NEAR-INFRARED SPECTROSCOPY TO ASSESS EXERCISE-INDUCED CHANGES IN SKELETAL MUSCLE OXYGENATION IN PATIENTS WITH SOFT TISSUE SARCOMA: A PRELIMINARY INVESTIGATION

Andrew Lewis Hoselton

A thesis submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Arts in the Department of Exercise and Sport Science (Exercise Physiology).

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Approved by:

Claudio Battaglini

Lee Stoner

William Eward

ABSTRACT

Andrew Lewis Hoselton: Near-infrared spectroscopy to assess exercise-induced changes in skeletal muscle oxygenation in patients with soft tissue sarcoma: a preliminary investigation
(Under the direction of Claudio L. Battaglini)

The initial purpose of this study was to examine the effects of single-joint resistance exercise on NIRS measurements, tumor necrosis percentage, functionality, and the rate of wound complications in patients with STS of the extremities undergoing preoperative radiation. Due to extraneous circumstances, only two patients were able to complete study-related activities; therefore, the revised purpose of this preliminary study was to report demographic data on all parameters and assess the feasibility of the current protocol in order to guide subsequent research. Although no statistical analyses were performed, exercised-induced changes in blood volume were reported. Feasibility was evaluated on 8 established benchmarks: acceptability, demand, implementation, practicality, adaptation, integration, expansion, and limited-efficacy testing. Ultimately, it was determined that the current protocol is feasible for patients with soft tissue sarcoma below the knee in the lower limb.

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LIST OF ABBREVIATIONS

1RM – One repetition maximum

AJCC – American Joint Committee on Cancer

ANOVA – Analysis of variance

CNT – Standard of care control

DNA – Deoxyribonucleic acid

DPF – Differential path-length factor

EX – Exercise

IFN- γ – Interferon-γ

KC – Keratinocyte chemoattractant

MCP-1 – Monocyte chemoattractant protein

MSTS – Musculoskeletal Tumor Society Rating Scale

MVC – Maximal Voluntary Contraction

NIRS – Near-infrared spectroscopy

RCT – Randomized controlled trials

RPE – Rating of perceived exertion

SD – Standard deviation

SRS – Spatial resolved spectroscopy

STS – Soft tissue sarcoma

TGFβ – Transforming growth factor beta

TNF-α – Tumor necrosis factor- α

UNC – University of North Carolina at Chapel Hill

VEGF – Vascular endothelial growth factor

CHAPTER 1

INTRODUCTION

Soft tissue sarcomas (STS) are comprised of a heterogeneous group of rare cancers that arise in nonepithelial extraskeletal tissue like muscle, fat, and fibrous supporting structures (Clark et al., 2005). This group of cancers represents one percent of all cancer diagnoses each year in the United States (Jemal et al., 2004, Siegel, Miller & Jemal, 2019). Although STS can form anywhere in the body, most cases (60%) present in, or in the girdles of, the upper and lower extremities (Clark et al., 2005, Linch et al., 2014). Identification of STS involves physical examination, imaging, and histological analysis (Clark et al., 2005). Once diagnosed, the standard treatment option for STS in the extremities consists of radiation therapy followed by surgical resection (O'Sullivan et al., 2002). The goal of this treatment strategy is to achieve local tumor control while preserving functionality in the extremity (Davis et al., 2005).

Radiation therapy has emerged as a central part in the curative treatment of STS (Lichter & Lawrence, 1995). Mechanistically, radiation produces oxygen free radicals that damage DNA in tumor cells and lead to cell death (Baskar et al., 2012). Inevitably, radiation damages healthy cells as well; therefore, treatment strategies that minimize the overall dose, like preoperative radiation therapy, are preferred (Sadoski et al., 1993). These treatment plans dampen the impact on healthy tissue and stave off reduced functionality (O'Sullivan et al., 2002). Despite the lower doses of radiation, some patients who undergo preoperative radiation treatment experience major wound complications because irradiating tissue compromises wound healing mechanisms and limits recovery (Davis et al., 2005, Tibbs, 1997).

Cancerous tissue is characterized by its hypoxic tumor microenvironment. This setting impacts the effectiveness of localized treatment like radiation, which relies on the production of oxygen free radicals for its cytotoxic effect (Baskar et al., 2012). In preclinical trials of human breast and prostate cancer models, low-to-moderate aerobic exercise has been shown to regulate tumor physiology by reducing hypoxia and improving perfusion (Jones et al., 2010, McCullough et al., 2013). Because similar mechanisms may apply to STS, improving the oxygenation in the affected limb may improve the effectiveness of radiation therapy. Furthermore, other animal models have shown that moderate intensity aerobic exercise potentially dampens the pro-inflammatory factors that arise after repetitive radiation treatments and slow the wound healing process (Keylock et al., 2018). A study by Emery and colleagues found that implementation of a 3-month moderate intensity aerobic exercise program significantly improved the wound healing process in healthy, older adults (Emery et al., 2005). Therefore, the use of exercise with the goal of improving tissue perfusion at the tumor site in patients being treated for STS may help improve radiation treatment efficacy as well as wound healing, leading to better treatment outcomes.

Near-infrared spectroscopy (NIRS) has emerged as a noninvasive method of examining perfusion, blood flow, and oxygen uptake by assessing the oxygenation state of heme compounds in skeletal muscle (Barstow, 2019). While NIRS has been used to investigate several clinical populations (De Blasi et al., 1997, Malagoni et al., 2010) its use in STS patients is lacking. To our knowledge, this study will be the first to explore the effects of exercise on perfusion, blood flow, and oxygen uptake in skeletal muscle using NIRS in patients with STS of the extremities. Additionally, this study will allow for an investigation into the potential effects of exercise on the rate of wound complications, limb functionality, and tumor necrosis percentage in this population. Furthermore, this preliminary study will shed light on the feasibility of implementing an exercise intervention into the current standard of care treatment for STS of the extremities.

STATEMENT OF PURPOSE

The purpose of this study was to examine the effects of single-joint resistance exercise on skeletal muscle perfusion, blood flow, and muscle oxygen uptake via NIRS in patients with STS of the extremities. A secondary purpose was to evaluate whether exercise significantly improves functionality and reduces the rate of wound complications associated with preoperative radiotherapy. A tertiary purpose was to investigate whether implementing an exercise program improves radiation treatment efficacy as determined by tumor necrosis percentage.

Due to extraneous circumstances, only two patients were able to complete study-related activities; therefore, the new purpose of this preliminary study is to present demographic data on all parameters assessed in the two patients and evaluate the feasibility of the current protocol as a means to inform future trials.

HYPOTHESES

- H1: Patients randomized to the exercise therapy group will significantly increase skeletal muscle perfusion, blood flow, and muscle oxygen uptake in the tumor affected limb immediately following an exercise session.
- H2: Patients randomized to the exercise therapy group will exhibit fewer wound complications and improved functionality measurements following surgical resection than their control group counterparts.
- H3: Patients randomized to the exercise therapy group will exhibit increased percent necrosis of the resected tumor than their control group counterparts.

LIMITATIONS

- Single site NIRS systems interrogate a discrete volume of tissue and extrapolate the findings to the whole muscle (Barstow, 2019).

DELIMITATIONS

- All patients will be recruited from and receive standard anti-cancer treatments for STS at the Duke Cancer Institute.
- Only patients diagnosed with STS in the extremities and scheduled to receive preoperative radiation therapy and surgical resection will be enrolled in the study.

DEFINITION OF TERMS

- Near-Infrared light: Light with a wavelength of 650 – 950 nm (Wolf, Ferrari & Quaresima, 2007).
- Neoadjuvant: Preoperative
- Occlusion: Absence of downstream blood flow or pulses (Barstow, 2019).
- Periprosthetic: In close relation to an implant.
- Resection: Removal; Excision.
- Scattering: Errant dispersing of photons across a medium (Barstow, 2019).

ASSUMPTIONS

- Homogeneity in skeletal muscle perfusion, blood flow, and muscle oxygen uptake across the muscle (Barstow, 2019, Jones et al., 2016)
- Blood volume measured by changes in total[Hb+Mb] remains constant during arterial occlusions (Jones et al., 2016).

- The rate of disappearance of oxy[Hb+Mb] reflects the rate of oxygen utilization by the underlying tissue (Barstow, 2019).

SIGNIFICANCE

Roughly half of all cancer patients will undergo radiation therapy over the course of treatment (Baskar et al., 2012). Radiation therapy in conjunction with surgical resection is the most common treatment strategy for patients with STS in the extremities (Davis et al., 2005, O'Sullivan et al., 2002). Preoperative radiation is advantageous in that patients receive a lower dose of radiation (Sadoski et al., 1993); however, the downside is that patients often experience major wound complications following tumor resection (Davis et al., 2005). Although its role in STS treatment process is currently unknown, exercise has the potential to not only mitigate the prevalent wound complications associated with preoperative radiotherapy, but also improve the efficacy of the radiotherapy itself. If the current protocol appears to be both feasible and efficacious, then larger trials may be warranted.

CHAPTER 2

REVIEW OF LITERATURE

BACKGROUND

In 2019, there were an estimated 1,762,450 new cancer diagnoses in the United States. In the same year, there were an estimated 606,880 deaths nationally. The latter figure made cancer the second leading cause of death in the United States behind heart disease (Siegel, Miller & Jemal, 2019). The insidious disease showcases six hallmark characteristics: evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion and metastasis, limitless replicative potential, and sustained angiogenesis (Hanahan & Weinburg, 2000). Death from cancer mainly results from infection, organ failure, infarction, hemorrhage, or carcinomatosis (Inagaki, Rodriguez & Bodey, 1974).

