced by an interaction exercise*time. No negative correlations between radiation fractions nor dose and any of the shoulder health indicators were noted for the control group. No correlations between radiation dose nor fractions and shoulder health indicators were noted for any of the movements (Table 26).

Table 26. Summary of differences. Variable comparisons between control and exercise groups for arm strength, activation, shoulder complex range of motion, and arm circumference in flexion-extension (Flex-Ext), abduction-adduction (Abd-Add), and external-internal rotation (ER-IR) movement tasks. Presence of interactions exercise*time (E*T) are represented by '✓', whereas absence is represented by 'X'. 'B' = baseline, 'M' = midpoint, 'E' = endpoint.

		Evaluated movements		
		Flex- Ext	**Abd- Add**	**ER-IR**
		E*T	**E*T**	**E*T**
Muscle Activation	**Latissimus Dorsi**	✓	X	X
	Teres Major	X	X	✓
	Pectoralis Major	X	X	X
	Serratus Anterior	X	X	X
Arm Strength		X	✓	X
Range of motion		X	X	X
Arm Circumference		X	X	X

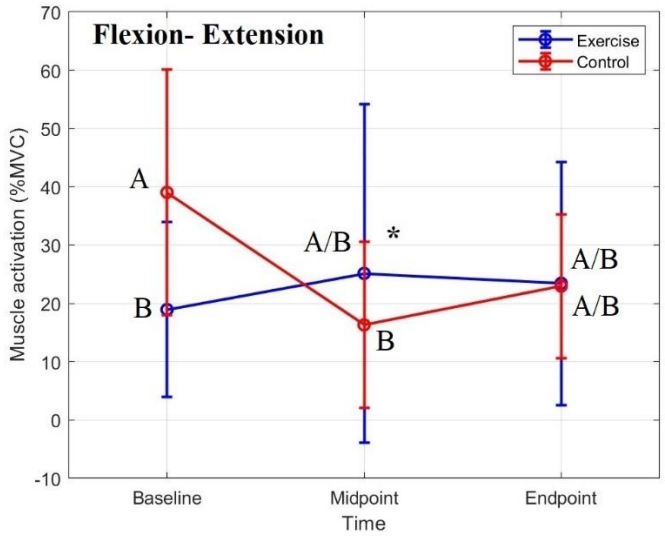
4.7 sEMG

4.7.1 Comparison of shoulder muscles activation across baseline, midpoint, and endpoint assessments in control versus exercise groups

4.7.1.1 Latissimus Dorsi

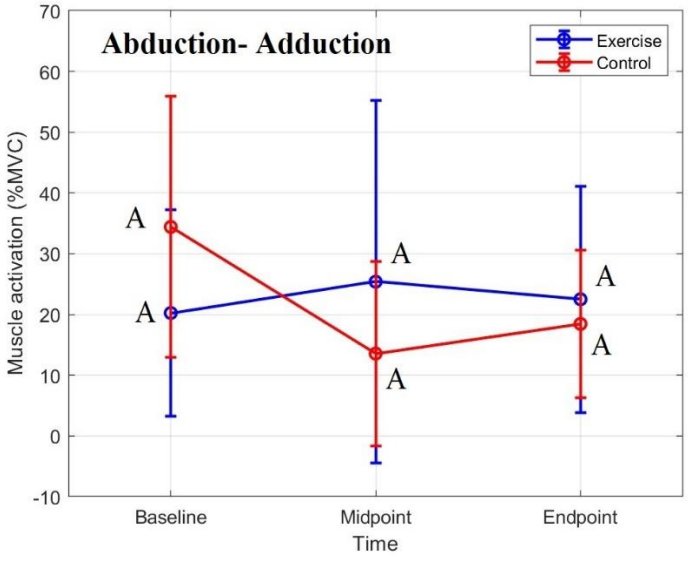
The ANOVA showed that the activation of latissimus dorsi in flexion-extension movements was influenced by an exercise*time interaction (p = 0.04) (Table 27). The post hoc Tukey test revealed this interaction in the control group between baseline and midpoint assessments (p = 0.03, Cohen's d= 1.296). This means that the effect of time of latissimus activation in the control group is different depending on the level at the baseline assessment. The mean activation of latissimus dorsi in the control group decreased over time from baseline to midpoint, whereas in the exercise group did not change (-23 %MVC in control group versus +6.2 %MVC in exercise group). There was no other statistically significant interaction exercise*time for the remaining movement tasks (p > 0.05) (Table 27) (Figure 23).

i.



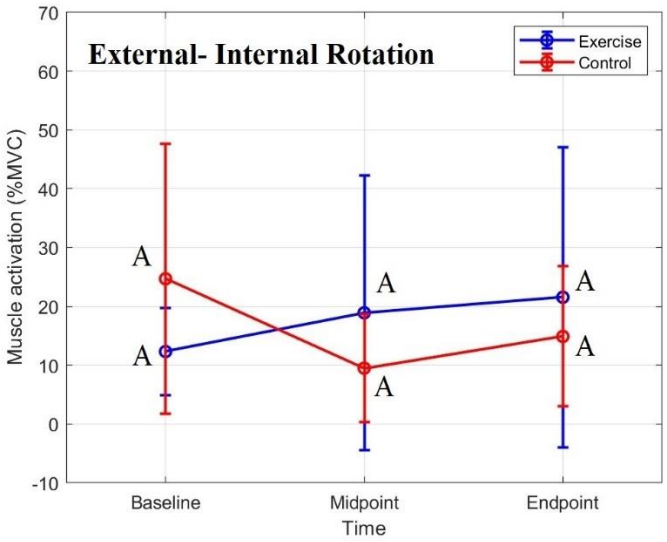
Latissimus dorsi activation in flexion-extension movements was influenced by an exercise*time interaction.

ii.



Latissimus dorsi activation in abduction-adduction movements was not influenced by an exercise*time interaction.

iii.



Latissimus dorsi activation in external-internal rotation movements was not influenced by an exercise*time interaction.

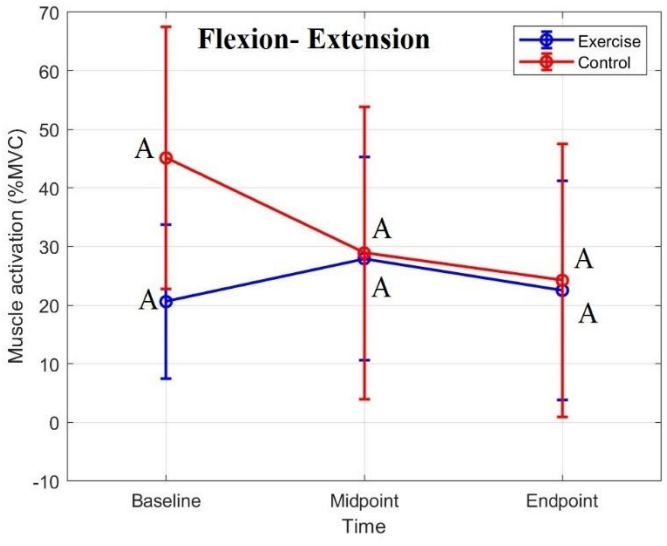
Figure 23. Interaction between time of treatment and exercise for latissimus dorsi activation and standard deviation for flexion-extension (i), abduction- adduction (ii), and external-internal rotation (iii) movement tasks. Data point not sharing the same upper-case letters are statistically significant from one another ($p < 0.05$). Significant interactions ($p < 0.05$) are represented by an asterisk *.

4.7.1.2 Teres Major

The Tukey post hoc test revealed that the activation of teres major in external-internal rotation movements was influenced by an exercise*time interaction (Table 27). There were

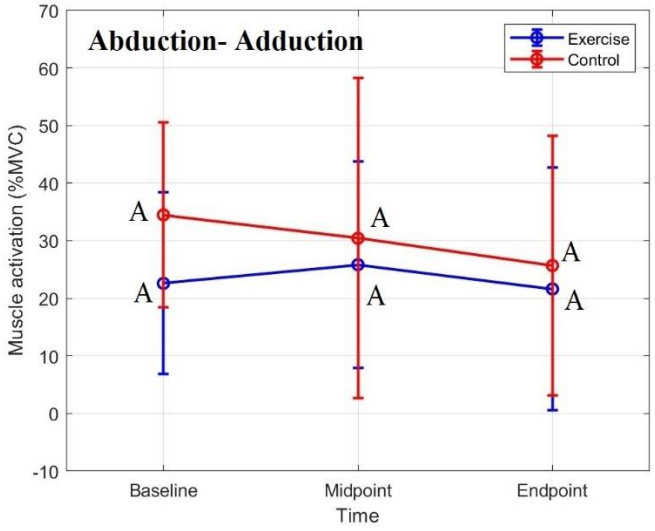
significant exercise*time interactions between baseline of the control group and midpoint of the exercise group (p = 0.03, Cohen's d = -1.222), between baseline of the control group and endpoint of the exercise group (p = 0.009, Cohen's d = -1.403), and between baseline of the control group and endpoint of the control group (p = 0.028, Cohen's d = 1.346). The effect of the teres major activation on the exercise group at midpoint and endpoint depended on the level of the control group at the baseline assessment. Moreover, the effect of time of teres major activation in the control group is different depending on the level at the baseline assessment. The mean activation of teres major in external-internal rotation movement tasks in the control group decreased over time from baseline to endpoint, whereas in the exercise group did not change (-20.7 %MVC in the control group versus -6 %MVC in exercise group). There was no other statistically significant interaction exercise*time for the remaining movement tasks (p > 0.05) (Table 27). (Figure 24).

i.



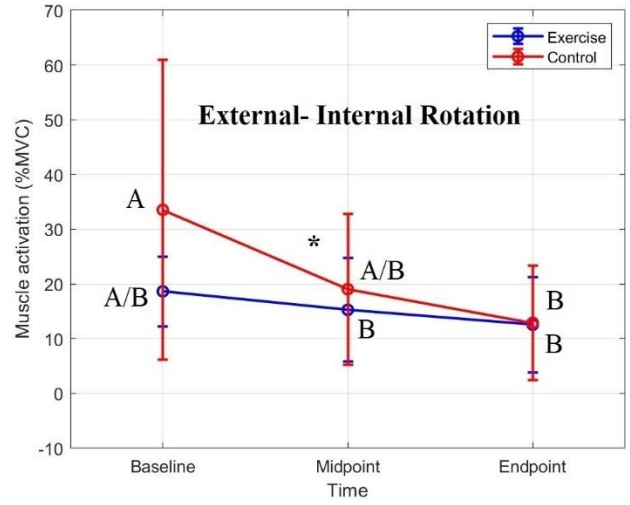
Teres major activation in flexion- extension movements was not influenced by an exercise*time interaction.

ii.



Teres major activation in abduction-adduction movements was not influenced by an exercise*time interaction.

iii.



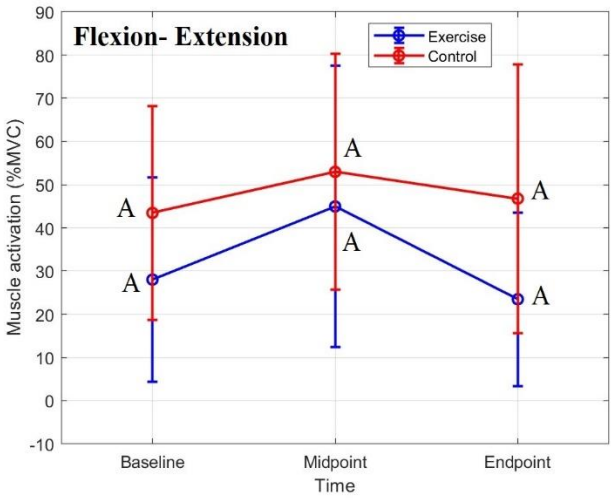
Teres major activation in external- internal rotation movements was influenced by an exercise*time interaction.

Figure 24. Interaction between time of treatment and exercise for teres major activation and standard deviation for flexion-extension (i), abduction- adduction (ii), and external-internal rotation (iii) movement tasks. Data point not sharing the same upper-case letters are statistically significant from one another ($p < 0.05$). Significant interactions ($p < 0.05$) are represented by an asterisk *.

4.7.1.3 Serratus Anterior

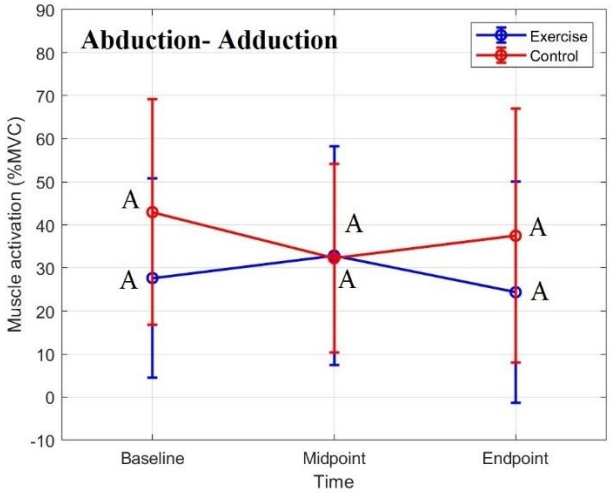
There was no statistically significant interaction exercise* time in any of the evaluated movement tasks for the serratus anterior activation ($p < 0.05$) (Table 27) (Figure 25).

i.



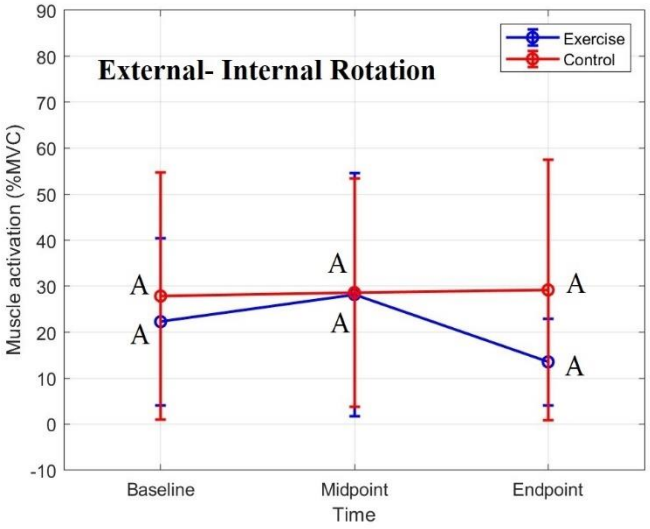
Serratus anterior activation in flexion- extension movements was not influenced by an interaction exercise*time.

ii.



Serratus anterior activation in abduction-adduction movements was not influenced by an interaction exercise*time.

iii.



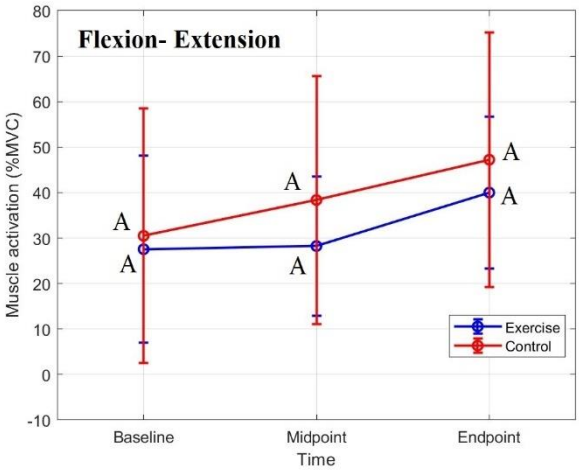
Serratus anterior activation in external-internal rotation movements was not influenced by an interaction exercise*time.

Figure 25. Interaction between time of treatment and exercise for serratus anterior activation and standard deviation for flexion-extension (i), abduction- adduction (ii), and external-internal rotation (iii) movement tasks. Data point not sharing the same upper-case letters are statistically significant from one another ($p < 0.05$). Significant interactions ($p < 0.05$) are represented by an asterisk *.

4.7.1.4 Pectoralis Major

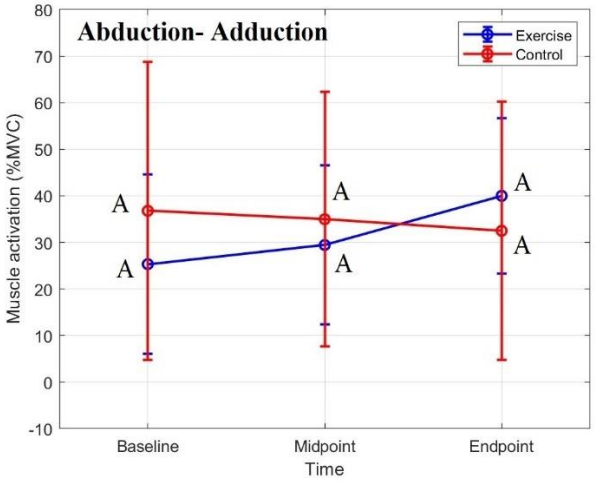
There was no statistically significant interaction exercise* time in any of the evaluated movement tasks for the pectoralis major activation ($p < 0.05$) (Table 27) (Figure 26).

i.



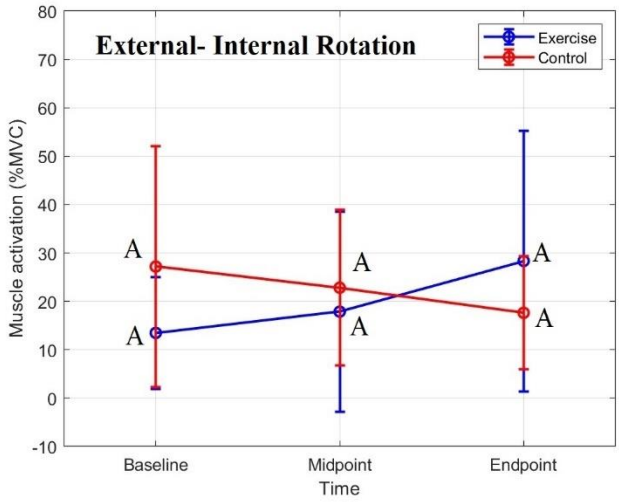
Pectoralis major activation in flexion-extension movements was not influenced by an interaction exercise*time.

ii..



Pectoralis major activation in abduction-adduction movements was not influenced by an interaction exercise*time.

iii.



Pectoralis major activation in external-internal rotation movements was not influenced by an interaction exercise*time.

Figure 26. Interaction between time of treatment and exercise for pectoralis major activation and standard deviation for flexion-extension (i), abduction- adduction (ii), and external-internal rotation (iii) movement tasks. Data point not sharing the same upper-case letters are statistically significant from one another ($p < 0.05$). Significant interactions ($p < 0.05$) are represented by an asterisk *.

Table 27. Mixed model ANOVA comparing exercise versus control groups. Time * exercise interactions results for latissimus dorsi, teres major, serratus anterior, and pectoralis major activation normalized to %MVC per muscle in flexion-extension (Flex_Ext), abduction- adduction (Abd_Add) and external-internal rotation (ER_IR) movement tasks (A) and Tukey-Kramer HSD Post Hoc results for significant exercise*time interactions (B).

A.

			Time*Ex	Tukey Post hoc significant?
Latissimus Dorsi		Flex_Ext	0.046	*
Teres Major		Flex_Ext	0.103	
Pectoralis Major		Flex_Ext	0.871	
Serratus Anterior		Flex_Ext	0.492	
Latissimus Dorsi		Abd_Add	0.07	
Teres Major		Abd_Add	0.831	
Pectoralis Major		Abd_Add	0.458	
Serratus Anterior		Abd_Add	0.362	
Latissimus Dorsi		ER_IR	0.08	
Teres Major		ER_IR	0.286	**
Pectoralis Major		ER_IR	0.09	
Serratus Anterior		ER_IR	0.511	

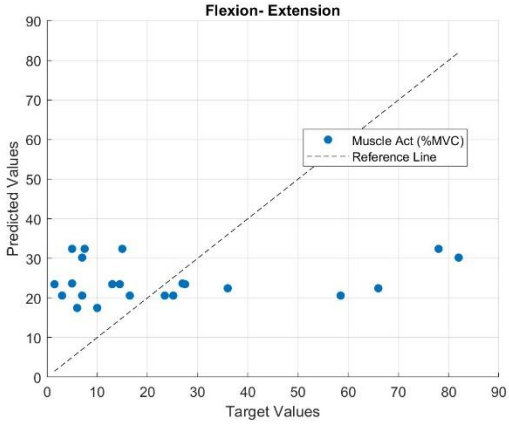
B.

	p value	levels	Cohen's d
*	0.02	baseline control- midpoint control	1.296
**	0.031	baseline control- midpoint exercise	-1.222
	0.009	baseline control- endpoint control	-1.403
	0.028	baseline control- endpoint control	1.346

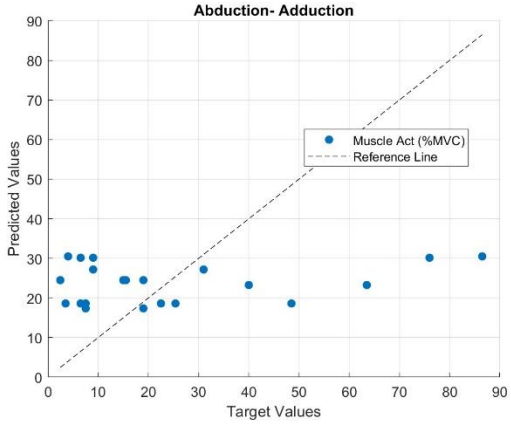
4.7.2 Radiation dose and radiation fractions as covariant for shoulder muscles activation in baseline, midpoint, and endpoint assessments for control versus exercise groups

A multiple linear regression was used to test if radiation dose and fractions significantly predicted muscles activation in the exercise group. A regression model was statistically significant in midpoint assessments of abduction- adduction movement tasks for teres major activation (r = 0.778, r ^ 2 = 0.605, p = 0.02). It was noted that radiation fractions positively predicted teres major activation with a strength of p = 0.008 (Table 28) (Figure 27). Similarity, there were positive correlations between radiation fractions and pectoralis major for the control group (p > 0.05). Multiple linear regression analysis for control group can be found in Chapter III, results, pages 53-60)

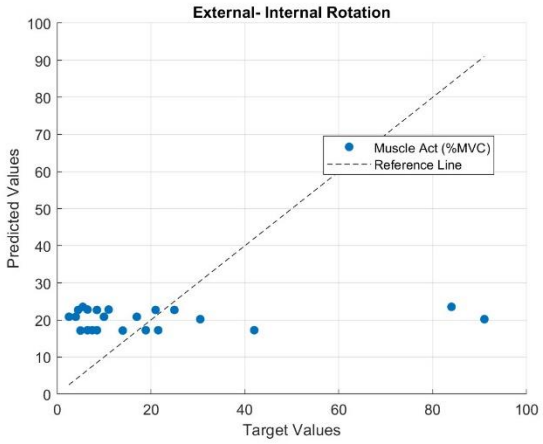
a.