Soft tissue sarcomas are a rare type of cancer, representing about 1 percent of all cancer cases in the United States (Siegel, Miller & Jemal, 2019). Roughly half of all patients diagnosed with STS will die from the disease (Enneking et al., 1981, Strander et al., 2003). These tumors impact nonepithelial extraskeletal tissue derived from the embryonic mesoderm like muscle, fat, and fibrous supporting structures (Clark et al., 2005). The WHO classification of STS consists of the following types: adipocytic, fibrolastic/myofibroblastic, so-called fibrohistiocytic, smooth muscle, pericytic/perivascular, skeletal muscle, vascular, chondro-osseous, tumors of uncertain differentiation, gastrointestinal stromal tumors, nerve sheath tumors, and undifferentiated unclassified sarcomas (Jo & Fletcher, 2014). Although STSs represent a heterogenous group of tumors, these tumors are grouped together because of similarities in pathologic appearance, clinical presentation, and natural history (Rosenberg et al., 1982). Altogether, there are over 50 subtypes of STS, which are labeled and grouped by the cell of origin (Strander et al., 2003).

STS often present with nonspecific clinical symptoms; however, some site-dependent symptoms like bladder pressure paresthesia, and distal edema have been reported. The size of the tumor at presentation is associated with location as distal tumors are recognized more easily than proximal tumors. Incidence rates of STS vary based upon anatomic location with roughly 60% of all cases occurring in the limbs or limb girdles. STS grow in a centrifugal fashion and at a variable rate depending upon the aggressiveness of the tumor (Clark et al., 2005). Sarcomas tend to respect fascial boundaries and rarely penetrate other compartments. Extension into bone and neural sheaths is uncommon. The most prominent source of cross compartment contamination is surgery due to open planes and neovascularity (Enneking et al., 1981). Nonetheless, a key characteristic of STS is early metastasis in the lungs (Rosenberg et al. 1982).

Determining the stage of STS allows physicians to estimate a prognosis (Clark et al., 2005). The American Joint Committee on Cancer (AJCC) has established an STS-specific version of the TNM system to differentiate the various stages of this rare cancer type. This system evaluates the grade of the primary tumor, the depth and size of the primary tumor (T), the involvement of regional lymph nodes (N), and the presence of distant metastasis (M). Grade refers to the differentiation of the primary tumor and ranges from “G1” to “G4” (GX is used if the tumor cannot be assessed). Low grade tumors are rated “G1” or “G2” while high grade tumors are designated as “G3” or “G4”. Depth and size are two subcategories of the primary tumor also considered. Ratings for this component of staging system range from “T0” to “T2” (In instances where the primary tumor cannot be evaluated, “TX” is assigned). If a primary tumor is not present, then “T0” is assigned. Tumors larger than 5 cm in the greatest dimension are assigned a “T2” rating, whereas tumors smaller than 5 cm in the greatest dimension are given a “T1” rating. The depth of the tumor further describes the “T” rating of the primary tumor. Superficial tumors that do not invade the superficial fascia receive an “a” rating while those that do affect the superficial fascia are given a “b” rating. Metastasis of the regional lymph nodes results in a “N1” rating while no absence of metastasis yields a “N0” rating (A “NX” rating is given if the regional lymph nodes cannot be assessed). The presence of distant metastases produces a “M1” rating. A “M0” rating is given if no distant metastases in presence (“MX” is given if distant metastases cannot be assessed). The combination of the components of the TNM system inform the stage of the STS. Notably, the presence of metastasis either in the regional lymph nodes or in a distant structure results in a stage IV prognosis (American Joint Committee on Cancer, 1997). Five-year survival rates for STS patients with stage I, II, III, and IV disease are 90, 70, 50, and 10-20 percent, respectively (Stojadinovic et al., 2002).

TREATMENT OPTIONS

A painless, growing mass is the most common finding at presentation; therefore, confirmation of STS relies on examination, imaging, and histological analysis. While physical examinations and imaging shed light on the tumor’s size, depth, and location in relation to adjacent structures, histological confirmation is required prior to the initiation of treatment. The most common procedure, the core needle biopsy, informs physicians of the subtype and grade of the STS roughly 80% of the time (Clark et al., 2005). Following histological conformation of STS, the goal of treatment is to achieve cure and conserve limb function (O’Sullivan et al., 2002). Because of the rarity of the disease, STS are best treated at multidisciplinary centers with prior experience (Strander et al. 2003). The three main anti-cancer treatments used to combat STS are surgery, radiation, and chemotherapy (Clark et al., 2005).

Surgery is a mainstay procedure in the treatment of STS of the extremities (Haas et al., 2012). The goal of surgery is to remove the tumor from the affected limb with wide margins when possible (Clark et al., 2005). The extent of the surgical margin is determined by the distance of the margin from the tumor’s reactive zone. The reactive zone is characterized by discoloration around the tumor consisting of hemorrhagic tissue, scar tissue, degenerated muscle, edema, or the tumor capsule itself. There are four classifications of surgical margins: curative, wide, marginal, and intralesional. Curative marginals are margins greater than 5 cm outside of the reactive zone of the tumor. Wide margins are those that fall within 1 to 4 cm outside the reactive zone. Marginal margins pass through the reactive zone while intralesional margins pass through the tumor parenchyma (Kawaguchi et al., 2004). Microscopic disease tends to persist following surgical excision of the primary tumor; therefore, in order to prevent local recurrence, additional treatment strategies like radiation and/or chemotherapy are necessary (Clark et al., 2005).

Roughly half of all cancer patients receive radiation therapy over the course of treatment. Although radiation therapy accounts for just 5% of the total cost of cancer care, it contributes about 40% of the curative treatment and is a key component of multimodal strategies to treat STS (Baskar et al., 2012). Radiation is delivered thorough either an external beam or via brachytherapy. External beam radiation is the more common approach and involves delivery from an external source to the target tissue. On the other hand, brachytherapy involves delivery inside the body directly into the tumor site (Clark et al., 2005). As mentioned previously, one of the hallmark characteristics of cancer is its limitless replicative potential (Hanahan & Weinburg, 2000). Radiation therapy is a physical agent used to mitigate the proliferative potential of cancerous cells via both direct and indirect mechanisms. The direct action of radiation therapy promotes cell death by way of DNA damage, whereas the indirect action of radiation therapy involves the production of free radicals. Ultimately, these free radicals cause DNA damage and lead to cell death. The unfortunate consequence of radiation therapy is that both normal and cancerous cells are affected. Because normal cells are more capable of repairing damaged genetic material than cancer cells, there is differentiated cell death among irradiated tissue. Nonetheless, a key objective of radiation therapy is to minimize healthy tissue exposure (Baskar et al., 2012).

Chemotherapy as part of a multimodal treatment plan for STS has been reserved for patients with more advanced stage disease. The goal of this treatment component is disease palliation and systemic control (Linch et al., 2012). The effectiveness of chemotherapy varies depending upon the tumor subtype, the tumor grade, the patient’s age, performance status, and the timing of metastatic disease (Clark et al., 2005). Ifosfamide and doxorubicin are the two most used cytotoxic agents in the systemic treatment of STS. This combination is typically used in situations where the goal is tumor shrinkage (Linch et al., 2012). A meta-analysis of RCT assessing the efficacy of adjuvant chemotherapy in adult patients with localized resectable STS determined that the combination of ifosfamide and doxorubicin conveyed a significant benefit is overall survival ($p = .01$) (Pervaiz et al., 2008). Contrarily, an RCT of 351 adult patients with intermediate to high grade STS evaluated the effects of adujuvant chemotherapy (ifosfamide plus doxorubicin) within 4 weeks or macroscopic resection and concluded that there was no difference in overall survival between the groups ($p = .72$) (Woll et al., 2012). Altogether, because of the heterogenous nature of STS and the debate among researchers, incorporating chemotherapy into the treatment plans is typically considered on a case-by-case basis (Linch et al., 2012)

EVOLUTIONS IN TREATMENT

Treatment strategies for patients with STS in the extremities have evolved since the 1960s. In years past, amputation at or above the joint proximal to the tumor was considered standard treatment (Lichter & Lawrence, 1995, Rosenberg et al., 1982). This approach was adopted following the work by Gerner et al. (1975), which determined that major or radical amputation produced the most efficient control at the primary tumor site. In 155 adults with operable STS, local recurrence rates were 93% and 60% in patients who underwent local and wide excisions of the primary lesion, respectively. In comparison, only 8% of patients who initially underwent major or radical amputations experienced local recurrence. Subsequent work by Enneking et al. (1981) shifted the dogma towards the preservation of a functional extremity rather than local eradication via amputation. In a study of 40 patients with STS of the thigh, local recurrence rates were 50% and 0% in those with low grade lesions treated with surgery featuring marginal and wide margins, respectively. Among patients with high grade lesions, the local recurrence rate was 30% with wide margins and 5% with radical margins. Another study by Lindberg et al. (1981) expanded upon the concept of limb preservation by implementing a multimodal treatment strategy consisting of conservative surgical excision and postoperative radiation therapy. With this treatment strategy, patients with STS of the extremities exhibited a local recurrence rate of 20% and a five-year disease-free survival rate of 69.4%. Ultimately, the work by Rosenberg et al. (1982) established limb-sparing therapy as the new standard of care. Forty-three adult patients with high grade STS of the extremities were prospectively randomized into either an amputation group or a limb-sparing (resection with adjuvant radiation therapy) group. There was no difference in disease free survival rate (71% vs. 78%; p = .75) or overall survival rate (83% vs. 88%; p = .99) at five years. Weitz, Antonsecu & Brennan (2003) investigated whether the treatment strategies for patients with STS of the extremities changed from 1982 to 2001. The results showed a significant reduction in the amputation rate in the period from 1982 to 1986 versus the period from 1997 to 2001 (13% vs. 5%; p = .0001). Additionally, the use of radiation significantly increased (p = .008) while the use of chemotherapy significantly decreased (p < .0001) in the same time span.

PREOPERATIVE RADIATION

Although a multimodal treatment strategy composed of surgical resection and radiation therapy is now accepted as standard of care for STS of the extremity, research is still being conducted to optimize treatment. The timing of radiation therapy is still a debated issue (Haas et al., 2012). The two prominent options for radiation therapy scheduling are before surgical resection of the tumor (preoperative) and after surgical resection of the tumor (postoperative). Theoretically, preoperative radiation therapy is more advantageous because it reduces the radiation field size, minimizes the number of joints involved, and results in a lower overall dose (Strander et al., 2003). Moreover, preoperative radiation can reduce the size of the tumor heading into the surgical resection and decrease the likelihood of intraoperation seeding of viable tumor cells (Cheng et al., 1998). These considerations translate into better functional outcomes in the affected limb (Strander et al., 2003**)**. The major setback for preoperative radiation treatment is the increased incidence rate of wound complications following surgical resection of the STS (Strander et al., 2003). Wound complications are often defined as an additional operation(s) to address wound repair or wound management. This includes wound dehiscence, tissue necrosis, eschar and seroma formation, irrigation, debridement, and drainage (O’Sullivan et al, 2002).

ROLE OF EXERCISE

Novel approaches are needed to address the increased rate of wound complications in patients with STS treated with preoperative radiation therapy. Repetitive radiation treatments disrupt the complex wound healing process by upregulating the proinflammatory factors that control the inflammatory and proliferative phases (Haubner et al., 2012). The inflammatory phase is characterized by the infiltration of neutrophils, macrophages, and lymphocytes into the affected area (Guo & DiPietro, 2010). TGFβ, VEGF, TNF-α, IFN- γ, and proinflammatory cytokines like interleukin-1 and interleukin-8 regulate the migration of inflammatory cells during the inflammatory phase. Following radiation treatment, overexpression of these cytokines results in uncontrolled matrix accumulation and fibrosis, jeopardizing the wound healing process (Haubner et al., 2012). Furthermore, the re-epithelialization, formation of granulated tissue, and neovascularization that occur during the subsequent proliferative phase may also be comprised by continued cytokine overexpression (Guo & DiPietro, 2010, Haubner et al., 2012). Exercise has the potential to mitigate the post-surgical morbidities following preoperative radiation therapy because of its ability to dampen the expression of the proinflammatory factors and accelerate the wound healing process. Albeit in an aged animal model, Keylock et al. (2018) determined that moderate intensity aerobic exercise significantly decreased expression of inflammatory cytokines (TNF-α, KC, and MCP-1) and facilitated the wound healing process. The results showed that mice assigned to the exercise group healed to 80% of the original wound size 51% faster than control group counterparts. Research involving the effects of exercise on wound healing is not limited to just animal models. Emery et al. (2005) investigated the effects of moderate intensity aerobic exercise on wound healing rate in older adults. Participants who completed a 3-month aerobic exercise regimen healed a standard wound significantly faster (29.2 days vs. 38.9 days; $p = .012$) than those in the nonexercised group. The researchers suggest that the underlying mechanism may involve exercise induced changes in immunologic function.

Implementation of exercise into a multimodal treatment plan for STS of the extremities goes beyond accelerated wound healing. In fact, exercise may be beneficial toward normalizing tumor physiology and radiosensitizing the tumor itself. In healthy tissue, cells are in close proximity to blood vessels, allowing for easy exchange of oxygen and nutrients. This feature is compromised in solid tumors because the rapid proliferation of tumor cells outpaces sustained angiogenesis. As a result, there is reduced vascular density and a greater distance between cells and vasculature (Minchinton & Tannock, 2006). These deviations create temporal and spatial heterogeneity in tumor blood flow and alter metabolism (Jain, 1998). Previous studies have investigated the role of hyperbaric oxygen therapy in improving the effectiveness of radiotherapy. The inclusion of hyperbaric oxygen therapy in multimodal treatment plans centers around increasing the oxygen load of the tumor. Thus, the increased oxygen load facilitates the indirect effect of radiation therapy, the production of oxygen free radicals (Baskar et al., 2012, Mayer et al., 2005). Exercise has the capability of improving systemic oxygenation like hyperbaric oxygen therapy. McCullough et al. (2013) investigated the effect of exercise training on tumor hypoxia in a rodent orthotopic prostate cancer model. Following a 5-7 weeks of low-to-moderate intensity treadmill exercise, the exercise trained mice exhibited tumor microvascular pO_2 more than double than that of their sedentary counterparts (12.2 mmHg vs. 6.0 mmHg; $p = .05$). Additionally, exercise significantly reduced resting tumor hypoxia (39% vs 4%; $p \leq .05$) without changes in vascular density, suggesting that intravascular hemodynamics may have contributed to the improved oxygenation status. Separate preclinical work by Jones et al. (2010) evaluated the effect of moderate and long-term wheel running on tumor physiology in an animal model of human breast cancer. Mice in the wheel running group exhibited a significantly higher number of perfused vessels (p = .03) and a greater percentage of perfusion in the total tumor area (p = .034) versus the sedentary control group.

USE OF NIRS

Assessing tissue oxygenation, local oxygen uptake, oxidative metabolism, and blood flow in skeletal muscle both at rest and during exercise can be performing non-invasively via NIRS (Jones et al. 2016). NIRS is based on the relative transparency of tissue in the near-infrared region of the spectrum and the spectral properties of chromophores (van Beekvelt, Colier, et al., 2001). Near-infrared light can penetrate several millimeters deep into biological tissue, where it is then absorbed by chromophores like hemoglobin, myoglobin, and cytochrome oxidase (Barstow, 2019). Oxygenation status of the chromophores dictates the absorbance of near-infrared light, allowing for differentiation between oxygenated and deoxygenated species (Jones et al., 2016). Hemoglobin and myoglobin are considered the primary sources of NIRS signals, but due to similarities in spectral characteristics the signals cannot be distinguished (Barstow, 2019). Near-infrared light that passes through blood vessels greater than 1 mm in diameter is almost completely absorbed, making NIRS an ideal tool for assessing localized skeletal muscle circulation. Using spatial resolved spectroscopy (SRS), changes in hemoglobin concentrations can be determined though comparison with an initial baseline value. Overall, the changes in the concentration of total[Hb+Mb] reflect changes in blood volume (Barstow, 2019).

Studies involving NIRS have been performed in and around exercise on various body parts in healthy populations to showcase the exercise-induced increases in blood flow and oxygen uptake (Jones et al., 2016). van Beekvelt, Colier, et al. (2001) measured local oxygen uptake and blood flow in the forearm of healthy individuals and determined that muscle oxygen uptake increased fivefold in the flexor digitorum superficialis and 1.6 times in the brachioradialis during isometric handgrip exercise. Additionally, blood flow also increased 1.4 times in the same musculature. Southern et al. (2014) assessed the reproducibility of NIRS outcomes in the medial gastrocnemius after plantar flexion exercise using multiple modalities (ergometer and resistance band) and determined that measurements of oxygen consumption were reproducible with either modality. Furthermore, Lucero et al. (2018) measured skeletal muscle blood flow and oxygen consumption in the vastus lateralis of healthy adults during rhythmic isotonic knee extensions six submaximal intensities (5, 10, 15, 20, 25, and 30% of MVC). It was determined that skeletal muscle blood flow and oxygen consumption increased with intensity and those both measures were highly reliable at the various intensities.

NIRS measurements have also been taken in several clinical populations. De Blasi et al. (1997) measured oxygen consumption in the brachioradialis of intensive care unit patients, who suffered from a variety of ailments, including acute respiratory distress, cardiocirculatory failure, and coma due to head trauma. Measurement of muscle oxygen consumption using occlusion techniques was considered safe and reliable in the population. Additionally, Malagoni et al. (2010) evaluated the feasibility of NIRS in a clinical setting for patients with peripheral artery disease. Resting muscle oxygen consumption was measured in the gastrocnemius using both venous and arterial occlusions. Values obtained using the venous occlusion technique were significantly higher than those collected using arterial occlusions (0.044 mL/100g per min vs. 0.035 mL/100g per min; $p < .0001$). Overall, the use of NIRS in cancer populations is limited and mainly focuses on surveying the compositional differences between cancerous tissue and healthy tissue. Tromberg et al. (2005) used NIR light to contrast the composition of tumor and normal tissue. Significant differences existed between the two regions for deoxy-hemoglobin ($p = .005$) and oxy-hemoglobin (p = 0.002). The use of NIRS to measure exercise-induced tissue oxygenation changes has not been investigated in a cancer population (Kondepat, Heise & Backhaus, 2008).

SUMMARY

Soft tissue sarcomas are a rare and often fatal type of cancer (Clark et al., 2005). For STS that arise in the extremities, a combined treatment plan of surgical resection and radiation therapy is the standard of care (Rosenberg et al., 1982). The use of preoperative radiation is advantageous in that patients receive a lower total dose, which leads to better functional outcomes. The downside of preoperative radiation is that patients experience a higher rate of wound complications (Strander et al., 2003). Previous research in animal models showed that exercise may help improve radiation treatment efficacy by normalizing the hypoxic tumor microenvironment (McCullough et al., 2013) while also reducing the pro-inflammatory signals that slow the wound healing process (Keylock et al., 2018). To our knowledge, the use of acute bouts of exercise immediately prior to radiotherapy with the goal of augmenting radiation treatment efficacy and enhancing the wound healing process has not been examined in patients with STS. Therefore, this preliminary study serves as the initial step in potentially optimizing the standard treatment of STS in humans.