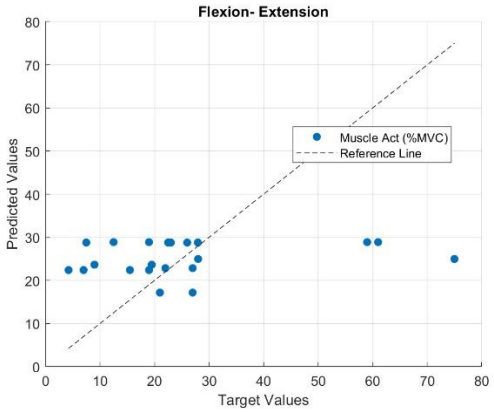
b.



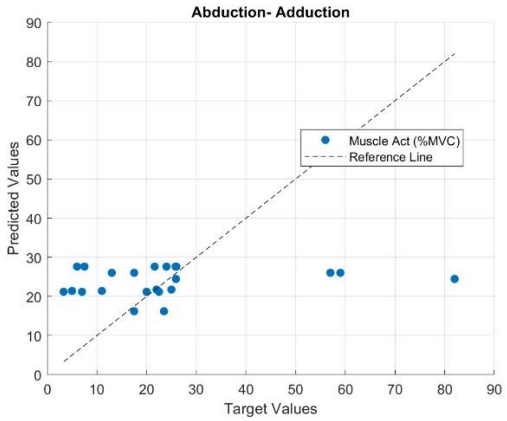
c.



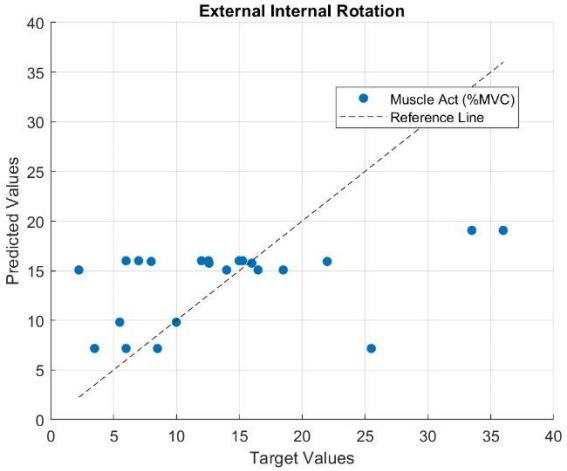
d.


Flexion- Extension
Muscle Act (%MVC)
Reference Line
Predicted Values
Target Values

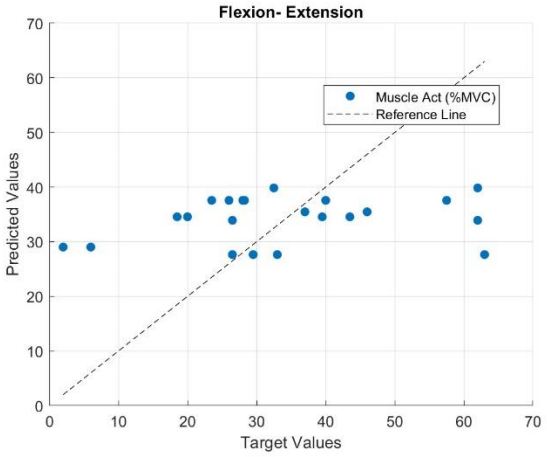
e.


Abduction- Adduction
Muscle Act (%MVC)
Reference Line
Predicted Values
Target Values

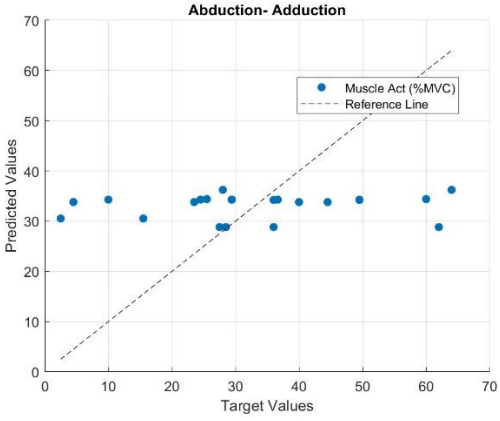
f.

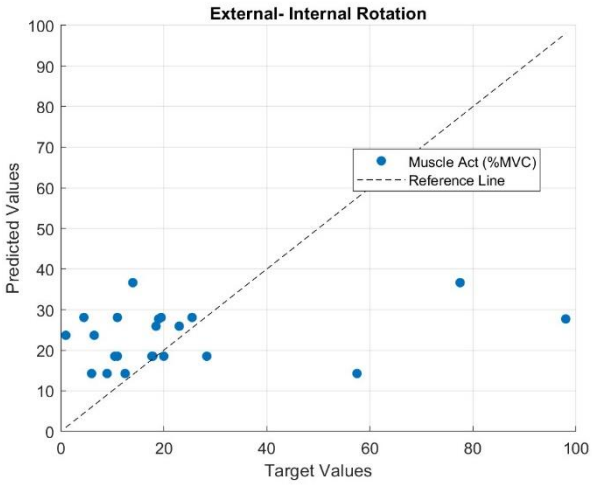

External Internal Rotation
Muscle Act (%MVC)
Reference Line
Predicted Values
Target Values

g.

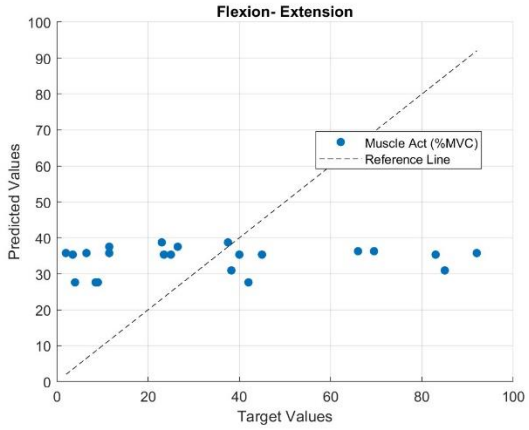

Flexion- Extension
Muscle Act (%MVC)
Reference Line
Predicted Values
Target Values

h.

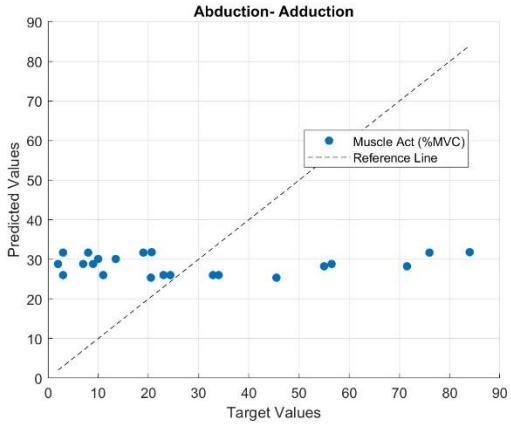

Abduction- Adduction
Muscle Act (%MVC)
Reference Line
Predicted Values
Target Values


External- Internal Rotation
Predicted Values
Target Values
Muscle Act (%MVC)
Reference Line

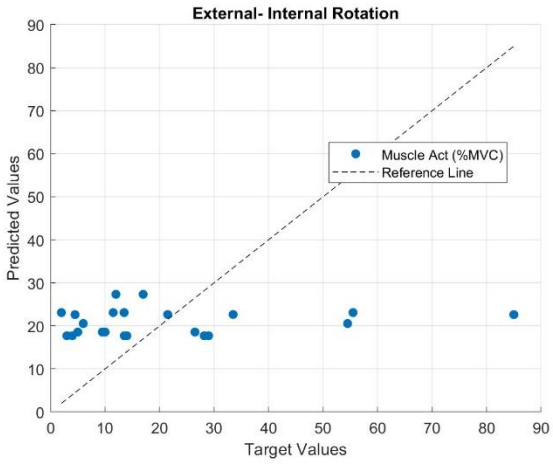
i.


Flexion- Extension
Predicted Values
Target Values
Muscle Act (%MVC)
Reference Line

j.


Abduction- Adduction
Predicted Values
Target Values
Muscle Act (%MVC)
Reference Line

k.



l.

Figure 27. Multiple linear regression scatter plot for exercise group showing target radiation dose and fractions versus predicted values of latissimus dorsi (a-b-c), teres major (d-e-f), pectoralis major (g-h-i), and serratus anterior (j-k-l) activation at flexion- extension, abduction-adduction, and external- internal rotation movement tasks.

Table 28. Multiple linear regression analysis results of exercise group for latissimus dorsi, teres major, pectoralis major, and serratus anterior for the three movement evaluation tasks, in midpoint and endpoint scenarios. Flex_Ext = Shoulder Flexion- Extension movement task, Abd_Add = Shoulder Abduction – Adduction movement task, ER_IR = Shoulder External- Internal Rotation movement tasks, Rad_F = radiation fractions, Rad_D = radiation dose, CI = Confidence Interval, t = t value (Coefficient estimate/ st error): negative sign (–) stands for negative correlation, positive sign (+) stands for positive correlation

Latissimus Dorsi

Flex_ Ext						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.173	0.415	0.886	0.403	0.634	0.492

Abd_Add						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.196	0.442	0.855	0.458	0.676	0.391

ER_IR						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.269	0.518	0.741	0.385	0.620	0.527

Teres Major

Flex_ext						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.641	0.800	0.120	0.319	0.564	0.651

Abd_Add						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.778	0.882	0.024	0.431	0.656	0.440
	Coefficients			Coefficients		
	t	p value	St error	t	p value	St error
Rad_F	3.483	0.008	1.001	0.999	0.347	1.692
Rad_D	-2.130	0.066	1.690	-0.022	0.983	2.858
	95 % CI			95 % CI		
	lower	upper		lower	upper	
Rad_F	1.178	5.795		-2.211	5.593	
Rad_D	-7.499	0.297		-6.652	6.528	

ER_IR						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.492	0.701	0.330	0.266	0.515	0.746

Pectoralis Major

Flex_Ext						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.494	0.702	0.326	0.233	0.482	0.801

Abd_Add						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.332	0.576	0.627	0.238	0.487	0.792

ER_IR						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.201	0.448	0.849	0.517	0.719	0.289

Serratus Anterior

Flex_Ext						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.456	0.675	0.394	0.456	0.675	0.394

Abd_Add						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.157	0.396	0.906	0.659	0.811	0.102

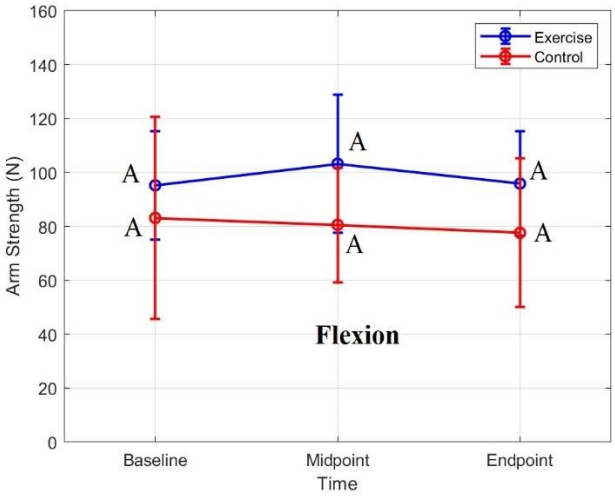
ER_IR						
	Midpoint			Endpoint		
	Model			Model		
	r	r^2	p value	r	r^2	p value
	0.085	0.291	0.971	0.545	0.738	0.244

4.8 Arm strength

4.8.1 Comparison of arm strength across baseline, midpoint, and endpoint assessments in control versus exercise groups

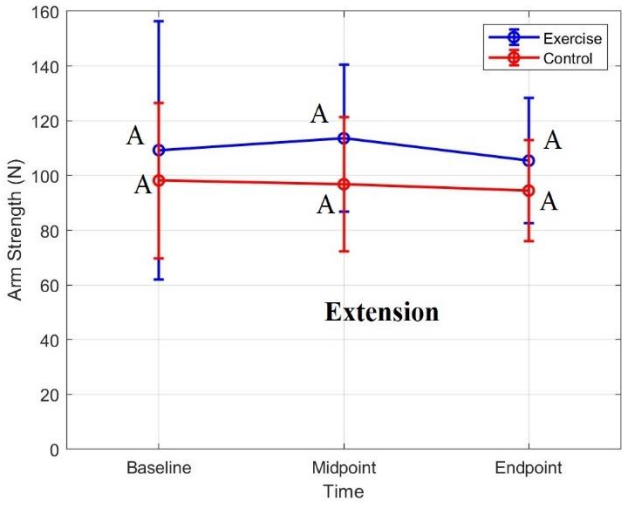
The Tukey post hoc test revealed that the arm strength in abduction movements was influenced by an exercise*time interaction (Table 29). There were significant exercise*time interactions between midpoint of the control group and midpoint of the exercise group ($p = 0.01$, Cohen's $d = 1.341$). The effect of the arm strength on the exercise group at midpoint assessments depended on the level of the control group at the midpoint assessment. The mean arm strength in the control group decreased over time from baseline to midpoint, whereas in the exercise group increased (95 N to 85 N in the control group versus 105 N to 120 N in exercise group). There was no other statistically significant interaction exercise* time in any of the evaluated movement tasks for arm strength ($p < 0.05$) (Figure 28) (Table 29).

i.



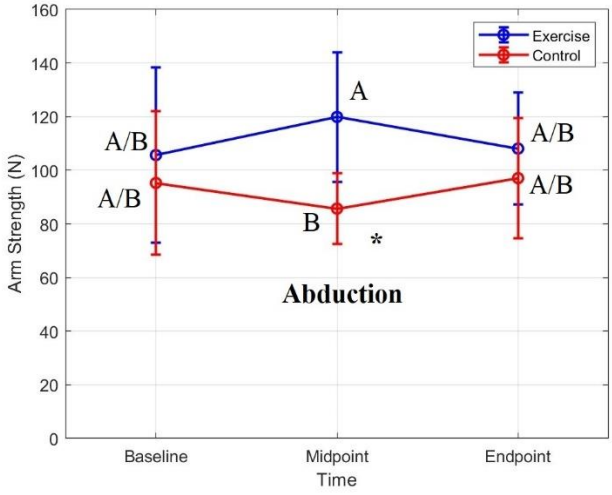
Arm strength in flexion movements was not influenced by an interaction exercise*time.

ii.



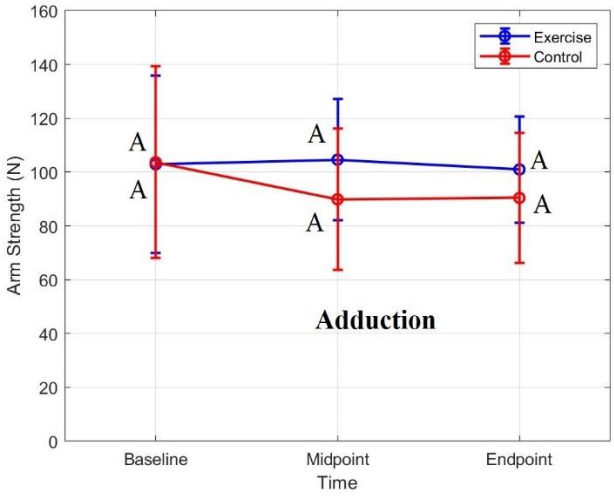
Arm strength in extension movements was not influenced by an interaction exercise*time.

iii.



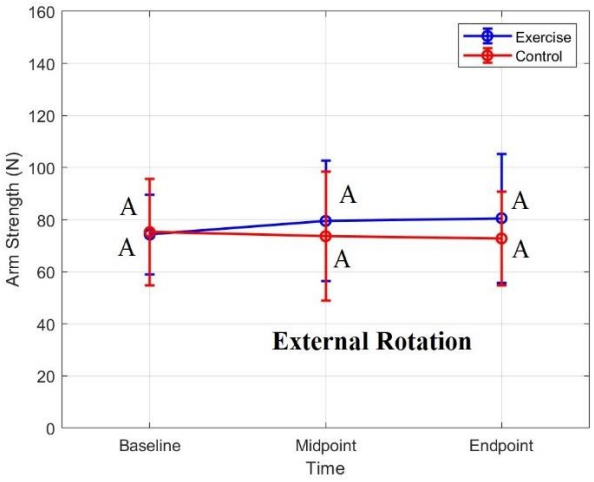
Arm strength in abduction movements was influenced by an interaction exercise*time.

iv.



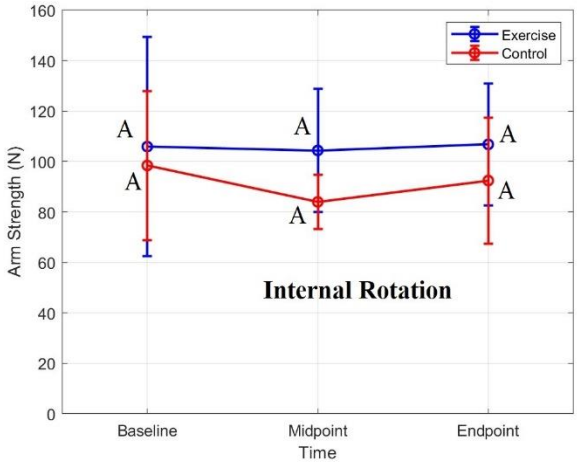
Arm strength in adduction movements was not influenced by an interaction exercise*time.

v.



Arm strength in external rotation movements was not influenced by an interaction exercise*time.

vi.



Arm strength in internal rotation movements was not influenced by an interaction exercise*time.

Figure 28. Interaction between time of treatment and exercise for arm strength and standard deviation for flexion (i), extension (ii), abduction (iii), adduction (iv), external rotation (v), and internal rotation (vi) movement tasks. Data point not sharing the same upper-case letters are statistically significant from one another ($p < 0.05$). Significant interactions ($p < 0.05$) are represented by an asterisk *.

Table 29. Mixed model ANOVA: time * exercise interactions results comparing exercise versus control groups for arm strength in flexion (Flex), extension (Ext), abduction (Abd), adduction (Add), external (ER), and internal rotation (IR) movement tasks (A) and Tukey-Kramer HSD Post Hoc results for significant exercise*time interactions (B).

A.

	Time*Ex	Tukey Post hoc significant?		
Flex	0.737			
Ext	0.953			
Abd	0.075	*		
Add	0.211			
ER	0.638			
IR	0.52			

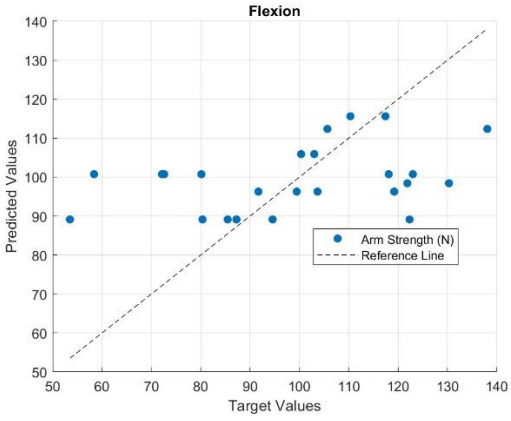
B.

	p value	levels	Cohen's d
*	0.018	midpoint control- midpoint exercise	1.341

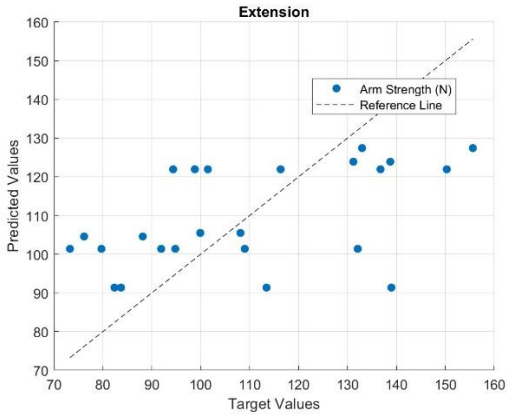
4.8.2 Radiation dose and radiation fractions as covariant for shoulder muscles strength in baseline, midpoint, and endpoint assessments for control versus exercise groups

A multiple linear regression was used to test if radiation dose and fractions significantly predicted arm strength in the exercise group. There were no significant regression models ($p > 0.05$) (Table 30) (Figure 29). Positive and negative regressions in arm strength and the dependent variables were noted in the control group ($p > 0.05$). Multiple linear regression analysis for control group can be found in Chapter III, results, pages 62-65).

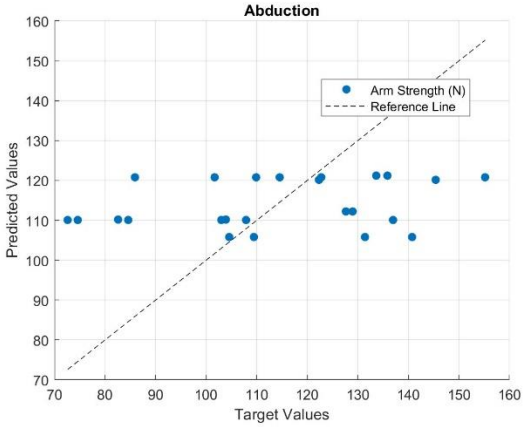
a.



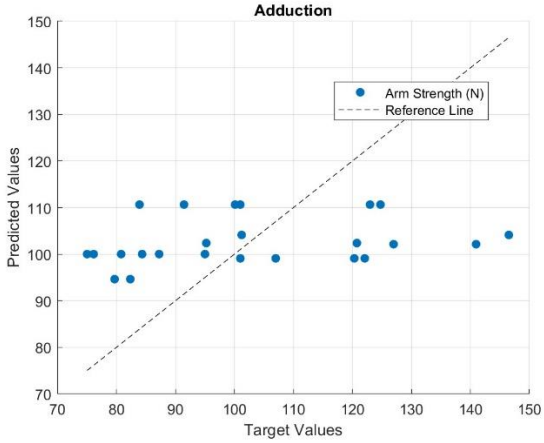
b.



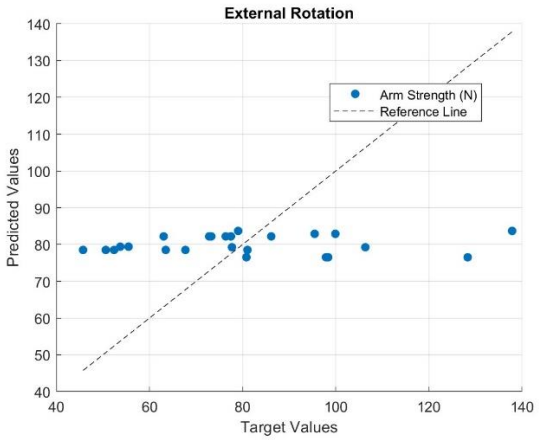
c.



d.



e.



f.

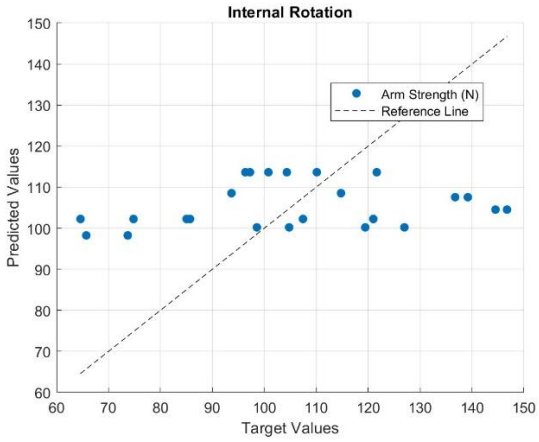


Figure 29. Multiple linear regression scatter plot for exercise group showing target radiation dose and fractions versus predicted values of arm strength at flexion (a), extension (b), abduction (c), adduction (d) external (e), and internal rotation (f) movement tasks.

Table 30. Multiple linear regression analysis results of exercise group for arm strength for the six movement evaluation tasks, in midpoint and endpoint scenarios.

Arm Strength

Flexion						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.384	0.619	0.488	0.380	0.616	0.496

Extension						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.669	0.817	0.07	0.390	0.624	0.476

Abduction						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.454	0.673	0.354	0.08	0.282	0.965

Adduction						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.346	0.588	0.564	0.401	0.633	0.457

External Rotation						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.463	0.680	0.338	0.265	0.514	0.720

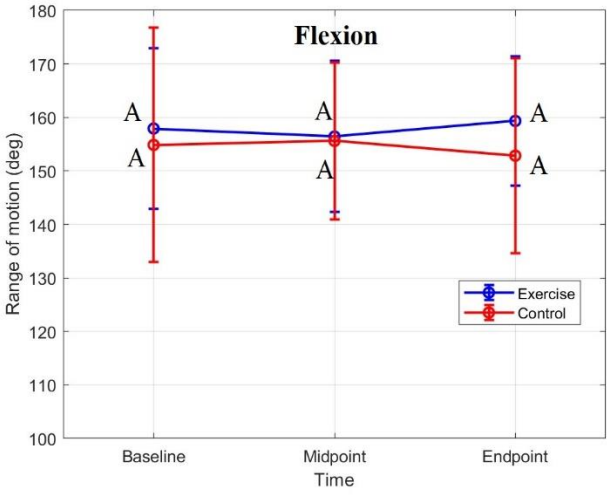
Internal Rotation						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.470	0.685	0.326	0.139	0.372	0.916

4.9 Shoulder complex range of motion

4.9.1 Comparison of shoulder complex range of motion across baseline, midpoint, and endpoint assessments in control versus exercise groups

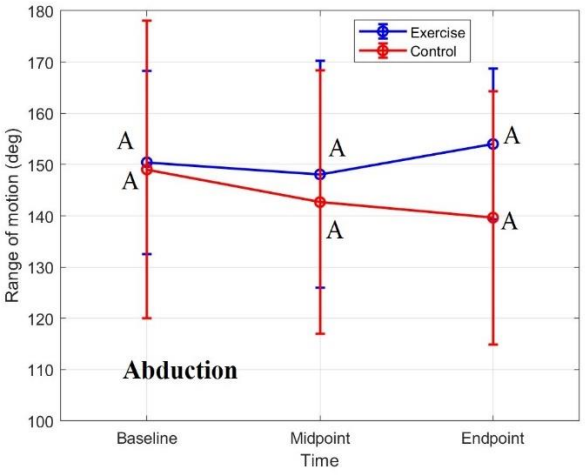
There was no statistically significant interaction exercise* time in any of the evaluated movement tasks for the shoulder complex range of motion ($p < 0.05$) (Figure 30) (Table 31).

i.



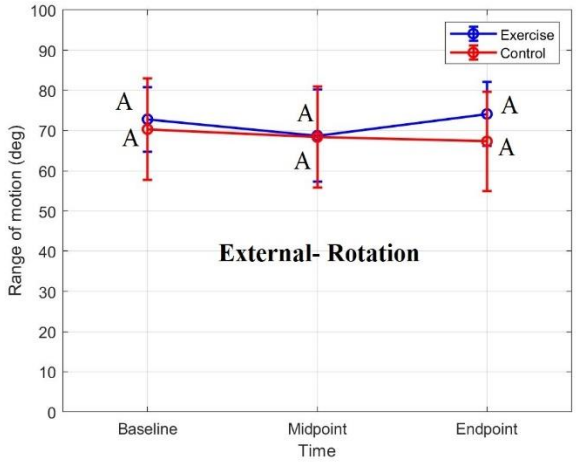
Shoulder flexion range of motion was not influenced by an interactions exercise*time.

ii.



Shoulder abduction range of motion was not influenced by an interactions exercise*time.

iii.



Shoulder external rotation range of motion was not influenced by an interactions exercise*time.

Figure 30. Interaction between time of treatment and exercise for shoulder complex range of motion and standard deviation for flexion (i), abduction (ii), and external rotation (iii) movement tasks. Data point not sharing the same upper-case letters are statistically significant from one another ($p < 0.05$). Significant interactions ($p < 0.05$) are represented by an asterisk *.

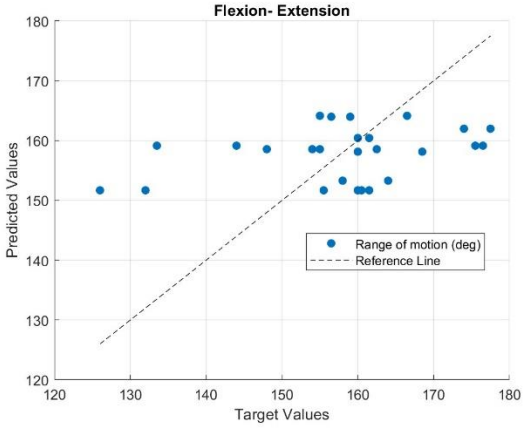
Table 31. Mixed model ANOVA : time * exercise interactions results comparing exercise versus control groups for shoulder complex range of motion in flexion (Flex), abduction (Abd) and external rotation (ER) movement tasks.

	Time*Ex	Tukey Post hoc significant?		
Flex	0.406			
Abd	0.103			
ER	0.147			

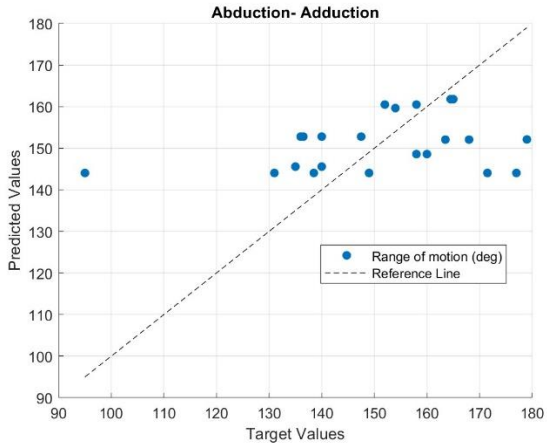
4.9.2 Radiation dose and radiation fractions as covariant for shoulder complex range of motion in baseline, midpoint, and endpoint assessments for control versus exercise groups

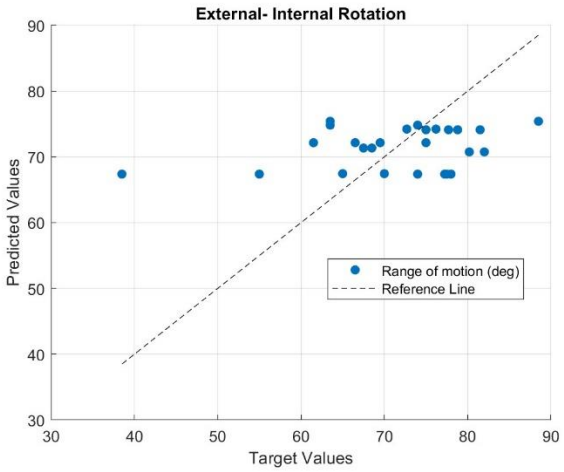
A multiple linear regression was used to test if radiation dose and fractions significantly predicted shoulder complex range of motion in the exercise group. There were no significant regression models ($p > 0.05$) (Table 32) (Figure 31). Positive and negative regressions in arm strength and the dependent variables were noted in the control group ($p > 0.05$). Multiple linear regression analysis for control group can be found in Chapter III, results, pages 67-69).

a.



b.





c.

Figure 31. Multiple linear regression scatter plot for exercise group showing target radiation dose and fractions versus predicted values of shoulder complex range of motion at flexion (a), abduction (b), and external rotation (c) movement tasks.

Table 32. Multiple linear regression analysis results of exercise group for shoulder complex range of motion for the three movement evaluation tasks, in midpoint and endpoint scenarios. Flex_Ext = Shoulder Flexion- Extension movement task, Abd_Add = Shoulder Abduction – Adduction movement task, ER_IR = Shoulder External- Internal Rotation movement tasks.

Shoulder complex range of motion

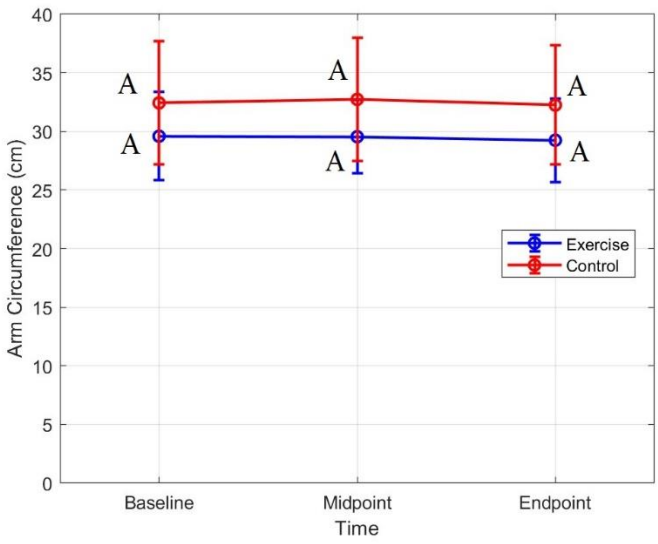
Flex_Ext						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.294	0.542	0.637	0.231	0.480	0.761

Abd_Add						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.331	0.573	0.560	0.394	0.627	0.430

ER_IR						
	Midpoint			**Endpoint**		
	Model			**Model**		
	r	**r^2**	**p value**	**r**	**r^2**	**p value**
	0.037	0.192	0.993	0.070	0.264	0.975

4.10 Arm Circumference

There was no statistically significant interaction exercise* time for the arm circumference ($p < 0.05$). The mean arm circumference in control group was 32.5cm in baseline, 32.7 cm in midpoint and 32.4 cm in endpoint, whereas in exercise was 29.5 cm in baseline, 29.6 cm in midpoint and 29.5 cm in endpoint (Figure 32). There was no significant regression between radiation dose nor fractions and arm circumference for control and intervention groups in any of the assessments ($p > 0.05$).



Arm circumference was not influenced by an interaction exercise*time.

Figure 32. Interaction between time of treatment and exercise for arm circumference and standard deviation. Data point not sharing the same upper-case letters are statistically significant from one another ($p < 0.05$). Lines not sharing the same lower-case letters are statistically significant from one another ($p < 0.05$). Significant interactions ($p < 0.05$) are represented by an asterisk *.

.

4.11 Discussion

The present research highlights the effects of an intervention program focused on shoulder muscles strengthening during the radiation therapy window in breast cancer patients. Differences in shoulder health indicators emerged between exercise and control groups. A main effect of time and an interaction exercise*time influenced the activation of latissimus dorsi and teres major. Participants of the exercise group had greater muscle activation further in time compared to the control group. The strengthening exercises influenced arm strength in the three evaluated movements. Participants of the exercise group had greater arm strength in all movements. The differences between groups elucidate the likely effectiveness of strengthening exercises in shoulder muscles to overcome potential shoulder performance decrements produced by radiation therapy during the treatment window.

4.11.1 Shoulder muscles activation

Muscle activation was influenced by exercise*time interaction in latissimus dorsi and teres major muscles. The first hypothesis suggested that pectoralis major activation would be higher in the control group at endpoint assessments, and that latissimus dorsi, teres major, and serratus anterior activation would be lower in control group at endpoint assessments. Abnormal muscle activation patterns, which include lower activity, can lead to a decrease in muscle capacity and cause shoulder morbidities (Brookham et al., 2018). This hypothesis was partially accepted, as reductions in the activity of latissimus dorsi and teres occurred in the control group. However, the activation of serratus anterior was higher in the control group and the pectoralis major activity did not experience any significant change.

The activation of serratus anterior was not influenced by the interaction exercise*time (Figure 25). The serratus anterior mainly functions in scapular protraction and is active during

anterior tasks (Moore et al, 2014), such as those performed in the present study. Previous strengthening intervention programs in cancer patients caused increased serratus anterior activity. Oral cancer patients received one month of an intervention program focused on strengthening the scapular muscles between neck dissection surgery and the initiation of radiotherapy. The sEMG of these muscles were tracked pre and post intervention and compared to a control group. The results showed a reduction in serratus anterior activation in the control group and an increase in the intervention group (Chen et al., 2019). The current study does not match these findings. These discrepancies may reflect different muscle strategy adaptations due to the type of movement performed. The highest activation of the serratus anterior occurs at 120-150 degrees of shoulder elevation (Mosely et al., 1992). The flexion-extension movements in which the main effect of exercise was observed involved 180 degrees of shoulder elevation range of motion. Therefore, serratus anterior dysfunctions are expected in extreme postures. The reduction of serratus anterior activation could also be an adaptation to other muscles not tracked improving their activation (Kruse et al., 2021).

Latissimus dorsi activation was influenced by the exercise*time interaction in flexion-extension movements (Figure 23). Similarly, teres major activation was influenced by the exercise*time interaction in external and internal rotation movements (Figure 24). The latissimus dorsi decreased 20% MVC at endpoint compared to baseline in the control group, whereas in the exercise group it increased 4.5% MVC. The teres major activation decreased in both exercise and control groups at endpoint compared to baseline. However, the average decrements were higher for the control group (20.7 % difference in control group versus 6% difference in exercise group). The muscle activity reductions of latissimus dorsi and teres major in the control group elucidates the influence of inflammation produced by radiation therapy. Despite locating

anteriorly, the inflammation affection in this muscle by radiation therapy is expected. The teres major and latissimus dorsi were sensitive to most of the radiation treatment plans simulated for breast cancer patients (Lipps et al., 2017). In the present research, the treatment plans were very individualized, but most of the patients received whole right and left breast radiation. This treatment plan is likely to irradiate the axilla (Jang et al., 2020). The expansion of the treatment volume, including the axilla, increases the irradiation to muscles such teres major and latissimus dorsi (Lipps et al., 2017). Moreover, it is possible that other muscles not being tracked may have compensated thereby enabling task performance.

The pectoralis major activation was not influenced by the interaction exercise*time. Previous studies following similar protocols as the present study encountered the same finding. A resistance training intervention program instructed in breast cancer patients tracked the EMG activity of shoulder muscles pre and post intervention during a maximal isometric chest press protocol. No significant differences in pectoralis major activation were noted between affected and un-affected sides (Hagstrom et al., 2019). In the current study, the lack of significant changes could be related to the tests selected to track muscle activation. The submaximal tests involved performing shoulder elevation movements up to 180 degrees. The pectoralis major reaches its maximum force capacity at lower shoulder elevation angles (Ackland et al., 2008). It is possible that its activation was not highly recruited during the current range of submaximal tests.

4.11.2 Arm strength

Arm strength was influenced by an exercise*time interaction in abduction-adduction movement tasks. It was hypothesized that control group would have lower arm strength at endpoint assessments compared to exercise group. This hypothesis was partially accepted. The

exercise group exhibited greater arm strength in shoulder abduction (Figure 28). Arm strength reductions following radiation therapy as noticed in the control group were documented in previous research. Blomqvist et al (2004) assessed shoulder health indicators 15 months after receiving oncological treatment in affected versus non affected side for irradiated and non-irradiated breast cancer patients. There were shoulder strength reductions ($p < 0.05$) in the irradiated group in flexion, extension, and abduction movements, whereas the non-irradiated only presented reductions in flexion. Breast cancer survivors 6 months after completing their treatment had lower strength in abduction and upward rotation, depression and adduction, flexion, external rotation, internal rotation, and scaption than healthy controls (Harrington et al., 2011). Shoulder protractors, retractors, and extensors were weaker in affected versus non-affected side of breast cancer survivors who received oncological treatment at least 6 months prior to the study (Merchant et al., 2008).These findings support the arm strength deficits experienced by the control group produced by radiation treatment.

Similar to the current findings, prior investigations suggested that resistance and strengthening exercises improved upper body strength in breast cancer survivors.) These interventions proved that strengthening exercises were successful for improving upper extremity strength in breast cancer survivors; however they were implemented months to year after the completion of oncological treatment. A 16-week resistance training intervention was prescribed to breast cancer survivors including machine-based and barbell exercises. Upper body strength was tracked through an isometric chest press protocol and compared to a control group. There were significant ($p < 0.05$) improvements in upper body strength at the end of the intervention compared with baseline for the exercise group and no differences for the control group (Hagstrom et al., 2017). In another investigation, breast cancer survivors completed a one-year

randomized controlled trial assigned to a strength training intervention or a stretching control program. Muscle strength was assessed through maximal bench press and leg press. Women in the intervention program significantly improved maximal leg and bench press strength compared to the control group ($p < 0.05$). The intervention group performed 56.3 lb in baseline versus 63.3 lb at 12 months for the bench press, and 167.9 lb versus 201.3 lb for the leg press. The control group performed 57.9 lb in baseline versus 61.1 lb at 12 months for the bench press, and 174 lb versus 191 lb for the leg press (Winters-Stone et al., 2012). This current study shared the same findings while performing an intervention within the treatment window, meaning that our early intervention program was effective on preventing those potential strength deficits in shoulder abduction.