CHAPTER 3

METHODS

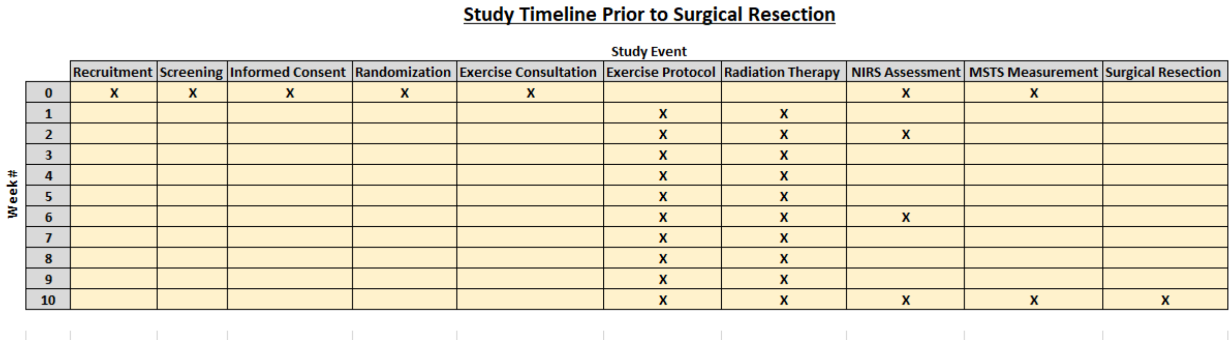
SUBJECTS

This preliminary study attempted to recruit twenty-four patients (ages 18 and above) from the Duke Cancer Institute. Only patients with a histologically confirmed diagnosis of STS would be enrolled in the study. Patients with first time or recurrent presentations from all disease stages, tumor grades, and histological subtypes were eligible. Inclusion criteria included: location of the STS in the upper or lower extremity, a treatment plan consisting of neoadjuvant radiation therapy followed by surgical resection, expected primary wound closure at the time of surgery, no prior history of vascular procedures that decrease perfusion in the affected limb, and no history of radiation therapy to the tumor and/or surgical area. Exclusion criteria consisted of: patient outside the target age range, a treatment plan that did not include neoadjuvant radiation therapy and surgical resection, location of the STS other than the upper or lower extremity, a history of radiation therapy to the tumor and/or surgical area, a high dose steroid therapy (>5mg prednisone) in the last 30 days, a plan for post-operative radiation therapy, underlying cardiovascular disease, prior surgery (excluding biopsies) at the site of disease, ulcerative or fungating tumors at presentation, vascular invasion that results in decreased perfusion, vascular disease that compromises blood flow, actively uncontrolled diabetes mellitus, active deep vein thrombosis in the affected extremity, and pregnant females. The procedures used in this protocol were approved by the Institutional Review Boards at Duke University and the University of North Carolina

(UNC). Due to extraneous circumstances, this preliminary study included only two patients. These two patients gave informed consent and complied with all the study protocol.

STUDY DESIGN

This preliminary study was originally designed to be a randomized controlled trial with patients evenly distributed between the exercise (EX) and control (CNT) groups but shifted toward a feasibility evaluation. Patients were planned to be stratified such that tumors less than 10 cm and greater than 10 cm in size were to be split evenly between the groups. Initially, all patients enrolled in the study were to undergo 10 weeks of preoperative radiation therapy per standard care. The dosing and treatment of the radiation therapy regimen were to be determined by a radiation oncologist at the Duke Cancer Institute. Patients randomized into the EX group would perform exercise training immediately prior to bouts of radiation therapy. Following completion of the radiation therapy regimen, all participants would undergo surgical resection of the STS by a surgical oncologist at the Duke Cancer Institute. All patients were to have standard of care follow-up visits with the surgical oncologist following surgical resection at 3-, 6-, 12-, and 24-weeks post resection. The study was designed to be partially blinded. The surgical oncologist, study coordinator, and personnel involved in the exercise program were not blinded. However, the wound surveyor was to be blinded to the treatment groups. Tables 1 and 2 depict the study timeline prior to and following surgical resection, respectively.

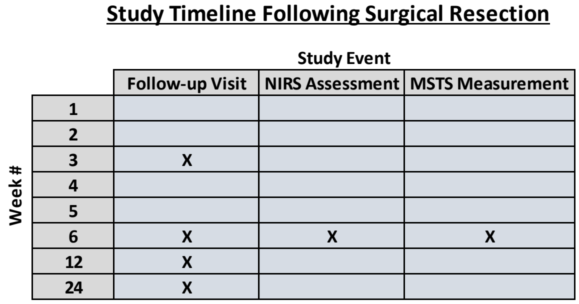


Study Timeline Prior to Surgical Resection

Study Event

Week #	Recruitment	Screening	Informed Consent	Randomization	Exercise Consultation	Exercise Protocol	Radiation Therapy	NIRS Assessment	MSTS Measurement	Surgical Resection
0	x	x	x	x	x			x	x	
1						x	x			
2						x	x	x		
3						x	x			
4						x	x			
5						x	x			
6						x	x	x		
7						x	x			
8						x	x			
9						x	x			
10						x	x	x	x	x

Table 1. Study Timeline Prior to Surgical Resection of the Soft Tissue Sarcoma.



Study Timeline Following Surgical Resection

Study Event

Week #	Follow-up Visit	NIRS Assessment	MSTS Measurement
1			
2			
3	X		
4			
5			
6	X	X	X
12	X		
24	X		

Table 2. Study Timeline Following Surgical Resection of the Soft Tissue Sarcoma.

GENERAL PROCEDURES

All patients with a diagnosis of STS in the extremities with treatment plans for neoadjuvant radiation therapy and surgical resection at the Duke Cancer Institute would be reviewed for study eligibility. The study was introduced to eligible patients during a clinic visit with the surgical oncologist or radiation oncologist. If interested, patients were consented by the study coordinator. Patients were able to decide to participate in the study and give consent up until the start of radiation treatment. Upon enrollment, patients that were randomized into the EX group had a phone consultation with a member of the UNC Exercise Oncology Laboratory regarding the exercise regimen. All NIRS-related assessments and exercise bouts were conducted by a member of the UNC Exercise Oncology Laboratory immediately prior to radiation therapy in the Radiation

Oncology unit at the Duke Cancer Institute. Pulse oximetry and heart rate were monitored at the start of each visit and immediately following the exercise protocol.

At each follow up visit after resection, the blinded wound surveyor was to inspect the patient's affected limb and determine the presence or absence of wound complications. Complications were defined as delayed wound healing (wound dehiscence, tissue necrosis, eschar formation, seroma formation), the need for local wound management (wound packing, negative pressure therapy, or advanced dressings), the presence of infection (at the surgical site or periprosthetic), or a secondary procedure (irrigation, debridement, drainage, secondary closures, or aspiration).

Measurements of extremity function were conducted by a trained member of the study staff using the Musculoskeletal Tumor Society Rating Scale (MSTS). The MSTS is a standardized system used to assess functionality and physical disability in patients with STS of the extremities. This measure of impairment evaluates the categories of pain, range of motion, strength, joint stability, joint deformity, overall acceptance of the surgery, and a global rating of function. Each category of the MSTS is scored from zero to five and summed. Overall scores for the MSTS range from zero to thirty-five with higher scores indicative of higher functionality (Davis et al., 2005). This assessment was to be performed at baseline, immediately prior to surgical resection, and at the follow up visit 6 weeks post-resection.

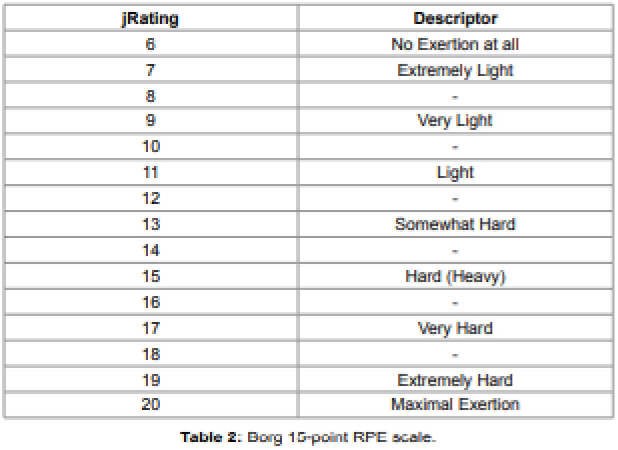
The percentage of tumor necrosis at the time of surgical resection was to be estimated microscopically by a pathologist at the Duke Cancer Institute. This standard, histopathological assessment was to be performed to determine the efficacy of radiotherapy.

EXERCISE PROTOCOL

Patients randomized into the EX group underwent a supervised exercise regimen in conjunction with radiation therapy. All exercise sessions occurred in the Radiation Oncology unit at the Duke Cancer Institute under the supervision of a member of the UNC Exercise Oncology Laboratory. EX patients performed 3 exercise sessions per week immediately prior to sessions of radiation therapy. The specific exercises performed during the sessions were implemented to promote contractions in the musculature of the affected limb. Patients used commercially available resistance bands (Thera-Band, The Hygienic Corp., Akron, Ohio, USA), adjustable ankle weights (Gymenist, Woodridge, New Jersey, USA), or an adjustable dumbbell (CAP Dumbbell) for added resistance.

In terms of exercise intensity, Lucero and colleagues (2018) reported that perfusion in the vastus lateralis when measured by NIRS was significantly greater than baseline following 3 minutes of rhythmic isotonic knee extensions at 15-30% of maximal voluntary contraction (MVC). Because one repetition maximum (1RM) assessments are not feasible within a clinical setting (Eston & Evans, 2009), RPE was used instead. Specifically, a modified 15-point Borg scale was used to conceptualize intensity (Figure 2) (Morishita et al., 2013). Several studies have investigated the conversion of 30% 1RM to measurements on the 15-point modified Borg scale. Lagally et al. (2002) determined that 15 repetitions at 30% MVC for triceps press and biceps curl corresponded to RPEs of 10.56 ± 1.85 and 10.00 ± 1.39 on the 15-point Borg scale, respectively. Additionally, Tiggemann et al. (2010) determined that 12 repetitions at a resistance that elicited a RPE of 11 on a 15-point scale corresponded to 34.59 ± 6.54 and 33.56 ± 7.39 % 1RM for bench press and leg press in sedentary adults.