4.11.3 Shoulder complex range of motion

The shoulder complex range of motion was not influenced by the interaction exercise*time. It was hypothesized that the control group would have lower range of motion at endpoint assessments compared to intervention group. This hypothesis was not accepted. The control group had a lower trend in range of motion than the intervention group. However, this difference was not significant. Shoulder complex range of motion reductions produced by radiation therapy were recognized by prior research. Shoulder abduction decreased in patients following radiation therapy and surgery (Smooth et al., 2016), and also decreased in breast cancer patients receiving radiation therapy comparing affected versus non-affected sides (Brookham et al., 2018). There is evidence of strengthening exercises implemented in breast cancer patients and the assessment of shoulder range of motion. A 6-week post-radiation program that consisted of upper limb strengthening exercises and stretching exercises was performed by breast cancer survivors and compared to a control group receiving standard care. The authors reported improvements in

shoulder external rotation and horizontal abduction in the intervention group 3 months after intervention. However, as in the current study, these improvements were not significant (Ibrahim et al., 2017). A 4-week intervention program for breast cancer survivors diagnosed with lymphedema that combined aerobic and upper extremity strengthening exercises was compared to a control. The findings showed significant reductions in the control group in flexion, extension, abduction, adduction, external and internal rotation (Park, 2017). The differences between the present study and Park's are that the latter included patients that were already diagnosed with lymphedema. The improvement in shoulder range of motion through strengthening exercises could be mostly allied to an improvement in arm lymphedema. Moreover, the time when Park's intervention program was implemented was up to three years after breast cancer surgery, whereas in the current study the exercises were prescribed in the treatment window. Another explanation of the lack of significant findings in the present research could be related to the type of radiation therapy prescribed to the patients. Most of the participants of both intervention and control groups received radiation confined to the whole breast. This type of radiation can lead to a decrease in lymphedema incidence compared to other treatment regimens and an improvement in potential shoulder range of motion impairments caused by the therapy (Lee et al., 2008).

Finally, the current study tracked shoulder movements such as flexion, abduction, and external rotation because they are involved in many activities of daily living and are most affected in breast cancer patients after receiving oncological treatment (Smoot et al., 2016; Brookham et al., 2018; Maciukiewicz et al., 2022). Future research could consider tracking other shoulder movements not studied in the present research, such as internal rotation, adduction, and

extension, to better understand the implications of an intervention program over the whole shoulder complex during the radiation therapy window in breast cancer patients.

4.11.4 Arm Circumference

It was hypothesized that the control group would have greater arm circumference at endpoint assessments compared to intervention group. This hypothesis was rejected. There was no interaction exercise*time between control and exercise groups. Future research may be more able to detect changes in this variable in a long-term study, since this condition usually develops months or years after the completion of radiation treatment (Shah & Vicini, 2011).

4.11.5 Intervention program, radiation dosage, and questionnaire

The strengthening exercises overcame the influence of radiation fractions in arm strength. It was hypothesized that radiation dose and fractions would be negatively correlated with reductions in arm strength, activation, and shoulder complex range of motion in controls. It was also hypothesized that the exercise group would have no significant negative correlations between radiation dose and fractions and arm strength, activation, and shoulder complex range of motion. These hypotheses were accepted. In the control group, there was a negative correlation between radiation dose and shoulder abduction range of motion, and between radiation fractions and arm strength in abduction movements. Additionally, there were no correlations between radiation fractions nor dose and any of the shoulder indicators in the intervention group. The intervention program was effective to compensate for shoulder abduction restrictions. The lack of negative correlations between radiation dose and fractions and the rest of the shoulder health indicators in the control group may be attributable to several reasons. It could be that other factors like age, BMI, and pre-existing conditions affect shoulder functionality more than radiation dose and fractions (Bazan et al., 2021). It also could be explained by the absence of

good spread of the predictor variable, being the radiation dose and fractions not varied enough to predict powerful correlations. Furthermore, all patients received IMRT regimen plans. This regimen was proved to be safer and target more accurately the tumors (Donovan et al., 2007). Additionally, the type of treatment prescribed to the majority of the patients in this study was whole breast irradiation. This treatment type accounted for less incidence of shoulder impairments (Lee et al., 2008) compared to other modalities including the axillary nodes irradiation (Lipps et al., 2017). Other parameters not explored in this study could be accounting for radiation dose and fractions. Stiffness and elastic shear modulus presented correlations with radiation dose in breast cancer survivors in irradiated muscles like pectoralis major (Lipps et al., 2018). Further research may quantify stiffness and elastic shear modulus during the radiation treatment window and determine if correlations with radiation dose still occur.

The improvements in shoulder health indicators by the exercise group were not influenced by other external exercises performed by their participants. When comparing the average number of hours of exercise per week performed by each group, no major differences between them are noted. The control group achieved 10 hours of strenuous exercise, 15 hours of moderate exercise, and 10 hours of mild exercise. Whereas the exercise group reached 7.5 hours of strenuous exercise, 18 hours of moderate exercise, and 17 hours of mild exercise. Many factors can influence the effectiveness of an intervention program. In terms of total physical activity performed by the patients, the reading of the questionnaire outcomes suggests that the improvements in health indicators in the exercise group were associated primarily with the performance of the strengthening exercise program. Although not assessed, motivation could have played an important role in the adherence of participants to the exercise group. Participants

had the choice to withdraw from the research at any point, and except for a few cases, most of them decided to complete the intervention program.

4.12 Limitations

Several considerations should delimit interpretation of these findings. As data collection for the current study was in conjunction with study 1, all the limitations stated in study 1 related to equipment and methods, apply also for study 2. Regarding the Mixed model ANOVA testing, baseline differences between groups were statistically tested. Except for the activation of the latissimus dorsi muscle during flexion-extension movement tasks, there were no significant baseline differences between the groups for all other findings ($p > 0.05$). The control and exercise groups had no significant baseline differences, except for the activation of the latissimus dorsi muscle during flexion-extension movement tasks ($p > 0.05$). Although the exercise group had more capability in most of the assessed variables from the beginning of the treatment, this difference was not statistically significant. The small sample size could be obscuring potential baseline differences. The lack of stratification in the randomized group allocation could have led to regression towards the mean. This could be due to some patients who were randomly allocated to the intervention or control group but did not want to participate in the study if the radiation treatment prescribed to them was shorter than 6 weeks (the intervention program length). In such cases, they were offered the option to be part of the observational group instead. Thus, only those patients who were stronger, willing to exercise, and were assigned to the exercise group completed the intervention program. This may explain why the exercise group performed better from the beginning of the treatment.

Regarding the intervention program, three patients withdrew from the study arguing shoulder pain and discomfort due to radiation therapy. Therefore, a potential limitation is that the program may not be effective for all patients due to differences in the severity of the symptoms experienced from the treatment. Withdrawals and low adherence to intervention programs in breast cancer survivors' population is relatively common due to factors such fear or pain of using the affected arm and cancer-related fatigue (Hagstrom et al., 2017). Prior work also reported withdrawals from an intervention program arguing difficulties with activities of daily living, lower mental health scores by recent cancer diagnosis, and lack of time commitment, (Winters-Stone et al., 2012; Kilbreath et al., 2012; Chen et al., 2020). In the current study, in case patients complained about shoulder discomfort, alternative ways to perform each exercise were proposed, as well as optional decreases in weight and repetitions. It was important to maintain constant follow-up with patients to make sure that they were feeling well and still willing to complete the program.

4.13 Conclusions

Study purpose: To examine the effects on shoulder function indicators of an intervention program focused on shoulder strength prescribed during the radiation therapy window in breast cancer patients.

Main findings:

- Mixed model ANOVA revealed significant exercise*time interactions in flexion-extension movements for latissimus dorsi activation between baseline and midpoint assessments of the control group. The latissimus dorsi activation in the control group decreased from baseline to midpoint and did not change in the exercise group. Another interaction was noted in external- internal rotation movements for teres major activation between baseline assessments of the control group and midpoint and endpoint assessments of the exercise group, and between baseline and midpoint assessments of control group. The teres major activation in the control group decreased from baseline to endpoint assessments. Finally, another interaction was reported in abduction movements of arm strength, between midpoint assessments of the control and exercise groups. The arm strength in the control group was lower in midpoint assessments than the exercise group. No other significant exercise*time interaction was observed in the remaining shoulder health indicators.
- Multiple linear regression analyses only reported negative significant regressions for radiation dose and fractions and shoulder abduction range of motion and abduction strength for the control group. No significant regressions occurred in the exercise group.

Recommendations:

- Future research shoulder should explore other forms of interventions to determine the improvement of all shoulder health indicators.
- Longer term follow-up of these shoulder health indicators to determine the persistency of these effects.

Chapter 5 - Use of quantitative ultrasound imaging of bone (QUSIB) for more accessible rib quality assessments in breast cancer patients

5.1 Introduction

Breast cancer is one of the most common types of cancer in women, with an estimated 2.1 million cases per year worldwide and over 627.000 deaths (WHO, 2019). Early detection and improved treatments have led to a decreased mortality rate from breast cancer in Europe by 23% between 1989 and 2006 (Bossetti et al., 2012). However, despite the decrease in mortality rate due to the disease itself, the complications and side effects of the treatments cause an increase of morbidity and a challenging path to recovery (Senkus-Konefka, and Jassem, 2006). Some of these adverse symptoms affect body composition changes, more specifically bone quality.

There is a well-known association between decreased bone quality and oncological treatment in breast cancer patients. The breast cancer population is predisposed to losses of bone mineral density (BMD) mainly due to direct or indirect effect of radiotherapy (Harris, 2016; Senkus- Konefka, 2006; Mesurolle et al., 2000). However, other therapies like the bisphosphonates promote the increase of BMD, which can also affect the bone quality and lead to fractures (Harris, 2016). Previous studies showed that breast cancer patients receiving oncological treatment had lower BMD in the forearm (Broeckel et al., 2000; Tisdale, 2022), and femoral neck (Artese, 2017) compared to healthy age and weight-matched controls. These BMD losses are also related to an increased risk of developing osteoporosis and fragility fractures, particularly in the rib sub-region (Mesurolle et al., 2000). Fragility fractures caused by oncological treatment in breast cancer patients are more common in the antero-lateral region of the 4^{th}, 5^{th}, and 6^{th} ribs (Mitchell & Logan, 1998). Rib fractures negatively impact the patients'

daily life, causing disability and potentially long-term presence of pain (Marasco et al., 2015), and increases the risk of developing infection and bone sarcomas (Yi et al., 2009). The incidence of rib fractures in breast cancer patients ranges from 2% to 19% (Harris, 2016; Overgaards, 1988). Yet, these statistics likely underestimate the true scope as bone quality assessments are only performed in 3% to 32% of cancer patients under high risk of bone loss (Guise, 2006). The average time for these fractures to appear is five years (Kim et al., 2021).

There are several approaches to assess bone quality. The standard approach is the dual energy X-ray absorptiometry (DXA) scan. This tool is accurate (~1-2% error), non-invasive (low radiation dose ~0.5 µSv), rapid, and requires no specific preparation. The physical principle behind the DXA scan is the transmission of x-rays through the body at high and low levels of energy (Bazzocchi et al., 2016). However, the non-portability makes the adaptability of DXA scan to research studies and clinics that require repeated measurements low (Schiavo et al., 2020). Quantitative Ultrasound Imaging of Bone (QUSIB) is a novel and attractive alternative to overcome the DXA limitations. QUSIB is an accessible, inexpensive, and portable tool with the ability to be used in repeated measurement in peripheral bone sites. Whereas DXA scan assesses bone in a two-dimensional projection image, typically of the spine and hip, and quantifies one parameter of the trabecular bone compartment only, all QUSIB offers a more comprehensive view of the cortical bone at multiple anatomical sites, providing multiple features like bone elasticity, microstructure, bone matrix constituents, and micro-damage accumulation components (Raum et al., 2014).

Quantitative ultrasound of bone approaches to predict fracture risk have evolved in the last three decades using dedicated non-imaging bone scanners. In contrast, modern QUSIB technology uses conventional medical ultrasound diagnostic scanners. Using the recently

developed methods of cortical bone backscattering ("CortBS") and measurement of sound refraction ("MultiFocus"), the frequency spectrum of the high-frequency ultrasound waves scattered by cortical bone structures and the sound refraction at the cortical bone boundaries can be analyzed. Acoustic attenuation and backscatter coefficient are the two main backscatter parameters of QUSIB and were previously employed to distinguish healthy versus diseased tissues (Insana et al., 2006). The acoustic attenuation is the rate at which sound waves decrease in intensity as they travel through tissue. The backscatter coefficient is the amount of sound waves that are scattered back to the transducer (Nam et al., 2011).

Structural features of the bones affect the resistance of bones to fractures. Structural parameters include bone shape determining moment of inertia, average mass distribution, and bone volume fraction (Raum et al., 2014). The mass distribution refers to how and where the bone material is distributed in a structure, and moment of inertia indicates where the mass is distributed around the center the specimen (Ulivieri & Rinaudo, 2021). The BV/TV is the ratio of bone volume to total volume (Huang et al., 2023).

Bone tissue is in constant remodeling and the age of the bone also plays an important role in the fracture risk prediction. The mineralization of collagen fibrils occurs in two stages: a fast primary stage and a slow secondary stage (Ruffoni et al., 2009). This process results in a variation of the elastic properties of the tissue that is dependent on the age of the tissue (Raum et al., 2014). Rib fragility fractures as consequences of bisphosphonates and radiation treatment, are considered long-term side effects (Harris, 2016). Therefore, not only the treatment damage would change the rib trabecular structure but also the tissue aging. Both factors should be considered together for potential bone quality assessments.

The CortBS model was used to assess these structural and mechanical bone parameters to predict bone fractures in cortical bones. The QUSIB has showed high accuracy in numerical, ex-vivo (on human tibia sample), and in-vivo (on the femoral neck in women with and without fragility fractures) scenarios (Iori et al., 2021; Armbrecht et al., 2022). Despite significant relationships found between ultrasonic measurements and the mechanical properties of human ribs on an ex-vivo study (Mitton et al., 2014), no focus was given to bone quality assessment in ribs in vivo with QUSIB so far. The CortBS method seems to be a promising alternative to accomplish this goal. Nevertheless, due to the small thickness of these bones (<1mm), the bone composition in ribs is mostly trabecular, and therefore an adopted trabecular version of this backscatter model was developed for the purpose of this study.

The aim of this feasibility study was to evaluate Quantitative Ultrasound Imaging of Bone (QUSIB) as a future potential tool to assess rib quality and compromised quality in response to oncological treatment in breast cancer patients. The study aimed to determine whether ultrasonic features could predict rib structural parameters that are associated with the risk of rib fracture in a pathological scenario with a pharmaceutical intervention. The study also intended to ascertain whether this prediction held true even when considering age-based variability in material properties, therefore accounting also for a natural intervention. The predictions were done within the context of ultrasonic simulation models of five years of radiation damage and bisphosphonate therapy.

5.2 Objectives and Hypotheses

The objective of study 3 was to determine if the Quantitative Ultrasound is sensitive to changes in rib trabecular structure and can predict moment of inertia, average mass distribution, and BV/TV parameters in a 5-year ultrasonic model simulating radiation damage and bisphosphonate consumption consequences .

The following hypotheses were tested in study 3:

- Correlations between backscatter coefficient and acoustic attenuation features, and moment of inertia, average mass distribution, and BV/TV rib parameters, would have a value of $R^2 > 0.7$.
- Correlations between backscatter coefficient and acoustic attenuation features, and moment of inertia, average mass distribution, and BV/TV rib parameters, would still have a value of $R^2 > 0.7$ when considering age-based variability in material properties.

In the medical field, R^2 values > 0.7 in a correlation would represent a moderate to strong correlation (Akoglu, 2018) and would indicate good predictions of trabecular structure changes from ultrasonic features.

5.3 Methods

5.3.1 Base Models

High-resolution rib images were obtained using micro Computer Tomography (µCT) to simulate the acoustic backscatter response from rib bones.

The µCT data was extracted from Perz et al (2015):

- Specimens: Seven left ribs were harvested from a 59 year-old male cadaver which was free of infectious diseases. The cadaver was removed from freezer and placed at room temperature for 24 hours before the ribs' extraction. Three slices were extracted from each rib, anterior from posterior of ribs 1 to 7 (Table 33).
- Imaging: A Scanco Viva µCT 40 was used to capture the images, with an in-plane resolution of 0.021 mm/pixel, and a slice thickness of 0.021 mm.

The total number of ribs harvested in the study of Perz were 12. However, for the present study only 7 were selected (3^{rd} to 8^{th} ribs). These ribs are considered to be at higher risk of fragility fractures due to oncological treatment in breast cancer (Kim et al., 2023). The µCT (DICOM files) data from these seven ribs were used to create the simulation models (Figure 34). Details of the correspondent rib and cut selected follow (Table 33). The sample size approximates previous studies that conducted numerical simulations of bone (Rhode et al., 2014; Rochbach et al., 2010).

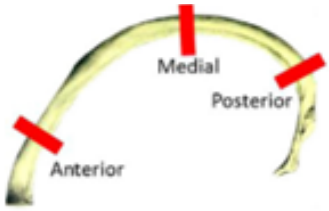
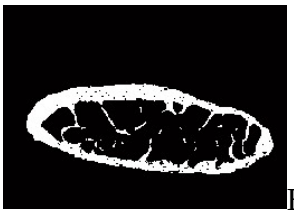
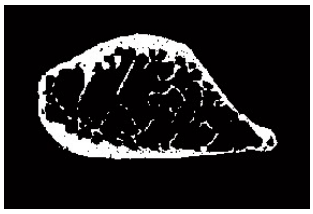
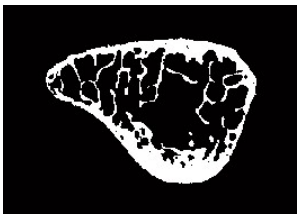
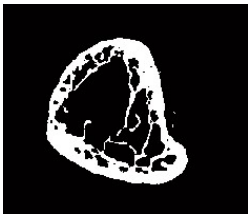
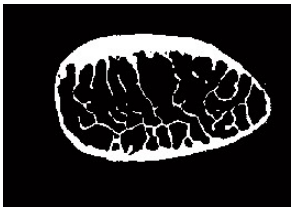


Figure 33. Ribs slide set-up (Prez et al., 2015).

A.  B.  C. 

D.  E.  F. 

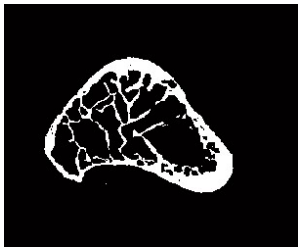
G. 

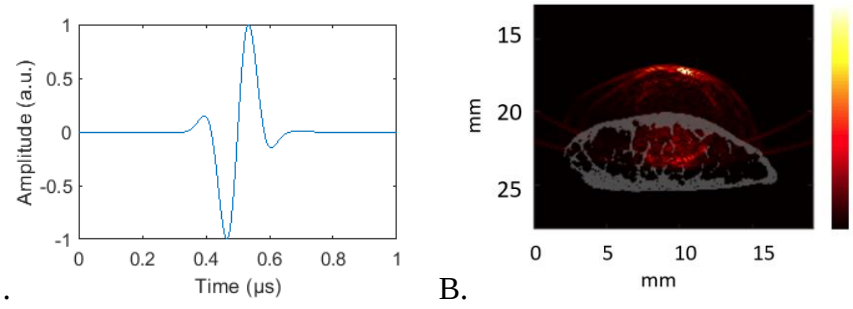
Figure 34. Ribs selected for the simulation.

Table 33. . Correspondent rib and cut of the selected ribs used for the simulation

Rib ID	Correspondent rib	Cut
A	3rd	Posterior
B	8th	Medial
C	2nd	Medial
D	6th	Medial
E	5th	Posterior
F	5th	Anterior
G	4th	Posterior

5.3.1.1 Simulations models

The models mimicked an ultrasonic scenario. The simulations were computed using Matlab^{TM} 2022b (Mathworks Inc., USA). It consisted of 35 µs long finite-difference time-domain SimSonic simulations of a 128-element array (element size 0.28 mm). The excitation signal was used 6 MHz +- pulse and the aperture of the backscatter elements were focused to a depth of 22mm (Figure 35).



. B.

Figure 35. . A. Excitation signal 6MHz +- pulse. B. Snapshot from simulation

Two models were created simulating radiation and bisphosphonates pharmaceutical intervention. Following radiation treatment, patients may receive bisphosphonate therapy. Radiation therapy is a crucial and effective approach for eliminating residual cancer cells after surgical tumor removal (Clarke et al., 2005). Bisphosphonates are commonly prescribed to prevent bone metastases in breast cancer patients and to reduce bone breakdown, making fractures less likely (CCS, 2024).