In order to determine an appropriate resistance for the exercise bout, participants performed a “discovery set” of 15 repetitions of the prescribed exercise at a given resistance. Participants were then asked to evaluate the intensity of the discovery set using the 15-point modified Borg RPE scale. If the participant did not report the target RPE of 11, then the resistance was adjusted at the discretion of the interventionalist. Participants performed up to 3 discovery sets with a 2-minute rest interval following each set. Once a resistance was identified that produced the target RPE on the 15-point modified Borg RPE scale, the participant performed a 3-minute bout of continuous repetitions with this resistance. All repetitions were 4 seconds long and incorporated a full range of motion. To ensure the proper cadence of each repetition, interventionalists implemented a metronome at 60 beats/minute during the discovery set(s) and the 3-minute bout.



jRating	Descriptor
6	No Exertion at all
7	Extremely Light
8	-
9	Very Light
10	-
11	Light
12	-
13	Somewhat Hard
14	-
15	Hard (Heavy)
16	-
17	Very Hard
18	-
19	Extremely Hard
20	Maximal Exertion

Table 2: Borg 15-point RPE scale.

Figure 1. The modified 15-point Borg RPE scale (Morishita et al., 2013).

NIRS PROTOCOL

All patients underwent periodic NIRS measurements throughout the study. Measurements were to occur at baseline (prior to initiating radiation therapy), week 2, week 6, week 10, and 6 weeks post-resection. A member of the UNC Exercise Oncology Laboratory performed all NIRS measurements. Upon arrival at the Radiation Oncology Unit at the Duke Cancer Institute, patients were seated such that the affected limb was in a horizontal orientation (Barstow, 2019). The NIRS probe was placed longitudinally over the belly of the target muscle in the affected extremity at the point of greatest circumference (Southern et al., 2014). To minimize variability in NIRS probe placement, the same investigator applied the probe at all assessment visits (Craig et al., 2017). Additionally, measurements were taken in relation to bony landmarks to ensure consistent placement. The NIRS probe was wrapped in a transparent vinyl sheet and fashioned to the patient's skin using a double-sided adhesive (Barstow, 2019). A dark cloth covered the probe to prevent infiltration of ambient light. To account for scattering of near-infrared light in the underlying tissue, a DPF of 4.0 was used (Cross & Sabapathy, 2017, van Beekvelt, Borguis, et al., 2001, van Beekvelt, Colier, et al., 2001). Data was collected from channel #3 and sampled at 10 Hz (Oxysoft; Artinis Medical Systems B.V., Elst, The Netherlands) (Lucero et al., 2018). Following placement of the NIRS device on the affected limb, the participant rested for 10 minutes and then completed all components of the exercise intervention. After completion of the 3 minutes of rhythmic exercise, the affected limb was returned to a horizontal orientation for a rest period of 2 minutes (Barstow, 2019).

NIRS MEASUREMENTS

Using SRS, changes in the concentration of total hemoglobin (total[Hb+Mb]) in µM were measured using a PortaLite continuous wave near-infrared spectrometer (Artinis Medical Systems B.V., Elst, The Netherlands). This NIRS system generates near-infrared light at two wavelengths (760 and 850 nm) from three optodes located 30, 35, and 40 mm away from a single receiver. To minimize the influence of subcutaneous adipose tissue, measurements from the deepest channel were utilized. Baseline levels of total[Hb+Mb] were calculated by averaging all measurements during the final minute of the 10 minute rest period. Exercise total[Hb+Mb] and Recovery total[Hb+Mb] were determined by averaging the measurements across each period. Determining the absolute change in the concentration of total[Hb+Mb] during the 3 minutes of rhythmic exercise and the subsequent 2 minutes of rest was done by comparing measurements to baseline total[Hb+Mb] levels. The average peak and trough total[Hb+Mb] were also determined by averaging the peak and trough measurements in the final 15 seconds of each exercising minute. Furthermore, the average peak and trough total[Hb+Mb] were used to determine the average peak to trough difference in total[Hb+Mb] during the final 15 seconds of each exercising minute.

STATISTICAL ANALYSIS

Due to a small sample size (n=2), no statistical analyses were performed. Only demographic data are presented to inform the reader on the preliminary responses to the study intervention in the two enrolled patients. For the remainder of this document, the two patients will be treated as case studies. The initial hypotheses statements are listed below.

- H1: Three one-way repeated measures ANOVA will be conducted to determine if there are significant differences between the mean changes in muscle perfusion, blood flow, and muscle oxygen uptake over time. The independent variable is time. The dependent variables are muscle perfusion, blood flow, and muscle oxygen uptake.
- H2a: A chi-squared test of association will be conducted to determine if there is a relationship between two categorical variables: group and presence of wound complications.
- H2b: A two-way mixed model ANOVA will be used to investigate the main effects of group and time on MSTS scores. The independent variables are group (between factor) and time (within factor). The dependent variable is MSTS score.

- H3: An independent samples t-test will be conducted to compare mean tumor necrosis percentage between the EX and CNT groups. The independent variable is group. The dependent variable is tumor necrosis percentage.

CHAPTER 4

RESULTS

Case Study #1: A 68-year-old African American female (Height: 157.5cm; Weight: 68.3kg) with confirmed diagnosis of stage II myxoid sarcoma of the right hindfoot being treated with 5 weeks of preoperative radiation. Prior to each radiation treatment Patient #1 completed "Gas Pedals", a single joint exercise involving plantar flexion, on the right lower limb. At baseline, Patient #1 received an MSTS score of 28 out of 35. PRE and POST exercise pulse oximetry and heart rate measurements for each training session are presented in Table 3. Table 4 displays total[Hb+Mb] concentrations and absolute differences from baseline levels at 3 separate timepoints for Patient #1. Absolute change in total[Hb+Mb] from baseline during the 3 minutes of rhythmic exercise and the 2 minutes of recovery are shown in Figure 2. Average total[Hb+Mb] in the final 15 seconds of each minute are shown in Figure 3. The average peak to trough differences in total[Hb+Mb] during the final 15 seconds of each exercising minute are shown in Table 5.

	SpO2		*HR*	
Session	**PRE**	**POST**	**PRE**	**POST**
1	97	96	75	80
2	96	96	76	74
3	--	--	--	--
4	--	--	--	--
5	98	96	74	74
6	96	95	88	87
7	97	96	86	85
8	97	97	70	72
9	97	96	90	90
10	98	96	88	83
11	96	96	83	79
12	97	96	97	94
13	96	96	84	84
14	97	96	85	81
15	97	95	90	82
Mean	97	96	84	82
SD	0.7	0.5	7.7	6.4

Table 3. Pulse Oximetry and Heart Rate Measurements for Patient #1.

(in µM)	**Baseline**	**Week 2**	**Week 5**
Baseline total[Hb+Mb]	1.018	-3.500	1.645
Exercise total[Hb+Mb]	1.389	97.577	-3.256
Recovery total[Hb+Mb]	1.014	1.596	-2.860
Baseline to Exercise Δ	0.371	101.077	-4.901
Baseline to Recovery Δ	-0.004	5.096	-4.505

Table 4. total[Hb+Mb] Measurements and Absolute Differences from Baseline During Exercise and Recovery for Patient #1.

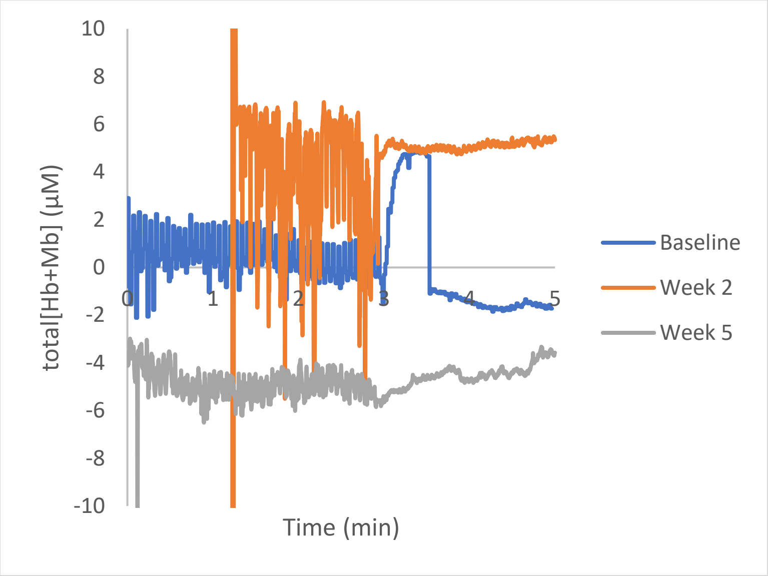


Figure 2. Normalized total[Hb+Mb] Measurements During Exercise and Recovery for Patient #1.