5.3.1.1.1 Erosion model

One set of rib data included simulated radiation damage. The parameters for long-term changes in trabecular bone caused by radiation were obtained by the study of Bandstra et al., 2008, in

which mice-single full body were irradiated for 117 days with 2 Gy dose daily, and trabecular bone changes were accounted. A decrease of BV/TV by 20% and an increase of trabecular spacing by 11% occurred. For the model, the original ribs were eroded by 5, 10, 15 and 20% for each year in a 4-year window (Figure 31). The entire bone structure (except for the periosteal layer) was eroded each year in a single intensity pixel value. The erosion model was applied to the whole bone tissue maintaining unaltered the periosteal layer. It was expected that the accumulated erosion by year would decrease the BV/TV, thereby weakening the bone and increasing the risk of rib fragility fractures.

5.3.1.1.2 Bone Growth model

A second set of rib data included simulating 5 years of bisphosphonates consequences. The parameters for long- term changes in trabecular bone caused by bisphosphonates were obtained by the study of Misof et al (2017). In this study, trans iliac biopsies analyses of cortical bone mineral density distribution (BMMD) of post-menopausal patients treated with bisphosphonates for more than three years. The BMMD parameters increased after the treatment: The weighted mean calcium- concentration of the bone area ‘CaMean’ by +3.9%, the most frequent measurement of calcium concentration ‘CaPeak’ by +3.1%, the percentage of highly mineralized bone areas ‘CaHigh’ by +100%, and the percentage of lowly mineralized bone areas ‘CaLow’ by -46%. Bisphosphonate therapy reduces bone turnover, which can lead to impaired microdamage repair and increased bone mineralization (Turner, 2002). The increase of mineralization increases bone stiffness, and consequently tissue rigidity. This results in a more brittle tissue leading to reduction work to failure (Currey, 1990).

For this model, the mineralization in the original ribs was increased by year, up to 5 years (Figure 36). Each year, a new layer of bone was added representing 3% of calcium content,

mimicking bisphosphonate affection (Misof et al., 2017). The transformation of calcium content into elastic coefficients to create the bone layer, was based on the calcium model previously described by Ruffoni (Ruffoni et al., 2007). The bone layer addition was applied to the whole bone tissue, and it changed the percentage of pixels in the image. It was expected that the accumulated bone growth by year would increase the bone density and stiffness, increasing the risk of rib fragility fractures.

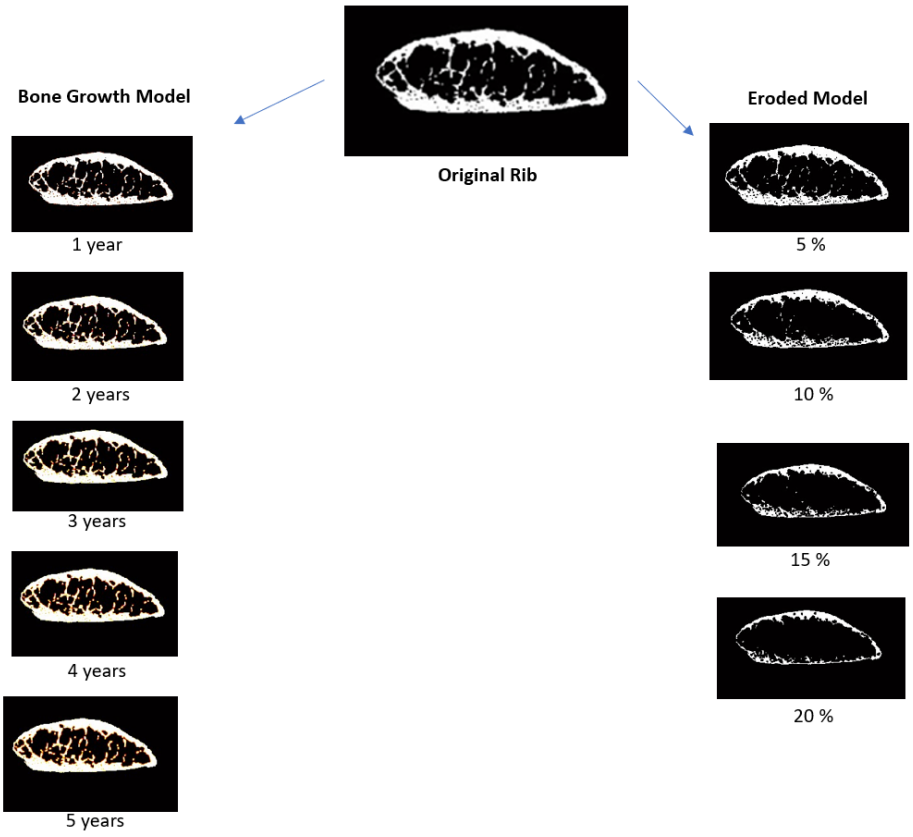


Figure 36. Example of rib model from original µCT data simulating 5 years of bisphosphonates treatment (bone growth model) and radiation treatment (eroded model).

5.3.1.2 Target parameters and ultrasonic features description

5.3.1.2.1 Target structural parameters

We estimated the target structural parameters on simulated rib corresponding to bone eroded model and bone growth model. The moment of inertia (I) indicates where the mass is distributed around the center the specimen (Ulivieri & Rinaudo, 2021). It was calculated by I = m*r, where m corresponds to each pixel and r corresponds to the distance from the geometrical center. A pixel referred to the white or non-black dots in the bone matrix. The average mass distribution refers to how and where the bone material is distributed in a structure (Ulivieri & Rinaudo, 2021). It was calculated by I/whole total mass, and it specified how far the pixels were from the geometrical center on average. Finally, the BV/TV is the ratio of bone volume to total volume (Huang et al., 2023). It was calculated by (number of bone pixels/number of pixels)*100%.

5.3.1.2.2 Ultrasonic features

Acoustic attenuation (Att) and backscatter coefficients (BSC) were the ultrasonic features selected to predict the bone trabecular structure. The acoustic attenuation is used as a biomarker to produce images and it refers to the reduction in the amplitude and intensity of ultrasound waves as they propagate through the tissue (Cloutier et al., 2021). The backscatter coefficient is a fundamental parameter that describes the ability of the tissue to backscatter ultrasound energy. Scatter is the phenomenon of sound waves being reflected in multiple directions when an acoustic wave encounters an obstacle whose mechanical properties differ from the surrounding tissue (Baddour, RE, 2004). The backscatter parameters were estimated from 5 to 8 MHz with 1 MHz band. The tissue frequency responses to transducer best at this range (Iori et al., 2021).

5.3.1.3 Tissue aging model- material properties alteration

A natural intervention accounting for aging was added for both radiation and bisphosphonates pharmaceutical intervention models. Bone tissue undergoes permanent remodeling. The first stage of the kinetics of the mineralization of collagen fibrils occurs in the first days/weeks of life, in which 70% of the final degree of mineralization is reached. The second stage can last several years and involves the deposition of and growth of nanosized hydroxyapatite crystals which with time, would lead to the heterogeneity of tissue age results in a characteristic bone mineral density distribution BMDD in bone tissue (Ruffoni et al., 2009 (Figure 37). The typical bone remodeling cycle (the time to bone synthesis to resorption) takes approximately 6.55 years, but it varies depending on the individual's age or in response to pathologies or treatment (Ruffoni et al., 2009).

The biphasic nature of the mineralization law can be described by sum of two hyperbolic growth functions with time constants:

$$c(\tau) = c_1 \frac{\tau / \tau_1}{1 + \tau / \tau_1} + c_2 \frac{\tau / \tau_2}{1 + \tau / \tau_2}$$

The coefficients c_1 and c_2 were 6 and 24 wt%, respectively, and the time constants τ_1 and τ_2 were 9.652 and 0.029 years, respectively (Ruffoni et al., 2009).

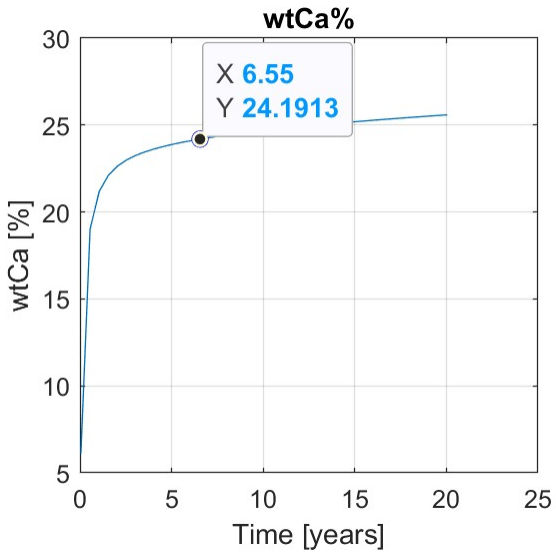


Figure 37. Ca model. The model describes the biphasic nature of the mineralization law.

Bone tissue is composed of collagen, mineral and water. While the collagen content can be invariant, the water content is gradually replaced by mineral during the process of tissue mineralization. Therefore, the mass density can be estimated by a rule of mixtures (Raum et al., 2006):

$$\rho_{\text{tissue}} = vf_{\text{HA}}\rho_{\text{HA}} + vf_{\text{col}}\rho_{\text{col}} + vf_{\text{H}_2\text{O}}\rho_{\text{H}_2\text{O}},$$

where *vfj* is the volume fraction of the component *j, ρj* is the density, followed by HA for mineral, col for collagen and H2O for water. As the properties of the individual components are known, the tissue-age dependent mass density can be derived from the Ca content model.

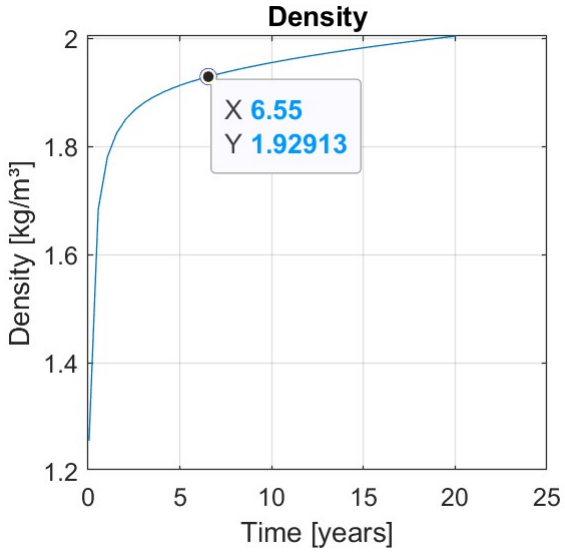


Figure 38. Kinetic tissue mass density model using a rule of mixtures adopted from Raum et al., 2006. The mass density used for the base model (dot) corresponds to a tissue age of 6.55 years.

The relationships between mass density and elastic coefficients of bone tissue have been investigated in previous studies (Raum et al., 2006; Iori et al,. 2021) and were used in the current study.

The bone is an anisotropic solid. The nine elastic constants that characterizes the bone tissue are included in the following matrix of coefficients (Ashman et al., 1984):

$$\left[c_{ij}\right]=\begin{bmatrix} c_{11} & c_{12} & c_{13} & 0 & 0 & 0 \\ c_{12} & c_{22} & c_{23} & 0 & 0 & 0 \\ c_{13} & c_{23} & c_{33} & 0 & 0 & 0 \\ 0 & 0 & 0 & c_{44} & 0 & 0 \\ 0 & 0 & 0 & 0 & c_{55} & 0 \\ 0 & 0 & 0 & 0 & 0 & c_{66} \end{bmatrix}.$$

For the present ultrasonic simulations, mass density and the elastic coefficients $c_{11}=c_{22}$, c_{12} and c_{66} from the elasticity matrix are needed. The time-dependent mass density and elastic coefficients are shown in kinetic ca model (Figure 38) and Kinetic tissue mass density model (Figure 38).

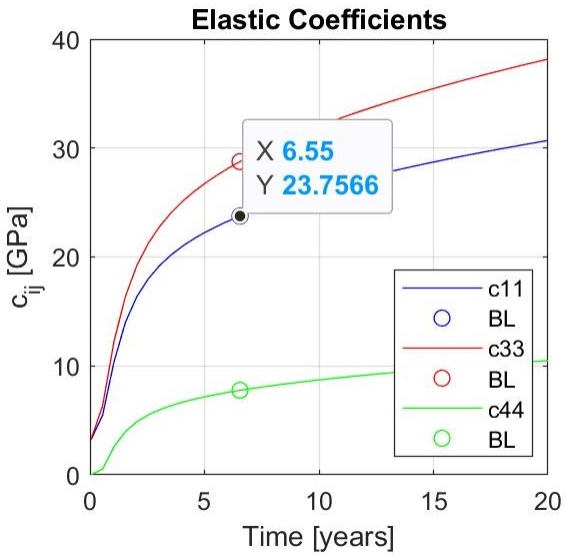


Figure 39. Kinetic tissue elastic coefficients using a rule of mixtures adopted from Raum et al., 2006 and density elasticity relations established in previous studies. The elastic coefficients used for the current model correspond to a tissue age of 6.55 years.

5.3.2 Simulation models specifications

Two subgroups of models were performed:

- Subgroup 1- Unaltered material properties: Only pharmaceutical intervention was accounted. Not accounting for age-based variability of material properties. It included erosion and bone growth rib models from 5 different bones in a total of 60 simulations. Ribs C, D, E, F, and G were randomly assigned to the subgroup 1. The reference material properties used to create the models of this subgroup were adapted from previous studies (Iori et al., 2021; Nguyen et al., 2022).
- Subgroup 2- All ribs- Unaltered material properties + Varied material properties: Both pharmaceutical and natural aging interventions were accounted for. The altered material properties group included erosion and bone growth rib models from 4 different bones in a total of 41 simulations. Ribs A, B, C, and G were randomly assigned to this group. The material properties associated with the corresponding tissue age of each pixel in the material map were assigned. Thereby, heterogeneous material properties mimicking tissue ageing and/or tissue formation were achieved. All ribs belonging to subgroup 2 involved a total of 101 simulations.

Both the ‘C’ and ‘D’ ribs were simulated for two groups: for the unaltered material properties and for the altered material properties. The ‘E’, ‘D’, and ‘F’ ribs were simulated exclusively for the first group, while the ‘A’ and ‘B’ ribs were simulated for the latter group. The purpose of this distribution was to add variability between groups.

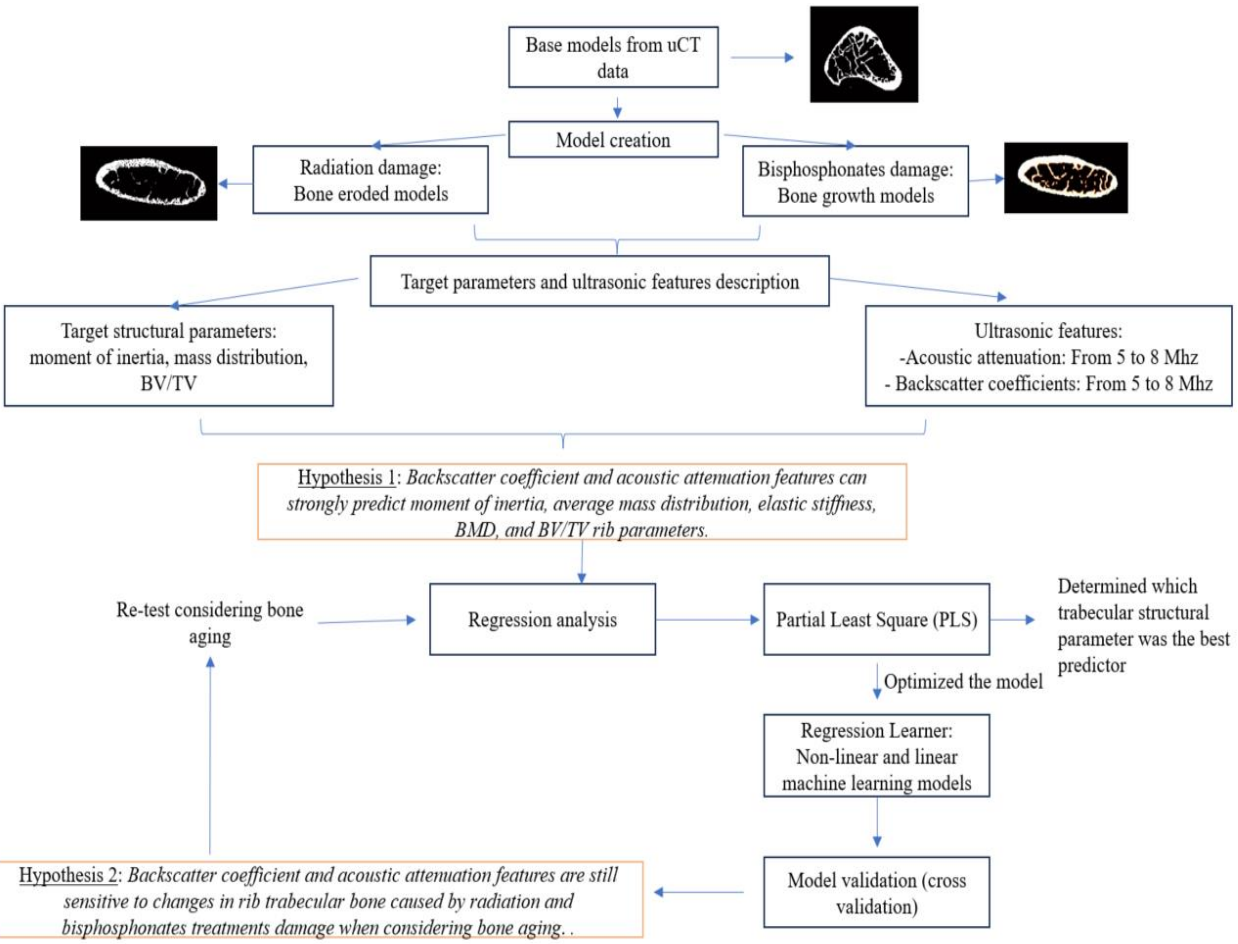


Figure 40. Study workflow. Numerical ultrasonic simulations of 2 sets of ribs mimicking radiation and bisphosphonates treatment damage were created. Ultrasonic featureswere extracted and target structural parameters were calculated. A regression analysis was perform to determine predictions between ultrasonic features and structural parameters.

5.3.3 Statistical analysis

Statistical analysis was performed using Matlab^{TM} 2022b (Mathworks Inc., USA). A regression analysis was done. For all the ribs, the target parameters were taken from each simulated rib for both eroded and bone growth models. Additionally, the predicted ultrasonic features were the mean values of backscatter coefficient (BSC) and acoustic attenuation (Att) calculated in each 1 MHz band from 5 to 8 MHz. For unaltered material properties models, a Partial Least Square (PLS) regression model with three-fold cross-validation using the libPLS library (Xu and Liang, 2014) was used to determine which trabecular structural parameter was the best predictor of ultrasonic features. The PLS regression model was preferred over multiple regression analysis because it performs better when there is collinearity between the independent variables, as in the present study with ultrasonic features (Armbrecht et al., 2021). Since the associations between ultrasonic features and tissue frequency is non-linear and this non-linearity is not captured by the PLS regression models, machine learning models were selected to obtain more accurate outcomes. The best PLS predictor was then optimized through a machine learning model using Regression Learner Tool in Matlab. The data was shuffled before it was given to the regression learner. The features selection for each machine learning model was done with a principal component analysis (PCA). The input were 8 ultrasonic features (acoustic attenuation and backscatter coefficient from 5 to 8 MHz), and the output were 4 parameters with the lower p value. The PCA parameters outputs were limited to 4 components in order to minimize the risk of overfitting (Njah et al., 2021). Linear and non-linear models (Support Vector Machines, Regression Trees, Ensembles of Trees, Gaussian process regression, and neural networks) were tested. The four models that predicted the best results were then validated using cross-validation with 4 folds. This number of folds were selected according to the data points presented per each simulation (Armbrecht et al., 2021). Cross-validation is a method using subsets of data or ‘folds’.

A learning method is repeated ‘x’ times, one of the folds is used for validation and test whereas the others are put together for training. The RMSE is averaged over all the trials to check how effective the model was (Ziong et al., 2020). In the current study, the models were optimized in 200 iterations, meaning that the cross-validation process with 4 folds was repeated 200 times.

The same procedure was then repeated for the altered material properties models.

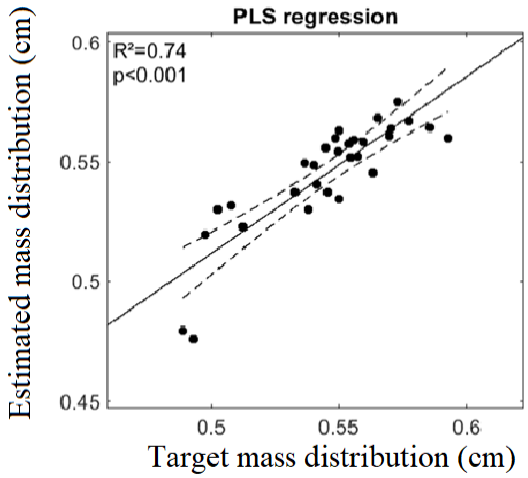
Table 34. Summary of measure outcomes for study 3.

Input	Dependent variables	Covariates
Backscatter parameters	Acoustic attenuation at 5MHz Acoustic attenuation at 6MHz Acoustic attenuation at 7MHz Acoustic attenuation at 8MHz Backscatter coefficient at 5MHz Backscatter coefficient at 6MHz Backscatter coefficient at 7MHz Backscatter coefficient at 8MHz	BV/TV Moment of inertia Average mass distribution

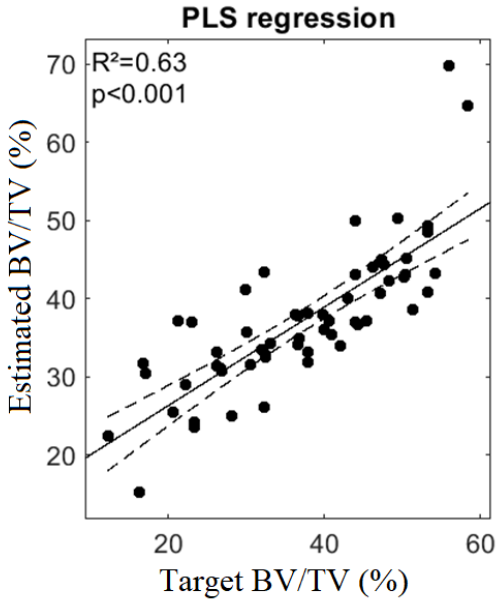
5.4 Results

5.4.1 Bone trabecular structural parameters prediction from ultrasonic features

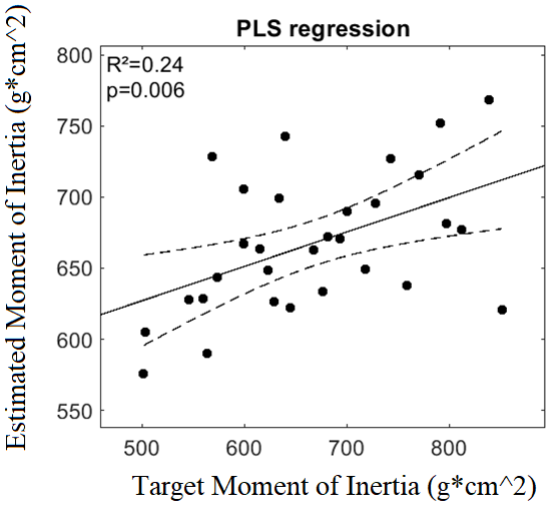
The average mass distribution parameter presented the best prediction (r ^ 2 = 0.74, p < 0.01) (Figure 41 A), followed by BV/TV (r ^ 2 = 0.63, p < 0.01) (Figure 41 B), and moment of inertia (r ^ 2 = 0.24, p = 0.006) (Figure 41 C).



A.



B.



C.

Figure 41. Partial Least Square scatter plots corresponding to A. Average mass distribution, B. BV/TV, C. Moment of inertia

5.4.1.1 Optimizing the model

Even though the mass distribution was the parameter that had the best prediction with ultrasonic features, BV/TV was selected for optimization. This structural parameter is well-established and clinically relevant for fracture prediction risk (Szulc et al., 2022; Nazarian et al., 2008). Linear and non-linear models were trained. Models with lower RMSE and higher R^2 were selected for validation. Support vector machines, Gaussian process regression, Neural Network, and Ensemble of Trees (Booster Tree) were the best 4 predicted models.

Table 35. Machine learning models. A. Linear models. B. Support Vector Machine model (SVM). C. Regression Trees. D. Ensembles of Trees. E. Neural networks. F. Gaussian process regression.

Model	R^2	RMSE
Linear	0.53	7.66
Interactions Linear	0.58	7.23
Robust Linear	0.53	7.67
Stepwise Linear	0.57	7.38

A.

Model	R^2	RMSE
Linear SVM	0.51	7.8
Quadric SVM	0.58	7.23
Cubic SVM	0.7	6.15
Fine Gaussian SVM	0.93	3.04
Medium Gaussian SVM	0.69	6.21
Coarse Gaussian SVM	0.51	7.8

B.

Model	R^2	RMSE
Fine Tree	0.74	5.73
Medium Tree	0.48	8.12
Coarse Tree	0	11.20

C.

Model	R^2	RMSE
Rational Quadratic	0.64	6.71
Squared Exponential	0.62	6.85
Matern 5/2	0.68	6.36
Exponential	1.00	0.002

D.

Model	R^2	RMSE
Narrow neural	0.71	5.98
Medium neural	0.99	1.27
Wide neural	1	4.52
Bi layered neural	0.84	4.52
Tri layered neural	0.95	2.51

E.

Model	R^2	RMSE
Rational Quadratic	0.64	6.71
Squared Exponential	0.62	6.85
Matern 5/2	0.68	6.36
Exponential	1.00	0.002

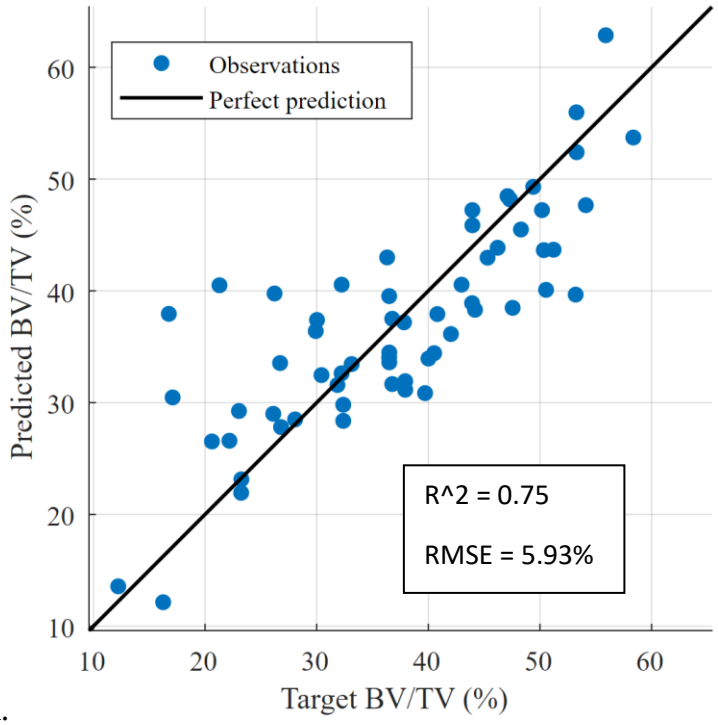
F.

5.4.1.2 Validation

Validation was done with 4 folds for the 4 best trained models (Table 36). GPR was the model that had better results (Figure 42).

Table 36. Machine learning model validation results

	No validation		4 folds	
Model	R^2	RMSE	R^2	RMSE
SVM	0.8	4.97	0.62	7.21
GPR	**1.00**	**0.002**	**0.75**	**5.93**
Neural network	0.99	1.02	0.44	8.8
Boosted tree	0.87	6.37	0.55	7.89

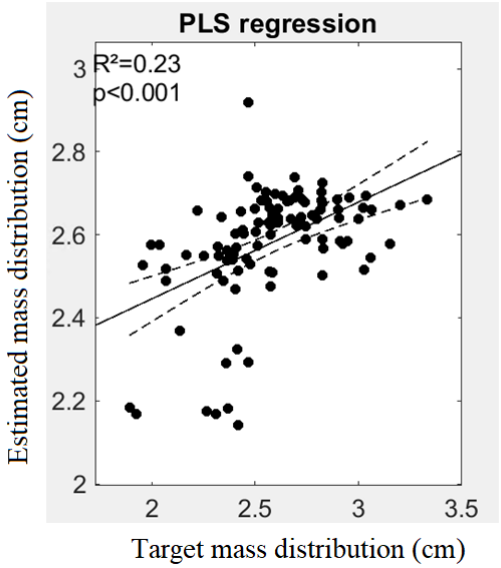


A.

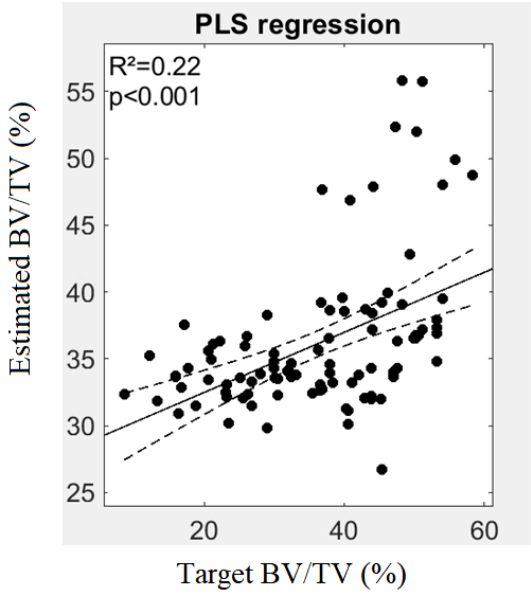
Figure 42. Optimized GPR model prediction of BV/TV 4 folds validation

5.4.2 Bone trabecular structural parameters prediction from ultrasonic features considering bone aging- change in material properties

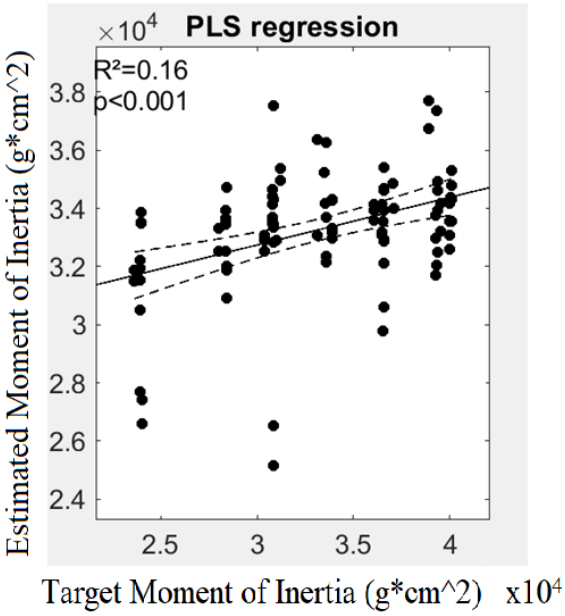
The average mass distribution parameter presented the best prediction (r ^ 2 = 0.23, p < 0.001) (Figure 43 A), followed by BV/TV (r ^ 2 = 0.22, p < 0.001) (Figure 43 B), and moment of inertia (r ^ 2 = 0.16, p < 0.001) (Figure 43 C) (Table 37).



A.



B.



C.

Figure 43. Partial Least Square scatter plots corresponding to A. Average mass distribution, B. BV/TV, C. Moment of inertia

Table 37. Partial Least Square Regression analysis results

Variable	BSC 5MHz	BSC 6MHz	BSC 7MHz	BSC 8MHz	Att 5MHz	Att 6MHz	Att 7MHz	Att 8MHz
BV/TV (p value)	0.5977	0.1463	0.0248	0.0147	0.2892	0.0917	0.4318	0.0044
Ave mass distribution (p value)	0.8829	0.3342	0.0972	0.0584	0.6423	0.1753	0.6912	0.0036
Moment of inertia (p value)	0.0515	0.2895	0.8242	0.8894	0.1222	0.5291	0.6299	0.1856

5.4.2.1 Optimizing the model

BV/TV was selected for optimization. Linear and non-linear models were trained. Models with lower RMSE and higher R^2 were selected for validation. Support vector machines, Gaussian process regression, and Ensemble of Trees (Booster Tree) were the best 4 predicted models.

Table 38. Machine learning models

Model	R^2	RMSE
SVM	0.32	9.72
GPR	0.59	7.45
Neural Network	0.52	8.17
Boosted tree	0.28	9.06

5.4.2.2 Validation

Validation was done with 4 folds for the 4 best trained models . GPR was the model that had better results (Figure 44).

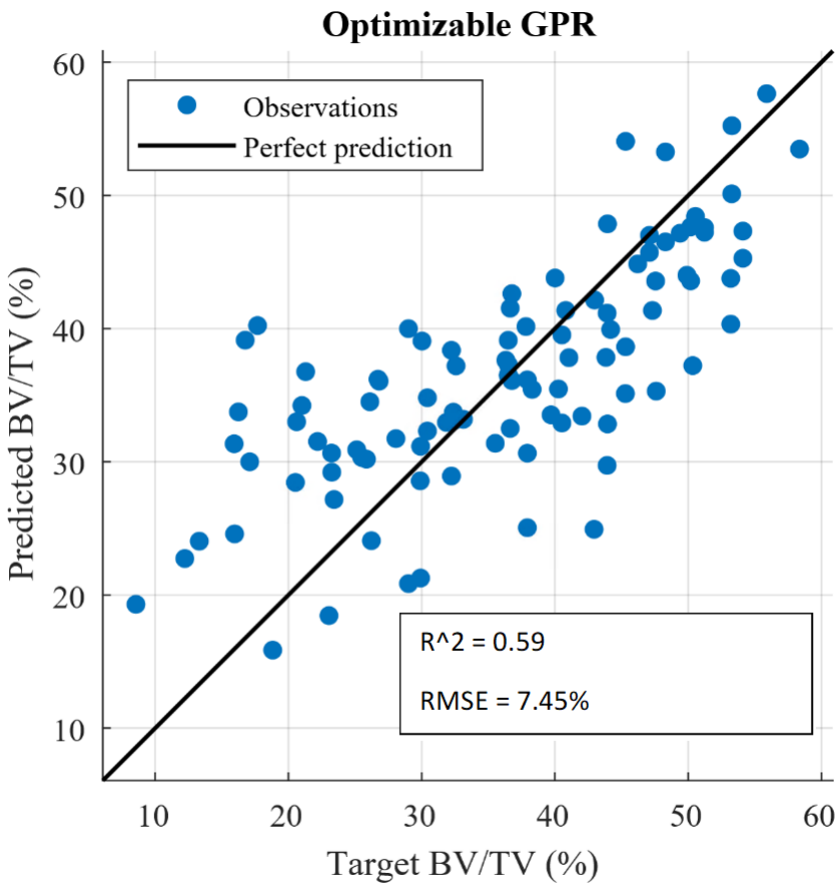


Figure 44. Optimized GPR model prediction of BV/TV with 4 folds. Altered material properties.

5.5 Discussion

The numerical ultrasonic simulations showed moderate to strong predictions of bone trabecular structures from ultrasonic features in pathological pharmaceutical interventions. These predictions were still moderate when material properties of the tissue were altered accounting for natural age-based variability intervention. The regression models used were optimized, trained, and validated. However, the model did not perform well at low levels of bone erosion and was unable to detect trabecular structure. Radiation treatment causes bone erosion that leads to potential fractures (Harris et al., 2016). Therefore, a method to predict fragility fractures must be sensitive enough to detect trabecular structure even when is highly eroded. The accuracy of this method must be improved prior to an in-vivo application.

5.5.1 Ultrasonic features can predict changes in trabecular structure produced by oncological treatment

Two out of three bone trabecular parameters showed moderate to strong correlations with ultrasonic features. The first hypothesis of the present study was that correlations between backscatter coefficient and acoustic attenuation features, and moment of inertia, average mass distribution, and BV/TV rib parameters, would have a value of $R^2 > 0.7$. This hypothesis was partially accepted. Mass distribution reached this target value, and BV/TV was slightly lower ($r^2 = 0.74$, $p < 0.001$, $r^2 = 0.63$, $p < 0.001$ respectively). Stronger correlations were noted between ultrasonic features and BV/TV after optimization and machine learning regressions, reaching a R^2 value of 0.75. However, the moment of inertia parameter did not show good correlations ($r^2 = 0.24$, $p = 0.006$).

Moment of inertia and mass distribution are macrostructural properties, which rely on the shape of the entire cross-section (Ural & Vashishth, 2006). In the present study, only trabecular

bone region was analyzed, which is not intrinsically associated with the entire rib bone shape. Bone strength in trabecular bone is associated mostly with shape, size, orientation, and connectivity of the trabeculae, whereas in cortical bone geometric properties of the cortical shell such as moment of inertia and bone mass distribution are more relevant (Reeb and Claes, 1996). Other features of the Ultrasound signal, e.g. the amplitude of the signal reflected from the rib surface would be directly associated with microstructural properties such as BMD. However, signal amplitudes are technically difficult to quantify in vivo (due to soft tissue attenuation, potential beam inclination, and variable soft tissue composition at the bone interface) (Raum et al., 2014). Therefore, the present study did not focus on these signal features. The current findings demonstrated that BV/TV had a strong predictive power for ultrasonic features, confirming to be a potentially useful biomarker for the trabecular structure.

5.5.2 Ultrasonic features can predict changes in trabecular structure even when considering bone aging.

Ultrasonic features could describe the pathological trabecular structure when the material properties are changed. It was hypothesized that correlations between backscatter coefficient and acoustic attenuation features, and moment of inertia, average mass distribution, and BV/TV rib parameters, would still have a value of $R^2 > 0.7$ when considering age-based variability in material properties. This hypothesis was not accepted. When the material properties of the bone changed, the R^2 of the correlations between target parameters and ultrasonic features became weaker ($R^2 = 0.23$ for mass distribution, $R^2 = 0.22$ for BV/TV, and $R^2 = 0.16$ for moment of inertia). However, after optimization and machine learning regression, moderate correlations were noted between ultrasonic features and BV/TV, reaching a value of $R^2 = 0.59$. More variability was included in the model but it became more realistic, as under real-life conditions constant tissue properties across individuals cannot be assumed.

This approach presented limitations. The assumption of a randomly distributed trabecular network was violated for large erosion (15-20%) leading to small BV/TV values (Figure 43C and 44). The CortBS analysis algorithm involves several steps, in which low amplitude signals are removed prior to averaging (Raum et al., 2006; Iori et al., 2021). By this, only a few locations, in which sound is still scattered at trabecular structures are kept, leading to an overestimation of the backscatter amplitude in these cases. Future work should refine the CortBS analysis algorithm to account for tissue regions without any trabecular structures and refine the erosion models with smaller erosion increments to avoid complete removal of the trabecular network, while maintaining the BV/TV loss.

5.5.3 Predictions of trabecular structure with ultrasonic features is more accurate and/or accessible than other approaches

Acoustic attenuation and backscatter ultrasonic accurately predicted changes in cortical bone. The changes were related to bone fractures in *in-vivo* cortical bone. The QUSIB through the 'CortBS' method was able to predict fractures in women with osteoporosis when compared to DEXA and HR-pQCT scans. Acoustic attenuation and backscatter coefficients were the selected ultrasonic output parameters in the determination of pore size distribution for the estimation of cortical fractures. Multiple univariate associations ($p < 0.001$) were found for attenuation and cortical pore diameter distribution from QUS with bone density, structure, and porosity from HR-pQCT (Armbrecht et al., 2021). The HR-pCT is an accurate method that allows the measurement volumetric BMD for both trabecular and cortical bone and an accurate reading of trabecular microstructure (Graeff etl a., 2013). However, the use of this approach in research is limited. The significant prediction of QUS with HR-qCT suggests that the QUS could be a more practical alternative for the assessment of trabecular structure.

The gold-standard approach to assess bone is the DEXA scan. DEXA scans excel in bone density assessment, offer lower radiation exposure, and provide additional insights into body composition compared to other approaches such as CT scanning. Through the assessment of bone quality, the fracture risk can be estimated. This method has a standard approach for the assessment of fracture risk which is the *T score.* This score comes from the measurement of areal BMD (aBMD) at major fracture sites like the spine and femoral head, through DEXA scan (Kanis et al., 2019). However, this approach underestimates the risk of fractures produced by increased BMD. It provides a reductionist view of bone strength, not considering the size, shape, composition, and architecture of the bone. Besides, it does not discriminate between cortical and trabecular bones. Lately, it has been demonstrated that many patients undergo osteoporosis-related fractures with *T scores* catalogued at 'low risk' (Choksi et al., 2018).

In the present study, the risk of fracture was not calculated. However, the numerical ultrasonic simulations suggest that the ultrasound could potentially assess in-vivo trabecular parameters related to fracture resistance. No BV/TV threshold for bone fragility fractures has been described in the literature. Conversely, a previous study reported that men with vertebral fractures had a lower BV/TV at the distal radius and tibia than men without fractures. These differences were exacerbated for severe vertebral fractures (Szulc et al., 2011). Another study determined that BV/TV in osteoporotic cancer specimens was 31% lower than the one in normal non-cancer specimens, whereas the BMD remained unaffected (Nazarian et al., 2008). Future work should focus on the study and determination of bone structural parameters thresholds for trabecular bone fragility fractures.