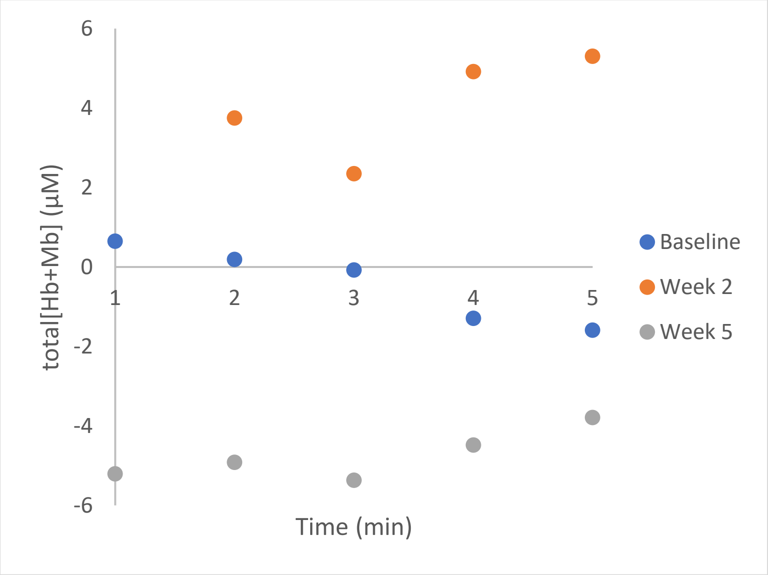


Figure 3. Average total[Hb+Mb] in the Final 15 Seconds of Each Minute for Patient #1.

(in µM)	**Baseline**	**Week 2**	**Week 5**
Minute 1	2.057	--	1.371
Minute 2	1.945	7.060	1.107
Minute 3	2.063	6.556	0.902

Table 5. Average Peak to Trough Differences in total[Hb+Mb] During the Final 15 Seconds of each minute for Patient #1.

Data presented on Patient #1 show that the current exercise prescription protocol is able to elicit changes in total[Hb+Mb]. Albeit skin contact issues were present during the Week 2 measurement, total[Hb+Mb] increased during the 2 minute recovery period compared to exercise at Week 2 and Week 5, suggesting an increase in blood volume in the limb of interest. Additionally, the prescribed exercise produced relatively stable peak to trough differences in the final 15 seconds across each exercising minute, indicating consistency in the muscular contractions.

Case Study #2: A 75-year-old white female (Height: 170.2cm; Weight: 78.3kg) with confirmed diagnosis of high-grade malignant cell neoplasm consistent with metastatic leiomyosarcoma in the right lateral calf being treated with two weeks of preoperative radiation. Prior to each radiation treatment Patient #2 completed "Gas Pedals", a single joint exercise involving plantar flexion, the right lower limb. At baseline, Patient #2 received an MSTS score of 27 out of 35. PRE and POST exercise pulse oximetry and heart rate measurements for each training session are presented in Table 6. Table 7 displays total[Hb+Mb] concentrations and absolute differences from baseline levels at 3 separate timepoints for Patient #2. Absolute change from baseline during the 3 minutes of rhythmic exercise and the 2 minutes of recovery are shown in Figure 4. Average total[Hb+Mb] in the final 15 seconds of each minute are shown in Figure 5. The average peak to trough difference in total[Hb+Mb] during the final 15 seconds of each exercising minute are shown in Table 8.

	SpO2		*HR*	
Session	**PRE**	**POST**	**PRE**	**POST**
1	96	94	92	94
2	96	91	96	91
3	97	91	94	91
4	96	94	101	94
5	96	91	96	91
6	97	91	97	91
Mean	96	92	96	92
SD	0.6	1.7	3.0	1.5

Table 6. Pulse Oximetry and Heart Rate Measurements for Patient #2.

(in µM)	**Baseline**	**Midpoint**	**Week 2**
Baseline total[Hb+Mb]	-1.561	-1.522	1.168
Exercise total[Hb+Mb]	-5.458	-0.330	-1.356
Recovery total[Hb+Mb]	-2.958	0.200	-0.138
Baseline to Exercise Δ	-3.897	1.193	-2.524
Baseline to Recovery Δ	-1.397	1.722	-1.306

Table 7. total[Hb+Mb] Measurements and Absolute Differences from Baseline During Exercise and Recovery for Patient #2.

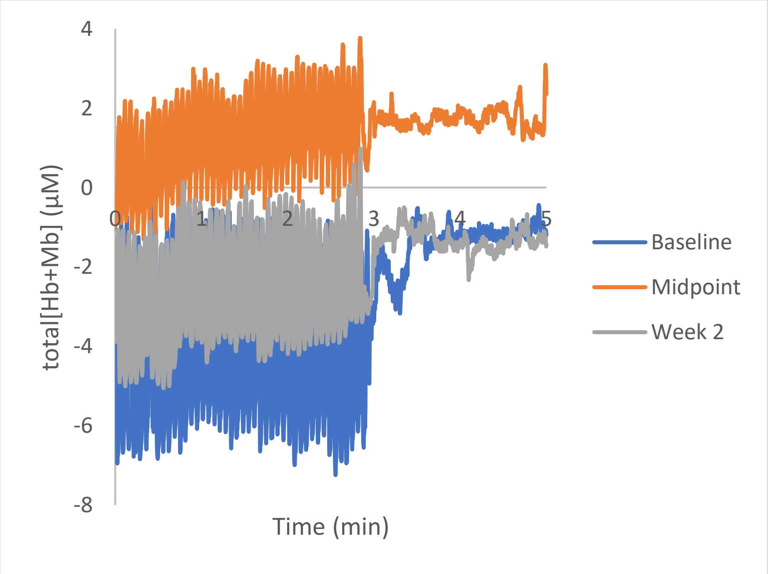


Figure 4. Normalized total[Hb+Mb] Measurements During Exercise and Recovery for Patient #2.

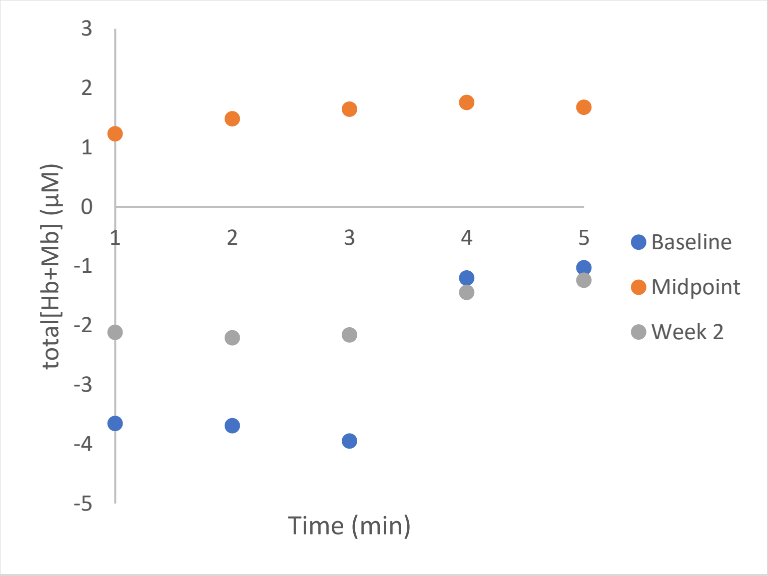


Figure 5. Average total[Hb+Mb] in the Final 15 Seconds of Each Minute for Patient #2.

(in µM)	**Baseline**	**Midpoint**	**Week 2**
Minute 1	5.547	3.072	4.251
Minute 2	5.419	2.997	4.345
Minute 3	5.409	3.262	4.073

Table 8. Average Peak to Trough Differences in total[Hb+Mb] During the Final 15 Seconds of each minute for Patient #2.

Data presented on Patient #2 show again that the current exercise prescription protocol is able to elicit changes in total[Hb+Mb], an indicator of blood volume. Across all three NIRS measurements for Patient #2, average total[Hb+Mb] in the final 15 seconds of each minute was greater during recovery (minutes 4 and 5) than exercise (minutes 1, 2, and 3). However, total[Hb+Mb] during recovery only exceeded resting levels at the Midpoint visit. Similar to Patient #1, the prescribed exercise produced relatively stable peak to trough differences in the final 15 seconds across each exercising minute, indicating consistency in the muscular contractions.

CHAPTER 5

DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

DISCUSSION

Due to extraneous circumstances, the purpose of the present study shifted from those previously mentioned to presenting available data on the primary outcomes and exploring the feasibility of the existing protocol. Because both patients have not yet undergone surgical resection of their STS, data related to wound complication rate and tumor necrosis percentage are unavailable. Periodic NIRS measurements and baseline MSTS scores were collected during the exercise intervention/preoperative radiation phase. Discussing the progress and current protocol is valuable to stakeholder as the study moves forward.

Feasibility studies are often used to determine whether an intervention warrants additional testing and to judge the sustainability of the current protocol. Specifically, feasibility studies determine if the current methods and protocols need modifications and how those modifications can be put into place to create a more effective intervention. Feasibility studies revolve around 8 areas of focus: acceptability, demand, implementation, practicality, adaptation, integration, expansion, and limited-efficacy testing (Bowen et al., 2009).

Acceptability addresses how the target population and interventionalists react to a protocol (Bowen et al., 2009). Although measurements for two of the four primary outcomes (presence of wound complications and tumor necrosis percentage) were unavailable due to the progression of the enrolled participants, acceptability was evaluated using other metrics. For instance, both patients attended all scheduled exercise sessions and radiation appointments. Additionally, both patients completed 3 NIRS measurements and a baseline MSTS measurement. Furthermore, the patients reported that the exercise intervention broke the monotony of daily radiation treatment and did not cause additional pain or discomfort above baseline levels.

Demand is another common area of focus for feasibility studies that assesses the likelihood that a program will be utilized within an organization (Bowen et al., 2009). As mentioned previously, STS are rare, representing just 1% of all cancer diagnoses in the United States (Siegel, Miller & Jemal, 2019). As a result, the potential pool of participants is small, especially considering a single site operation. The participant pool is further condensed through exclusion of patients with STS in the head, neck, and torso. These patients, which account for 40% of all STS cases (Clark et al., 2005), are unable to stimulate affected musculature via single joint resistance exercises. Since the present study went live in April, there were a total of 10 positive screens at the Duke Cancer Institute. Ultimately, 2 patients enrolled. Thus, there appears to be some demand for the study as the low cost, high reward nature is attractive for patients with STS in the extremities undergoing radiation treatment; however, competition exists between the present study and other studies at the Duke Cancer Institute with other clinical studies taking precedence.