5.6 Limitations

This study has limitations that should be considered when interpreting the results. Limited literature describes the quantification of radiation damage in bone parameters such as BV/TV. Therefore, animal models were included in the present study to describe these changes. This erosion quantification was overestimated and impacted on the numerical simulations. The model did not perform well in radiation-damage scenarios where the bone was highly eroded and only 30% of the original bone mass remained. In the future, erosion models with smaller erosion increments need to be refined to avoid complete removal of the trabecular network, while maintaining the BV/TV loss. Moreover, to predict fractures caused by radiation treatment, it is essential to have a method that can detect the trabecular structure with high sensitivity, even when it is radically eroded. The accuracy of this method must be improved prior to an in-vivo application. Direct validations of this method with DEXA scan are challenging. DEXA scans assess bone mineral content over a projected bone area (Kanis et al., 2019). The amplitude of the signal reflected from the rib surface would be directly associated with BMD (Armbrecht et al., 2021). However, signal amplitudes are technically difficult to quantify in vivo (due to soft tissue attenuation, potential beam inclination, and variable soft tissue composition at the bone interface) (Raum et al., 2014). Yet, other features of the ultrasonic signal have been correlated with DEXA. Garra et al., (2009) reported that the spectral centroid shift of the backscattered signal was correlated with BMD in spine ($r = -0.61$). Therefore, the approach used in the current study could be considered appropriate. Lastly, we utilized male rib data to simulate the effects of radiation and bisphosphonate treatments in breast cancer patients. Given that breast cancer predominantly affects females (CCS, 2020), this choice may not fully represent the female population. Additionally, the availability of μCT data for creating bone models was limited. Notably, no existing literature has explored the feasibility of Quantitative Ultrasound Imaging of

Bone (QUSIB) in detecting changes in trabecular structure resulting from oncological treatments. Despite these limitations, the findings from our current study, although based on male ribs, remain valid. Future research should focus on using female bones to assess the risk of rib fractures associated with radiation and bisphosphonate treatments.

5.7 Conclusions

Study purpose: To determine whether ultrasonic features could predict rib structural parameters that are associated with the risk of rib fracture in a pathological scenario and to ascertain whether this prediction held true even when considering the simulated aging of bone**.**

Main findings:

- Numerical ultrasonic simulations showed strong predictions of bone trabecular structures from ultrasonic features in pathological scenarios.
- BV/TV was the bone trabecular structure that had the best predictions in unaltered material properties scenario and when the material properties of the bone tissue were altered simulating bone aging.
- However, the model did not perform well in pathologically altered conditions where only and only 30% of the original bone mass remained.

Recommendations:

- The accuracy for low BV/TV values must be improved prior to an in-vivo application.
- Bone structural parameters thresholds for trabecular bone fragility fractures should be determined.

Chapter 6 - Research Outcomes and Future Directions

6.1 Summary of research

This dissertation produced novel findings in breast cancer research regarding shoulder function changes during radiation therapy. In study 1, shoulder functional indicators varied during radiation treatment. Significant reductions in latissimus dorsi and teres major activation occurred during shoulder flexion- extension, abduction- adduction and external-internal rotation tasks. This reflects that the inflammation produced by the treatment appears to have affected the muscle tissue and that other muscles may have compensated thereby enabling task performance. There was a significant decrease in shoulder abduction at the end of the treatment compared to baseline. This range of motion restriction can have long-lasting effects on patients, affecting their quality of life by interfering with essential daily activities and impact their ability to return to work. Shoulder disability prevention programs for breast cancer patients should target the recruitment of latissimus dorsi and teres major muscles as well as shoulder abduction mobility exercises.

In study 2, control and shoulder strength intervention groups were compared throughout the radiation treatment window, and the performance of shoulder strength exercises starting at the beginning of the radiation treatment improved some measures of shoulder functionality. Specifically, the intervention group demonstrated an enhanced muscle capacity compared to the control group by greater activation of serratus anterior and teres major. It also evidenced a better retention of arm strength performance in abduction. The prescription of these shoulder strength exercises may provide benefits for many patients receiving radiation therapy.

In study 3, trabecular structural parameters were calculated from two sets of numerical ultrasonic simulations mimicking 5 years of radiation damage and bisphosphonate treatment on

human ribs. These target parameters relate to determinination of bone strength, stiffness, and fracture resistance. A regression analysis determined the ability of acoustic attenuation and backscatter coefficient ultrasonic features to detect changes in trabecular structure in pathological scenarios. Strong correlations existed between ultrasonic features and trabecular structural parameters. The approach of assessing bone quality in trabecular bones using a conventional ultrasound is new and this simulation study suggests that its *in- vivo* application is plausible, but would require refinement.

6.2 Clinical Implications of Research

This thesis project produced novel findings in breast cancer research related to radiation treatment that are clinically relevant.

1) Shoulder function decreased during the radiation treatment therapy window

Oncological treatment including radiation therapy causes long-term shoulder disabilities including shoulder strength deficits (Shamley et al., 2012); shoulder complex range of motion restrictions (Blomqvist et al., 2004); and shoulder muscle activation impairments (Brookham et al., 2018). Studies 1 and 2 indicated that shoulder health indicators change across the radiation treatment window, and shoulder functionality decrements may appear as soon as the treatment starts. There was a decrease in shoulder abduction. This restriction in shoulder range of motion could potentially affect the quality of life and work ability of patients. Activities of daily life that involve raising and rotating the arm, such as combing hair, washing the axilla, eating with a spoon, performing perineal care, and unfastening a bra from the back, can become challenging

when shoulder abduction range of motion is restricted. Future rehabilitation programs may find benefits in promoting shoulder abduction mobility from the start of therapy.

2) An intervention program focused on shoulder strength alleviated some shoulder functional changes during the radiation treatment therapy window

Strengthening exercises in breast cancer survivors previously demonstrated success in the improvement of shoulder functionality post-treatment (Stan et al., 2016; Chen et al., 2019), but previously focused on longer term outcomes and later implementation. Study 2 demonstrated that a shoulder strength intervention program improved shoulder abduction strength, compensating for potential muscle damage or loss caused by radiation therapy. Shoulder strength programs may benefit patients if started concurrently with their radiation treatments. While changes in shoulder functionality consequent to radiation therapy may be difficult to eliminate, this approach could limit these outcomes.

3) The QUSIB is a promising tool to assess rib quality in breast cancer patients

The simulation models of study 3 showed that ultrasound parameters including acoustic attenuation and backscatter coefficients were sensitive to structural changes in trabecular rib bones produced by simulated radiation and bisphosphonates treatments. The CortBS algorithm can assess bone quality, providing valuable insights into bone health even when accounting for bone attenuation (Armbrecht et al., 2021) and can be used with any conventional ultrasound. Due to the use of ultrasound systems (mobile by design), this solution can be used anywhere in- or outside the hospital, (e.g., primary care, elderly homes, or even pharmacies). It creates the ability to use the technology for prevention (screening); being able to diagnose patients already at the onset of osteoporosis. The assessment of rib fragility fractures using QUSIB may not only

provide a more accessible way to assess the appearance of this fractures, but has the potential also to increase the sensitivity of the predictions. However, the accuracy of the method needs improvement.

4) Developing responses to questions of the health community can guide researchers

An important element of this dissertation lies in its relevance for the health community and needs-based origins. As embedded in the UW 'CBB-CREATE' program, this project was built upon needs arising from the health system, and the planning of the dissertation was in conjunction with several health professional experts in the field.

5) Biomechanical research is possible in clinical settings and not just in laboratories.

This research project presented several challenges for data acquisition, including working with a vulnerable population during the COVID pandemic, the use of different wearable devices from different brands, and measuring several variables in a single, short session. Despite these aspects, these experiments were successfully completed. The use of wearable devices in clinics allows assessment of several biomechanical variables without taking participants into the labs, allowing patients to remain in the more practical and comfortable hospital setting, and establishing the potential for larger future dataset compilation.

6.3 Future directions

Significant decreases in muscle activation in study 1 were only noted in teres major and latissimus dorsi muscles. Other muscles that contribute to shoulder functionality are affected by oncological treatment including radiation therapy (Maciukiewicz et al., 2022; Brookham et al., 2018; Shamley et al., 2012). To gain a better understanding of the mechanisms behind shoulder

impairments that occur during radiation treatment, future research could focus on assessing additional scapular and shoulder muscles and on a muscle-driven model to specific muscles.

In both studies 1 and 2, all patients underwent IMRT radiation treatment, which is more precisely targeted to the tumor site and considered safer than previous conventional methods (Donovan et al., 2007). Despite its safety, the IMRT regimen still led to limitations in shoulder abduction range of motion and shoulder abduction strength deficits. Emerging radiation approaches, such as proton therapy, propose reduced long-term side effects due to their precise targeting at specific depth of the tissue (Kammerer et al., 2018). However, the existing literature remains limited. Future research should explore these innovative approaches to assess shoulder health indicators in the context of safer radiation treatment plans.

As evidenced with cortical bone (Iori et al., 2021; Armbrecht et al., 2022) the simulation model demonstrated that the ultrasound parameters are also sensitive to changes in trabecular bone structure. Further steps involve the use of QUSIB to quantify these structural changes in human ribs. This project has already reached an experimental phase, radio frequency data was extracted from the antero-lateral region of 4^{th}, 5^{th}, and 6^{th} ribs in 10 volunteers using conventional ultrasound. This data is still in the processing stages. Following this, the same experiment will be conducted *in-vivo* on breast cancer patients.

6.4 Overall Conclusion

Radiation therapy is one of the most effective treatments to mitigate breast cancer and its frequent application is likely to continue. This research aimed to better understand the consequences of this treatment across dimensions of shoulder function. We found early deficits in shoulder functional indicators affecting mostly muscle activation and shoulder range of

motion. The main implications of the radiation treatment for shoulder function included the muscle activation decrease of latissimus dorsi and teres major in flexion-extension, abduction-adduction, and external-internal rotation movement tasks, as well as reductions in shoulder abduction range of motion. An intervention program focused on shoulder muscles strength reduced several shoulder functional impairments, achieving improved muscle capacity by mitigating teres major activation reductions and also generated higher arm strength in flexion-extension, abduction-adduction, and external- internal rotation tasks. Additionally, ultrasound parameters were quantitatively sensitive to simulated changes in rib structure. This important finding concludes that the QUSIB can be used to predict rib fragility fractures and to provide more consistent and accessible bone quality assessments to breast cancer patients. Radiation therapy affects shoulder functionality causing restrictions in shoulder range of motion and interfering with the muscle capacity, thus impacting negatively in the quality of life of breast cancer patients. Shoulder strengthening during treatment proved to be a powerful intervention to improve arm strength. By preventing strength deficits, we can reduce the need to compensate for restricted shoulder range of motion. Breast cancer is a challenging disease, but with the right treatment and support, it is possible to overcome it. This dissertation has shown that strengthening exercises can help mitigate the negative effects of radiation therapy on shoulder functionality, providing hope for breast cancer patients seeking to maintain their quality of life. By identifying the benefits of strengthening exercises, this thesis provides a promising avenue for improving the physical well-being of breast cancer patients undergoing radiation therapy.

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Appendices

Appendix A: Information Consent and Participation Information

Study 1:

Information and Consent form to Participate in Research Study:

OBSERVATIONAL GROUP

Title of Project:	Addressing effective rehabilitation of post-treatment breast cancer patient functional capacity
Local Investigator:	Hannah Stracey, RN (EC), BScN, MSsN Grand River Hospital, Regional Cancer Center hannah.stracey@grhosp.on.ca
Student Investigator:	Cristina Herrera, MSc PhD Student University of Waterloo, Department of Kinesiology m6herrer@uwaterloo.ca
Faculty Supervisor:	**Clark Dickerson, PhD** University of Waterloo, Department of Kinesiology 519-888-4567 Ext. 37844 cdickers@uwaterloo.ca

Introduction

I would like to invite you to participate in this research study. This Information and Consent form explains the research study and what we will ask you to do. This consent form may have words that you do not understand. Please ask the researcher to explain anything or if you have other questions. You may take your time to think about the study and your participation or not. If you want to discuss the study with family, friends, your doctor, a health care professional, or any members of your community that you trust, that is okay. Participation is entirely your choice. You are being invited to participate in this study because you are about to start radiation therapy as part of your oncological treatment for breast cancer.

Purpose of this Study

This study is being conducted by Cristina Herrera, from the department of Kinesiology and Health Sciences, at the University of Waterloo, under the supervision of Dr. Clark Dickerson and is a requirement for her PhD thesis in Kinesiology. The purpose of this study is to identify the consequences of the application of radiation therapy in the shoulder and in the arm. More specifically, we would be assessing shoulder muscle strength and activation, shoulder range of motion, and the appearance of arm lymphedema. Fifty patients receiving treatment for breast cancer will be recruited at Grand River Hospital.

For this study, you will execute several shoulder muscle contractions and shoulder movements in evaluation meetings.

Procedures Involved in this Study

Please review the information in this consent letter and ask any questions you may have about the study.

This study comprises one evaluation meeting before the starting of your radiation treatment, and two other evaluations while you are receiving the therapy. In these meetings, the assessment of shoulder muscles activation, shoulder range of motion, and arm lymphedema will be accomplished. The duration of each meeting will be of approximately one hour. The evaluations meetings will be scheduled to coincide with visits to the hospital. Moreover, research visits would be relative to schedule medical procedures.

Additionally, you will be provided with a questionnaire at the beginning of the first session in which you will have to state how often you currently exercise.

During these evaluations four assessments will occur:

- Shoulder muscle activation: Several skin-mounted sensors will be placed on your shoulder and arm to track muscular activity during several tasks.

- Shoulder strength: Maximum force produced against a device held by the researcher in a desired direction will be measured, for a three second exertion.

- Shoulder range of motion: A sensor similar to a smart watch will be placed on your wrist and you will have to perform several movements in specific directions.

- Arm lymphedema: A measurement around the affected side arm will be taken.

Photography:

During the study protocol, there may be times when photographs of the study protocol/participant setup may be helpful to include in future publications, manuscripts, and at conferences. Photographs are often required in manuscripts to show the protocol set-up and study procedure, and may also help other scientists replicate our procedures. To protect anonymity, any features that would reveal identity such as face, tattoos etc will be blurred. It is your choice if you agree to be photographed, and this decision will not affect your ability to participate in the study. There is place on the consent form that you may initial beside if you agree that photos may be taken of you.

Time Commitment

Each evaluation meeting will require approximately 60 minutes of your time (there will be 3 evaluation sessions).

Risks to Participation and Associated Safeguards

Associated with the evaluation sessions:

The evaluations sessions have minimal anticipated risks. There are specific shoulder movements that will require force to move a small amount of weight or maintain a certain position for a few seconds. There is always a risk of muscle, joint or other injury in any physical effort. However, the risks in this study are anticipated to be lower than those encountered from a workout.

You may feel some muscle soreness or discomfort due to the limited physical activity involved.

Soreness or stiffness may persist for 2 or 3 days following the study if you are unaccustomed to this type of activity. However, this soreness or discomfort is normal and should disappear within a couple of days. If, at any time, you feel excessive discomfort or fatigue from the tasks you may stop at any time. Between tasks, you will be given the opportunity to rest and drink water.

There is also a possibility of mild skin reaction from using the skin patches. The placement of the skin mounted sensors may overlap with the area receiving radiation treatment, and some individuals may have sensitive skin resulting in skin irritation. Normally this irritation disappears shortly after the patch is removed. However, in order to mitigate this problem, a cotton swab with water and an unscented skin lotion will be provided to you after the sensor is removed from the skin. Additionally, the location of the sensors will be consistent throughout the sessions in order to minimize the skin exposure to the adhesive patches.

If you have any allergies to adhesives, you should not participate in this study. If you have sensitive skin, you may experience irritation from the tape used to secure the patches. Normally, this irritation disappears once the sensor is removed.

In the unlikely event of physical injury as a direct result of participating in the study, you would obtain medical care in the same manner as you would ordinarily obtain any other medical treatment.

Costs for participants:

Participation in this study will incur no cost to you.

COVID precautions:

Each evaluation session will last around one hour, and the total time that participants will be in close contact with the researcher will be 12 minutes. Additional COVID related risks and precautions are described in a separate letter.

Changing Your Mind about Participation

Participation in this study non-mandatory and voluntary and you may withdraw from this study at any time without penalty. To do so, indicate this to the researcher or one of the research assistants by saying, "I no

longer wish to participate in this study". You may contact the researchers to withdraw your data and have all study records destroyed up until data analysis begins.

If you change your mind about your participation in this study at any time, it won't have any impact on the care you receive at the Cancer Center.

If during the course of the study, new information emerges that might affect your decision to participate, it will be informed to you by both email and phone.

You may have 4 weeks after participating in the study to withdraw your data before analysis.

Personal Benefits of Participation

There will be not direct benefit to the participants.

The findings of this study may facilitate the development of rehabilitation protocols following radiation therapy, and will help to inform strategies to maintain shoulder function during treatment.

Appreciation

To thank you for participating in this study, you will receive a Conestoga Mall gift card of $50. If you decide to withdraw from the study before the final completion, you will still receive the gift card.

Confidentiality

To ensure the confidentiality of individuals' data, each participant will be identified by a participant identification code. Participant names will only be linked to ID codes on a separate file which will be stored separately. Only the investigators will have access to this code. Data without identifiers may be shared publicly. Your name will be confidential. Electronic data will be stored on a password protected computer or an electronic hard drive for at least 1 year. All paper copies of information and other records will be stored in a locked room (BMH 1404, B.C. Matthews Hall building, University of Waterloo), located in a secured hallway for at least 1 year. These records will be archived following the conclusion of the study.

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Study results
After the manuscript of the study is completed, a copy will be sent via email to you.

Participant's rights

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De-identified data

De-identification refers to the process of removing personal information from a data set aiming to preserve the privacy of the research participants. The de-identified data will be made accessible and available to other researchers. This process is integral to the research process as it allows other researchers to verify results and avoid duplicating research. The data that will be shared in publications and will not contain any information that can identify the participant.

Concerns about Your Participation

This study has been reviewed and received ethics clearance through a University of Waterloo Research Ethics Board (REB 42902). If you have questions for the Board contact the Office of Research Ethics, at 1-519-888-4567 ext. 36005 or reb@uwaterloo.ca and also the THREB Chair, Dr Alison Williams, at alison.williams@grhosp.on.ca.

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- I allow access to my medical record as explained in this consent form.
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Signatures

Participant:	Person Obtaining Consent:
_____	_____
Print Name	Printed Name, Role
_____	_____
Signature of Participant	Signature
_____	_____
Date	Date

Initials

☐ I agree to allow photographs in which I appear, to be used in teaching, scientific presentations and/or publications with the understanding that I will not be identified by name, and if the image includes my face or other identifying features, this will be blurred/obscured.

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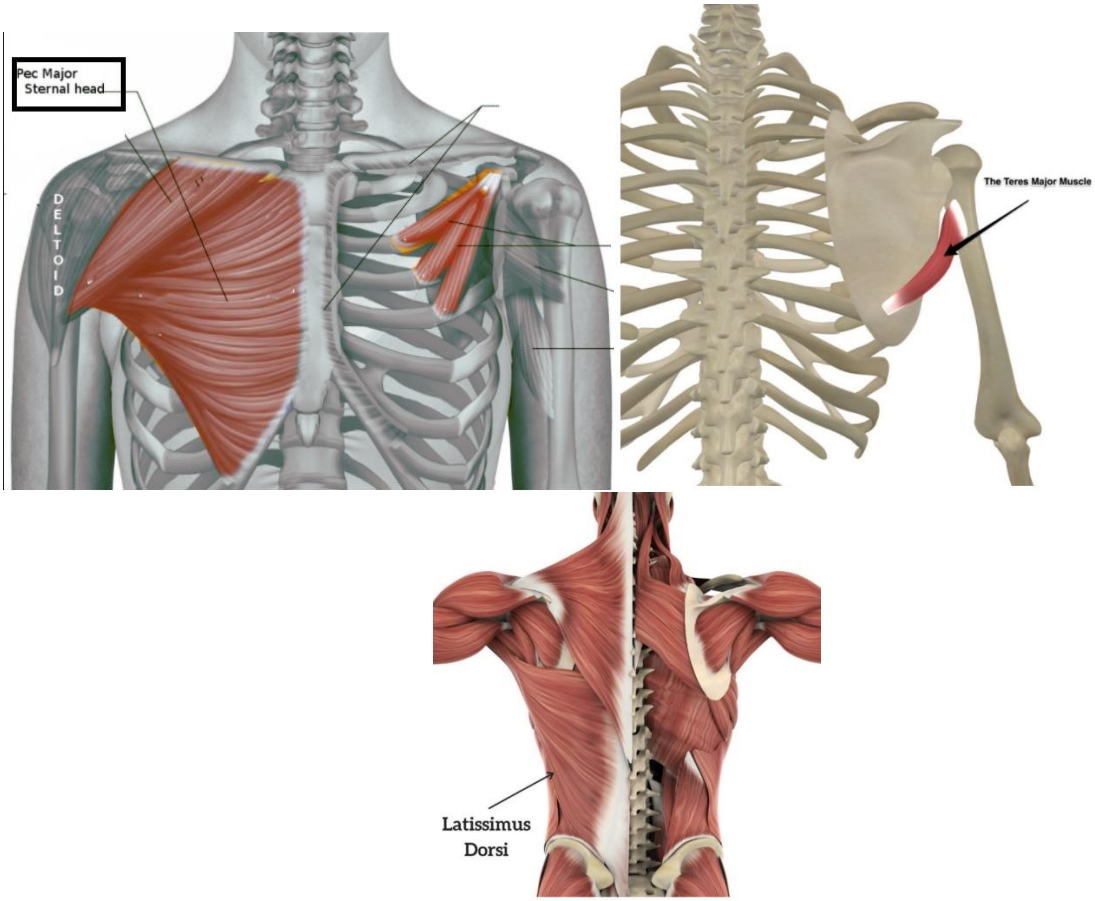
Addendum
Guide of detailed instructions for the procedures

Shoulder muscle activation assessment:

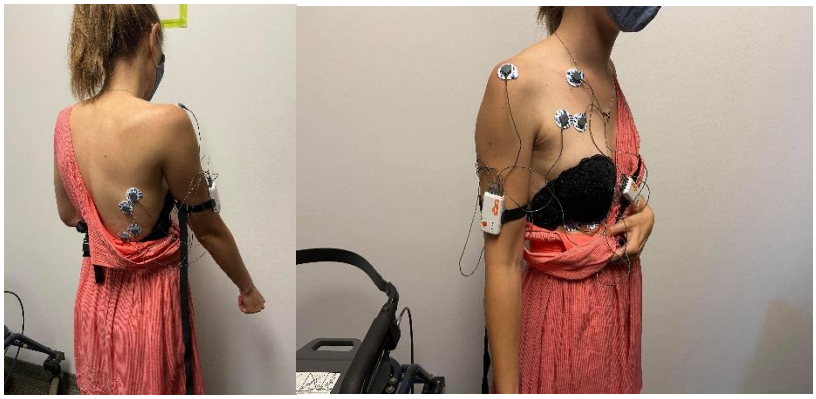
Electromyography (EMG) is a research procedure to assess the health of muscles and the nerve cells that control motor neurons (motor neurons transmit electrical signals that cause muscles to contract). EMG uses small devices called electrodes to translate these signals into graphs, sounds or numerical values. For this study, the electrodes will be skin mounted patches (Shimmer Sensing, Dublin, LE, Ireland) applied by a female researcher to the following shoulder muscles: pectoralis major, latissimus dorsi, and teres major. The skin overlying the muscle target area will first be shaved and cleansed with abrasive gel and wet cloth. The placement of sensors doesn't require you to disrobe, however it is advice to wear a sports bra. The bra or the bra's straps might need to be re-adjusted for this purpose After the fitting of the sensors you will be informed that it is optional as to whether you would like to wear a loose fitting t shirt.