Implementation, or the extent to which a new protocol can be successfully delivered (Bowen et al., 2009), was also evaluated in the present study. Overall, the bulk of study-related activities were successful; however, several issues occurred while performing NIRS measurements that required replication of the test at the subsequent patient visit. Specifically, a data management error at baseline for Patient #1 and a power unit issue at the midpoint for Patient #2 caused the retests. Contact issues between the NIRS probe and the patient’s skin also surfaced at Patient #1’s

Week 2 visit. The non-laboratory setting complicated the implementation of the current protocol and was further compounded by time considerations. Specifically, the designated study space was a spare waiting area and lacked amenities typically found in a physiology lab such as furniture to maintain consistent patient positioning. Additionally, patients had designated radiation appointment times; therefore, any delays in starting a study visit or during the visit itself had the potential to make patients tardy for their appointments. Nonetheless, the exercise intervention was successfully completed across all visits without complications and patients proceeded to scheduled radiotherapy appointments in a timely manner.

The extent to which a protocol can be executed as intended on the target population with existing resources is called practicality and it's another key area of focus for feasibility studies (Bowen et al., 2009). Although we did not meet the target sample size, we were able to recruit and enroll 2 patients with STS in the lower extremity. Both patients completed their prescribed radiation regimen and the exercise intervention with the equipment on hand. The progression through the treatment process so far has allowed us to collect NIRS measurements at multiple timepoints and a baseline MSTS measurement as intended for both patients. However, the two other primary outcomes, wound complication rate and tumor necrosis percentage, were incapable of being measured as intended because neither patient has undergone surgical resection of the STS.

Adaption is an essential area of focus for feasibility studies. This component evaluates the effectiveness of a protocol when it is subjected to a new format or a different patient population (Bowen et al., 2009). Notably, the high degree of adaptation within the current design of the protocol was needed to address the heterogeneous nature of STS. One of the inclusion criteria for the study was diagnosis of an STS in the upper or lower extremity. The location of the tumor and the affected musculature can vary tremendously within that criterion; therefore, we needed to have exercise equipment available to stimulate a wide variety of musculature. Additionally, because of the clinical setting, all equipment needed to be portable. This further reduced the exercise equipment options in the present study. Although the 2 patients who enrolled in the study both performed plantar flexion of the foot, we have the equipment necessary to stimulate the musculature of the upper and lower extremities to some degree. The use of the RPE scale to address exercise intensity added another layer of adaption within the protocol. Fatigue is a common side effect reported by up to 80% of cancer patients undergoing radiation (Jereczek-Fossa et al., 2002). To address this potential fluctuation, patients provided subjective feedback that informed the interventionalists on how to adjust intensity within and across exercise sessions.

Yet another area of focus for feasibility studies is integration. This evaluates the extent to which a program can fit within an existing system (Bowen et al., 2009). The current process of moving patients through treatments within the Radiation Oncology Unit at the Duke Cancer Institute is established and streamlined. Patients are asked to arrive a half hour prior to their radiation appointment. After checking in, patients wait in the general waiting area before being called into to the radiation suite. The intervention for the present study occurs in that half hour after the patient checks in and before they are taken back to the radiation suite. The current protocol is designed to take between 15 and 20 minutes depending upon how many discovery sets are needed to find a resistance that produces a RPE of 11 from a set of 15 repetitions. Visits that include a NIRS measurement last roughly 20 minutes longer than exercise sessions. As a result, patients were asked to arrive even earlier than what is suggested by the Radiation Oncology Unit. Notably, the designated study space is separate from the general waiting area; therefore, communication is essential between the interventionalists and the Radiation Oncology staff to inform each other on the location of the patient. The current arrangement appears to be sustainable if communication persists between the two parties. Accessibility was an issue for UNC interventionalists at the Duke Cancer Institute. Under current policies, the study equipment needed to conduct the exercise intervention and NIRS measurements and the designated study space are restricted without an escort from the Duke study coordinator. Communication between the Duke study coordinator and UNC interventionalists was vital to incorporating the present study into the established treatment process.

Expansion is the seventh area of focus for feasibility studies. Collectively, this evaluates how a program can grow within an organization (Bowen et al., 2009). Although just two patients enrolled, the present study is in line with the goals of the Duke Cancer Institute and can fit within the boundaries of the current operation. If the present study turns out to be beneficial, then the protocol can be applied to other patients with similar forms of cancer. Notably, melanoma of the soft parts shares several characteristics with STS, including primary location in deep soft tissue, lack of cutaneous invasion, and preference for lymph node and pulmonary metastasis (Mavrogenis et al., 2013). Additionally, expanding the present study to additional sites could unlock a larger pool of potential participants.

The final area of focus for feasibility studies is limited-efficacy testing. This component evaluates whether the protocol shows successful results in the target population (Bowen et al., 2009). Unfortunately, the two patients who enrolled in the study have not progressed through all timepoints in the current protocol; therefore, our results are limited. Although, we were able to complete NIRS measurements at multiple timepoints and a baseline MSTS measurement for both patients, in the absence of statistical analysis, we cannot determine whether the exercise protocol had significant effects on the key variables.

CONCLUSION

In conclusion, the present study was the first to question the role of single joint resistance exercise in the treatment process of STS in the extremities. While the initial purposes were to determine the effects of single joint exercise on blood flow, functionality, wound complication rate, and tumor necrosis percentage is patients with STS of the extremities receiving preoperative radiation, extraneous circumstances shifted the project toward an analysis of feasibility. As a result, the study was evaluated on 8 areas of focus: acceptability, demand, implementation, practicality, adaptation, integration, expansion, and limited-efficacy testing (Bowen et al., 2009). Ultimately, the current protocol appeared to be feasible in STS patients with tumors in the lower extremity. We were able to advance 2 patients through the exercise intervention and radiation treatments and inform stakeholders on the relevance and sustainability of the current protocol.

RECOMMENDATIONS FOR FUTURE RESEARCH

Future research should continue to expand the feasibility discussion and address the efficacy and effectiveness of the current protocol. Despite the heterogeneity of STS, both patients who enrolled in the present study had tumors below the knee in the lower limb. As a result, the efficacy and effectiveness of the protocol has yet to be evaluated in patients with tumors above the knee or in the upper limb. Subsequent trials should also attempt to expand the participant pool through inclusion of other similar cancers and additional sites of operation. This adjustment could help to combat enrollment issues that affected the present study. Furthermore, subsequent studies in STS patients utilizing NIRS should attempt to incorporate physiological inventions like venous and arterial occlusions to investigate changes in oxygen uptake and blood flow. Although, this could potentially add to the overall subject burden, it would address a gap in the research.

REFERENCES

American Joint Committee on Cancer. (1997). *AJCC Cancer Staging Manual* (I. D. Fleming, J. S. Cooper, D. E. Henson, R. V. P. Hutter, B. J. Kennedy, G. P. Murphy, B. O'Sullivan, L. H. Sobin, & J. W. Yarbro (eds.); 5th ed.). Lippincott-Raven Publishers.

Barstow, T. J. (2019). Understanding near infrared spectroscopy and its application to skeletal muscle research. *REVIEW Cores of Reproducibility in Physiology J Appl Physiol*, *126*, 1360–1376.

Baskar, R., Lee, K. A., Yeo, R., & Yeoh, K. W. (2012). Cancer and radiation therapy: Current advances and future directions. *International Journal of Medical Sciences*, *9*(3), 193–199.

Bowen, D. J., Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D., … Fernandez, M. (2009). How We Design Feasibility Studies. American Journal of Preventive Medicine, 36(5), 452–457.

Cannon, C. P., Ballo, M. T., Zagars, G. K., Mirza, A. N., Lin, P. P., Lewis, V. O., Yasko, A. W., Benjamin, R. S., & Pisters, P. W. T. (2006). Complications of combined modality treatment of primary lower extremity soft-tissue sarcomas. *Cancer*, *107*(10), 2455–2461.

Cheng, E. Y., Dusenbery, K. E., Winters, M. R., & Thompson, R. C. (1996). Soft Tissue Sarcomas: Preoperative Versus Postoperative Radiotherapy. *Journal of Surgical Oncology, 61*, 90–99.

Clark, M. A., Fisher, C., Path, F. R. C., Judson, I., & Thomas, J. M. (2005). Soft-Tissue Sarcomas in Adults. *New England Journal of Medicine, 353*, 701–711.

Craig, J. C., Broxterman, R. M., Wilcox, S. L., Chen, C., & Barstow, T. J. (2017). Effect of adipose tissue thickness, muscle site, and sex on near-infrared spectroscopy derived total-[hemoglobin myoglobin]. *J Appl Physiol*, *123*, 1571–1578.

Cross, T. J., & Sabapathy, S. (2017). The impact of venous occlusion per se on forearm muscle blood flow: implications for the near-infrared spectroscopy venous occlusion technique. *Clinical Physiology and Functional Imaging, 37*(3), 293–298.

Davis, A. M., O'Sullivan, B., Turcotte, R., Bell, R., Catton, C., Chabot, P., Wunder, J., Hammond, A., Benk, V., Kandel, R., Goddard, K., Freeman, C., Sadura, A., Zee, B., Day, A., Tu, D., &

Pater, J. (2005). Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiotherapy and Oncology*, *75*(1), 48–53.

De Blasi, R. A., Almenräder, N., Aurisicchio, P., & Ferrari, M. (1997). Comparison of two methods of measuring forearm oxygen consumption (v˙o 2) by near infrared spectroscopy. *Journal of Biomedical Optics*, *2*(2), 171–175.