After the patch placement on each muscle, you will be asked to perform muscle specific maximal voluntary contractions, pushing as hard as you can. You will be asked to slowly ramp to maximum, hold the contraction for 3 seconds, and then slowly ramp down. Afterwards, you will be instructed to perform a strength assessment task while wearing the sensors.

Target Muscles:



Shimmer Sensors:


(17)

Shoulder strength assessment:

When assessing the strength, you will be instructed to produce maximum force in the desired direction against an instrument called a hand-held dynamometer for five seconds. You will be asked to slowly ramp to maximum, hold the contraction for 3 seconds, and then slowly ramp down. Two isometric measurements of each muscle group will be recorded. The required movements will be shoulder flexion, extension, adduction, abduction, internal, and external rotation.

Hand-held dynamometer:

The picture shows a participant pressing against the hand-held dynamometer.

Shoulder range of motion assessment:

Shoulder range of motion will be measured with the Shimmer sensor placed at your wrist. You will be instructed to execute some functional movements to calibrate the device, and then you will have to perform the following movements:

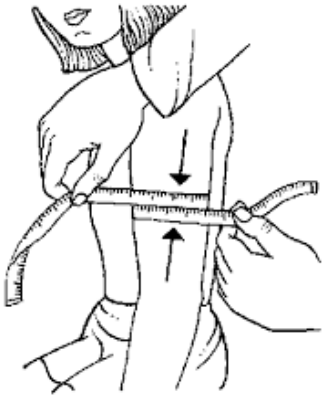
- shoulder flexion: you will move your arm from resting position (arm by your side) to straight above your head.
- shoulder extension: you will move your arm from straight above your head to resting position (arm by your side).
- shoulder abduction: you will raise your arm out of the side of your body from resting position, towards above of you head.
- shoulder adduction: you will move your arm from above of your head, towards the middle of your body until reaching resting position.
- shoulder rotation: with arm straight at your side with 90 degrees of abduction, you will bend your elbow 90 degrees with your hand pointing forwards. In that position, keeping the elbow bent, you will have to move your hand upwards (external rotation) and downwards (internal rotation).

Three measurements of each motion will be performed.

Arm lymphedema assessment:

Lymphedema refers to the swelling of the arm commonly caused by the removal or damage of the lymph nodes as part of the oncological treatment. Lymphedema assessment will be performed through arm circumference measurement in your affected arm. Your hand will rest on a pillow to suspend the arm, and the circumferences will be measured using a tape. Three sites will be assessed: the midpoint of the upper arm, the superior border of the elbow, and the midpoint of the forearm. Three measurements of each site will be recorded.

Arm circumference measurement:



Study 2:

Information and Consent form to Participate in Research Study: INTERVENTION STUDY

Title of Project: Addressing effective rehabilitation of post-treatment breast cancer patient functional capacity

Local Investigator: Hannah Stracey, RN (EC), BScN, MSsN Grand River Hospital, Regional Cancer Center hannah.stracey@grhosp.on.ca

Student Investigator: Cristina Herrera, MSc
PhD Student
University of Waterloo, Department of Kinesiology
m6herrer@uwaterloo.ca

Faculty Supervisor: **Clark Dickerson, PhD**
University of Waterloo, Department of Kinesiology
519-888-4567 Ext. 37844
cdickers@uwaterloo.ca

Introduction

I would like to invite you to participate in this research study. This Information and Consent form explains the research study and what we will ask you to do. This consent form may have words that you do not understand. Please ask the researcher to explain anything or if you have other questions. You may take your time to think about the study and your participation or not. If you want to discuss the study with family, friends, your doctor, a health care professional, or any members of your community that you trust, that is okay. Participation is entirely your choice.

You are being invited to participate in this study because you are about to start radiation therapy as part of your oncological treatment for breast cancer.

Purpose of this Study

This study is being conducted by Cristina Herrera, from the department of Kinesiology and Health Sciences, at the University of Waterloo, under the supervision of Dr. Clark Dickerson and is a requirement for her PhD thesis in Kinesiology. The purpose of this study is to identify how radiation therapy for breast cancer affects shoulder and arm function, and to further determine if an exercise intervention affects shoulder health functional indicators. More specifically, it assesses shoulder strength and muscle activation, shoulder range of motion, and arm lymphedema presence. Fifty patients receiving treatment for breast cancer will be recruited at Grand River Hospital.

As a participant in this study, you will perform several simple arm actions and movements while non-invasive measurements are taken in short meetings that coincide with your scheduled radiation treatments,

and will occur in GRH.

This is a randomized study design. The randomization sequence will be created using a software called 'REDCap'. Upon joining the study as a participant, you will be randomized into one of two groups. You have an equal chance of being assigned to either group (like the flip of a coin). Depending on which group you are placed in, you will be given instructions to begin a home-based intervention program focused either on aerobic exercises or shoulder strength training. Instructions for each group will be provided following randomization.

Procedures Involved in this Study

Please review this consent letter and ask any questions you may have about the study.

This study consists of two sections, (both contribute to the overall research):

Section 1 focuses on three meetings that include simple measurements related to shoulder function.

There is an initial evaluation meeting before the start of your radiation treatment, and two evaluations during the therapy window. In these meetings, several functional measures will be assessed (below). Each meeting will last less than one hour. The evaluations will be scheduled to coincide with treatment visits to the hospital.

During these evaluations four assessments will occur:

- Shoulder muscle activation: Several skin-mounted sensors will be placed on your shoulder and arm in order to track muscular activity during several tasks.

- Shoulder strength: Maximum force produced against a device held by the researcher in a desired direction will be measured, for a three second exertion.

- Shoulder range of motion: A sensor similar to a smart watch will be placed on your wrist and you will have to perform several movements in specific directions.

- Arm lymphedema: A measurement around the affected side arm will be taken.

Section 2 focuses on a home-based exercise program, with a frequency of 3 times per week, 30 minutes each.

This exercise will depend on randomization to one of two groups: aerobic exercise (such as walking, running, bike riding, or dancing), or a shoulder-specific strength training program.

You will be asked to start this assigned activity at the beginning of your radiation treatment for a duration of 6 weeks.

Additionally, you will be provided with a questionnaire at the beginning of the first session which asks how often you currently exercise.

Photography:

During the study protocol, there may be times when photographs of the study protocol/participant setup may be helpful to include in future publications, manuscripts, and at conferences. Photographs are often required in manuscripts to show the protocol set-up and study procedure, and may also help other scientists replicate our procedures. To protect anonymity, any features that would reveal identity such as face, tattoos etc will be blurred. It is your choice if you agree to be photographed, and this decision will not affect your ability to participate in the study. There is place on the consent form that you may initial beside if you agree that photos may be taken of you.

Time Commitment

Each evaluation will last approximately 60 minutes of your time (there will be 3). The exercise portion will require 1.5 hours per week (and six weeks in total). The total time commitment for this study will be 12 hours, including exercise sessions (self-directed or guided).

Risks to Participation and Associated Safeguards

Associated with the evaluation sessions:

The evaluations sessions have minimal anticipated risks. There are specific shoulder movements that will require force to move a small amount of weight or maintain a certain position for a few seconds. There is always a risk of muscle, joint or other injury in any physical effort. However, the risks in this study are anticipated to be lower than those encountered from a workout.

You may feel some muscle soreness or discomfort due to the limited physical activity involved.

Soreness or stiffness may persist for 2 or 3 days following the study if you are unaccustomed to this type of activity. However, this soreness or discomfort is normal and should disappear within a couple of days. If, at any time, you feel excessive discomfort or fatigue from the tasks you may stop at any time. Between tasks, you will be given the opportunity to rest and drink water.

There is also a possibility of mild skin reaction from using the skin patches. The placement of the skin mounted sensors may overlap with the area receiving radiation treatment, and some individuals may have sensitive skin resulting in skin irritation. Normally this irritation disappears shortly after the patch is removed. However, in order to mitigate this problem, a cotton swab with water and an unscented skin lotion will be provided to you after the sensor is removed from the skin. Additionally, the location of the sensors will be consistent throughout the sessions in order to minimize the skin exposure to the adhesive patches.

If you have any allergies to adhesives, you should not participate in this study. If you have sensitive skin, you may experience irritation from the tape used to secure the patches. Normally, this irritation disappears once the sensor is removed.

In the unlikely event of physical injury as a direct result of participating in the study, you would obtain medical care in the same manner as you would ordinarily obtain any other medical treatment.

Associated with the shoulder muscles strength intervention program:

There is also a risk to feel some sort of distress while performing the online intervention program exercises. However, the risks are not anticipated to be greater than those encountered while performing any workout. You must stop exercising if you are feeling dizzy or if you are unsteady on your feet. Additionally, you must stop exercising if you are noticing swelling, pain, dizziness, or blurred vision and call your doctor right away.

To avoid distress during the online class, you will be reminded to drink water throughout the class, and to take breaks whenever you need it.

If you need help during the class, you can use the raise hand feature and speak into your microphone. The class will be paused so that the researcher can assess and take appropriate measures to help deal with the situation.

Costs for participants:

Participation in this study will incur no cost to you.

COVID precautions:

Each evaluation session will last around one hour, and the total time that participants will be in close contact with the researcher will be 12 minutes.

Additional COVID related risks and precautions are described in a separate letter.

Changing Your Mind about Participation
Participation in this study non-mandatory and voluntary and you may withdraw from this study at any time without penalty. To do so, indicate this to the researcher or one of the research assistants by saying, "I no longer wish to participate in this study". You may contact the researchers to withdraw your data and have all study records destroyed up until data analysis begins.

If you change your mind about your participation in this study at any time, it won't have any impact on the care you receive at the Cancer Center.

If during the course of the study, new information emerges that might affect your decision to participate, it will be informed to you by both email and phone.

You have 4 weeks after participating in the study to withdraw your data before analysis.

Personal Benefits of Participation
The findings of this study may facilitate the development of rehabilitation protocols following radiation therapy, and will help to inform strategies to maintain shoulder function during treatment.

The completion of an exercise program may benefit the participants.

Appreciation

To thank you for participating in this study, you will receive a Conestoga Mall gift card of $50. If you decide to withdraw from the study before the final completion, you will still receive the gift card.

Confidentiality
To ensure the confidentiality of individuals' data, each participant will be identified by a participant identification code. Participant names will only be linked to ID codes on a separate file which will be stored separately. Only the investigators will have access to this code. Data without identifiers may be shared publicly. Your name will be confidential. Electronic data will be stored on a password protected computer or an electronic hard drive for at least 1 year. All paper copies of information and other records will be stored in a locked room (BMH 1404, B.C. Matthews Hall building, University of Waterloo), located in a secured hallway for at least 1 year. These records will be archived following the conclusion of the study.

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Addressing effective rehabilitation of post-treatment breast cancer patient functional capacity

Consent Form

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Signatures

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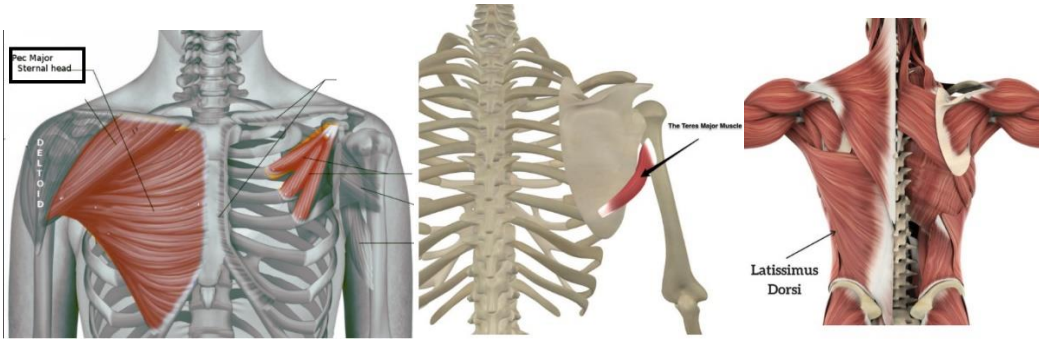

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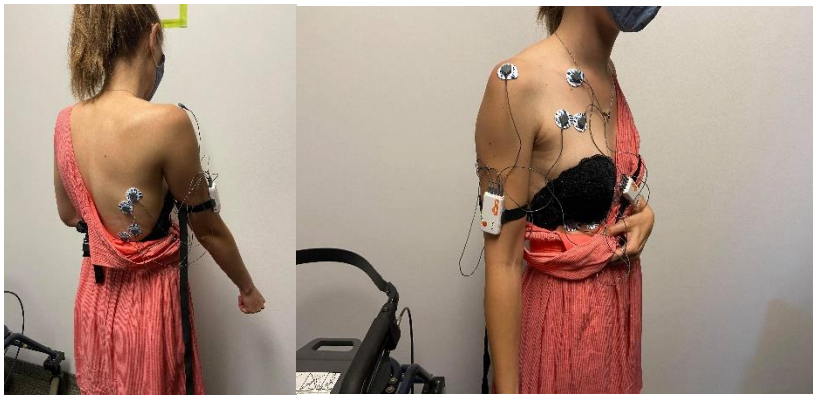

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Hand-held dynamometer:

The picture shows a participant pressing against the hand-held dynamometer.

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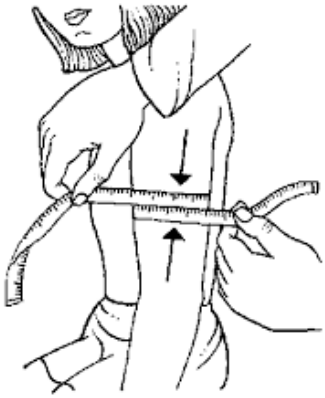
Three measurements of each motion will be performed.

Arm lymphedema assessment:



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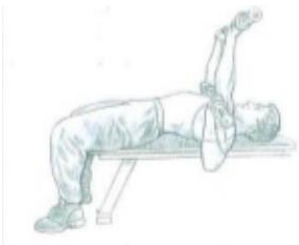
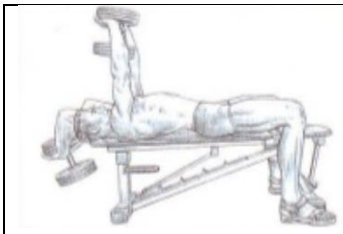
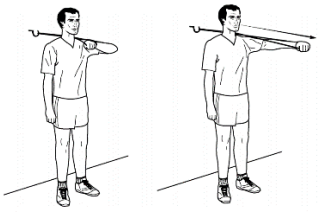
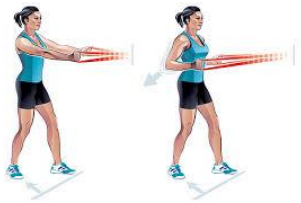
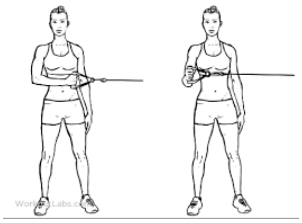
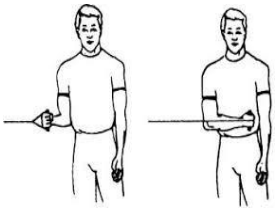
Shoulder intervention program- Exercises description:

Exercise	Initial position	Action	Repetitions
Vertical row with dumbbell 	Standing position, elbows completely extended, and weight held with both hands with the overhand grip.	Lift the weight straight up until elbows are fully flexed.	Week 1: 3x8 Week 2: 3x10 Week 3: 3x15 Only for patients receiving 30 fractions of radiation: Week 4: 3x8 Week 5: 3x10 Week 6: 3x15
Bench press with dumbbell 	Lying supine on training bench or similar, holding one dumbbell with each hand in overhand grip. Shoulder flexed 100° and elbows completely flexed.	Completely extend elbows while protracting scapula.	
Pull over with dumbbell	Lying supine on training bench or similar, shoulder flexed 160°, elbows	While maintaining elbows extended, move weight forwards until 100°	

	completely extended, holding weight with both hands.	of shoulder flexion.	
Forward punch with elastic band 	Standing position, elastic band held with both hands and placed behind the back. Shoulders flexed 100° and elbow completely flexed.	Completely extend elbows with scapula fully protracted.	
Horizontal row with elastic band 	Standing position, elastic band held with both hands and placed forward. Shoulder and elbow completely extended.	Completely flex elbow and extend shoulder.	
Outward elevation with one hand with elastic band 	Seated in chair, fasten elastic band under foot and hold the other end of the band with one hand.	Move shoulder to 100° of flexion and 20° of abduction, while maintaining the elbow completely extended and the scapula protracted.	
Sword pulling with elastic band 	Standing position, fasten elastic band without any slack under one foot, and hold the other end of	Stretch band performing a semi-circle movement until 20° of shoulder abduction while	

	the band with opposite side hand.	maintaining the elbow completely extended.	
Shoulder external rotation at side 	Standing position, grab elastic band with slight resistance, with arm across body and elbow bent 90°.	with an open hand grip and keeping the upper arm steady, rotate the hand outwards until is lined up with the side of the body. Return to initial position.	
Shoulder internal rotation at side 	Standing position, grab the end of the band securely attached at waist-height.	Grab the other end of the band with tension, and pull the band away from the wall, rotating forearm inward.	

Appendix B: Questionnaire

Questionnaire:

Please complete at the end of each week.

You can include any other activity not mentioned in the list (vacuum, gardening, mopping, washing the dishes, etc).

Week #:

	Times per week
d) Strenuous exercise (heart beats rapidly) (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	
e) Moderate exercise (not exhausting) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	
f) Mild/light exercise (minimal effort) (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-moiling, easy walking)	

Appendix C: REMOTE PROGRAMMING EMERGENCY PROTOCOL

Participant is NOT home alone	
Injury not severe – not an emergency	Injury severe – is an emergency

• Pause class
• Ensure participant is okay
• Suggest they take a short break and resume when able
• If participant does not think they will be able to resume exercise:
  ○ Suggest they inform their caregiver/spouse what happened
  ○ If caregiver is responding allow participant to log off video call
• May be necessary to check in with participant before next class
	• Pause class
	• If participant's caregiver/spouse sees incident and is able to respond ask if they need your help or if you can provide assistance
	  ○ If assistance is needed:
	  ▪ Instruct other participants to log off the video call and follow pre-recorded videos if interested in continuing their workout
	  ○ If assistance is not needed:
	  ▪ Remove injured participant from video call and continue with class
	  ▪ Follow up with caregiver/spouse after class with a phone call
	• If participant's caregiver/spouse does not respond, follow steps outlined in table below

Participant IS home alone	
Injury not severe – not an emergency	Injury is severe – is an emergency

• Pause class
• Ensure participant is okay
• Suggest they take a short break and resume when able
• If participant does not think they will be able to resume exercise:
  ○ Suggest that they stay on the call so that you can continue monitoring them while continuing the class
  ○ Check in with them again at the end of the class
  ○ If all is okay, allow them to hang up
• May be necessary to check in with participant before next class
	• Stop class
	• Instruct other participants to log off video call and follow pre-recorded videos if interested in continuing their workout
	• Keep injured participant on the call
	• Open database and look up participant's address/emergency contact
	• Call 911
	  ○ Provide them with participant's name and address
	  ○ Describe to them what happened along with any other relevant medical info on the database
	• While waiting for EMS to arrive, stay on video call with participant and call their

	emergency contact to let them know what is happening • When EMS arrives find out if you can be of any more assistance – if not, end video call • Follow up with the participant or their emergency contact within the next day or so