Emery, C. F., Kiecolt-Glaser, J. K., Glaser, R., Malarkey, W. B., & Frid, D. J. (2005). Exercise Accelerates Wound Healing Among Healthy Older Adults: A Preliminary Investigation. *Journal of Gerontology: MEDICAL SCIENCES*, *60A*(11), 1432–1436.

Enneking, W. F., Spanier, S. S., & Malawer, M. M. (1981). The Effect of the Anatomic Setting on the Results of Surgical Procedures for Soft Parts Sarcoma of the Thigh. *Cancer*, *47*, 1005–1022.

Eston, R., & Evans, H. J. L. (2009). The validity of submaximal ratings of perceived exertion to predict one repetition maximum. Journal of Sports Science and Medicine, 8(4), 567–573.

Gerner, R. E., Moore, G. E., & Pickren, J. W. (1975). Soft Tissue Sarcomas. *Ann.Surg.*, *181*(6), 803–808.

Guo, S., & DiPietro, L. A. (2010). Critical review in oral biology & medicine: Factors affecting wound healing. *Journal of Dental Research*, *89*(3), 219–229.

Haas, R. L. M., Delaney, T. F., O'Sullivan, B., Keus, R. B., Le Pechoux, C., Olmi, P., Poulsen, J. P., Seddon, B., & Wang, D. (2012). Radiotherapy for management of extremity soft tissue sarcomas: Why, when, and where? *International Journal of Radiation Oncology Biology Physics*, *84*(3), 572–580.

Hanahan, D., & Weinberg, R. A. (2000). The Hallmarks of Cancer Review evolve progressively from normalcy via a series of pre. *Cell*, *100*, 57–70.

Haubner, F., Ohmann, E., Pohl, F., Strutz, J., & Gassner, H. G. (2012). Wound healing after radiation therapy: Review of the literature. *Radiation Oncology*, 7(162), 1–9.

Inagaki, J., Rodriguez, V., & Bodey, G. P. (1974). Causes of death in cancer patients. *Cancer, 33*(2), 568–573.

Jain, R. (1998). The next frontier of molecular medicine: Delivery of therapeutics. *Nature Medicine 4*(6).

Jemal, A., Tiwari, R. C., Murray, T., Ghafoor, A., Samuels, A., Ward, E., Feuer, E. J., & Thun, M. J. (2004). Cancer Statistics, 2004. *CA Cancer J Clin*, *54*, 8–29.

Jereczek-Fossa, B. A., Marsiglia, H. R., & Orecchia, R. (2002). Radiotherapy-related fatigue. Critical Reviews in Oncology/Hematology, 41(3), 317–325.

Jo, V. Y., & Fletcher, C. D. M. (2014). WHO classification of soft tissue tumours: An update based on the 2013 (4th) edition. *Pathology*, *46*(2), 95–104.

Jones, L. W., Viglianti, B. L., Tashjian, J. A., Kothadia, S. M., Keir, S. T., Freedland, S. J., Potter, M. Q., Moon, J., Schroeder, T., Herndon, J. E., & Dewhirst, M. W. (2010). Effect of aerobic exercise on tumor physiology in an animal model of human breast cancer. *J Appl Physiol*, *108*, 343–348.

Jones, S., Chiesa, S. T., Chaturvedi, N., & Hughes, A. D. (2016). Recent developments in near-infrared spectroscopy (NIRS) for the assessment of local skeletal muscle microvascular function and capacity to utilise oxygen. *Artery Research*, *16*, 25–33.

Kawaguchi, N., Ahmed, A. R., Matsumoto, S., Manabe, J., & Matsushita, Y. (2004). The Concept of Curative Margin in Surgery for Bone and Soft Tissue Sarcoma. *Clin Orthop*, *419*, 165–172.

Keylock, K. T., Vieira, V. J., Wallig, M. A., Dipietro, L. A., Schrementi, M., & Woods, J. A. (2008). Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. *Am J Physiol Regul Integr Comp Physiol*, *294*, 179–184.

Kondepati, V. R., Heise, H. M., & Backhaus, J. (2008). Recent applications of near-infrared spectroscopy in cancer diagnosis and therapy. *Analytical and Bioanalytical Chemistry, 390*, 125–139.

Lagally, K. M., Robertson, R. J., Gallagher, K. J., Gearhart, R., & Goss, F. L. (2002). Ratings of percevied exertion during low- and high-intensity resistance exercise by young adults. Perceptual and Motor Skills, 94, 723–731.

Lichter, A. S., & Lawrence, T. S. (1995). Medical progress review article recent advances in radiation oncology. *The New England Journal of Medicine*, *332*(6).

Linch, M., Miah, A. B., Thway, K., Judson, I. R., & Benson, C. (2014). Systemic treatment of soft-tissue sarcoma - Gold standard and novel therapies. *Nature Reviews Clinical Oncology*, *11*(4), 187–202.

Lindberg, R. D., Martin, R. G., Romsdahl, M. M., & Barkley, H. T. (1981). Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. *Cancer*, *47*(10), 2391–2397.

Lucero, A. A., Addae, G., Lawrence, W., Neway, B., Credeur, D. P., Faulkner, J., Rowlands, D., & Stoner, L. (2018). Reliability of muscle blood flow and oxygen consumption response from exercise using near-infrared spectroscopy. *Experimental Physiology*, *103*(1), 90–100.

Malagoni, A. M., Felisatti, M., Mandini, S., Mascoli, F., Manfredini, R., Basaglia, N., Zamboni, P., & Manfredini, F. (2010). Resting muscle oxygen consumption by near-infrared spectroscopy in peripheral arterial disease: A parameter to be considered in a clinical setting? *Angiology*, *61*(6), 530–536.

Mavrogenis, A. F., Bianchi, G., Stavropoulos, N. A., Papagelopoulos, P. J., & Ruggieri, P. (2013). Clinicopathological features, diagnosis and treatment of clear cell sarcoma/melanoma of soft parts. Hippokratia, 17(4), 298–302.

Mayer, R., Hamilton-Farrell, M. R., Van Der Kleij, A. J., Schmutz, J., Granström, G., Sicko, Z., Melamed, Y., Carl, U. M., Hartmann, K. A., Jansen, E. C., Ditri, L., & Sminia, P. (2005). Hyperbaric oxygen and radiotherapy. *Strahlentherapie Und Onkologie*, *181*(2), 113–123.

McCullough, D. J., M-D Nguyen, L., Siemann, D. W., & Behnke, B. J. (2013). Effects of exercise training on tumor hypoxia and vascular function in the rodent preclinical orthotopic prostate cancer model. *J Appl Physiol*, *115*, 1846–1854.

Minchinton, A. I., & Tannock, I. F. (2006). Drug penetration in solid tumours. *Nature Reviews*

Cancer, *6*(8), 583–592.

Morishita, S., Yamauchi, S., Fujisawa, C., & Domen, K. (2013). Rating of Perceived Exertion for Quantification of the Intensity of Resistance Exercise. *International Journal of Physical Medicine & Rehabilitation*, *1*(9), 1–4.

O'Sullivan, B., Davis, A., Turcotte, R., Bell, R., Catton, C., Chabot, P., Wunder, J., Kandel, R., Goddard, K., Sadura, A., Pater, J., & Zee, B. (2002). Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet*, *359*, 2235–2241.

Pervaiz, N., Colterjohn, N., Farrokhyar, F., Tozer, R., Figueredo, A., & Ghert, M. (2008). A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer*, *113*(3), 573–581.

Rosenberg, S. A., Tepper, J., Glatstein, E., Costa, J., Baker, A., Brennan, M., Demoss, E. V, Seipp, C., Sindelar, W. F., Sugarbaker, P., & Wesley, R. (1982). The Treatment of Soft-tissue Sarcomas of the Extremities Prospective Randomized Evaluations of (1) Limb-sparing Surgery Plus Radiation Therapy Compared with Amputation and (2) the Role of Adjuvant Chemotherapy. *Ann. Surg.*, *196*(3), 305–314.

Sadoski, C., Suit, H. D., Rosenberg, A., Mankin, H., & Efird, J. (1993). Preoperative Radiation, Surgical Margins, and Local Control of Extremity Sarcomas of Soft Tissues. *Journal of Surgical Oncology*, *52*, 223–230.

Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. *CA: A Cancer Journal for Clinicians*, *69*(1), 7–34.

Southern, W. M., Ryan, T. E., Reynolds, M. A., & Mccully, K. (2014). Reproducibility of near-infrared spectroscopy measurements of oxidative function and postexercise recovery kinetics in the medial gastrocnemius muscle. *Applied Physiology, Nutrition and Metabolism*, *39*(5), 521–529.

Stojadinovic, A., Leung, D. H. Y., Allen, P., Lewis, J. J., Jaques, D. P., & Brennan, M. F. (2002). Primary adult soft tissue sarcoma: Time-dependent influence of prognostic variables. *Journal of Clinical Oncology*, *20*(21), 4344–4352.

Strander, H., Turesson, I., & Cavallin-Ståhl, E. (2003). A systematic overview of radiation therapy effects in soft tissue sarcomas. *Acta Oncologica*, *42*(5–6), 516–531.

Tibbs, M. K. (1997). Wound healing following radiation therapy: a review. *Radiotherapy and Oncology*, *42*, 99–106.

Tiggemann, C. L., Korzenowski, A. L., Brentano, M. A., Tartaruga, M. P., Alberton, C. L., & Kruel, L. F. M. (2010). Perceived exertion in different strength exercise loads in sedentary, active, and trained adults. The Journal of Strength and Conditioning Research, 24(8), 2032–2041.

Tromberg, B. J., Cerussi, A., Shah, N., Compton, M., Durkin, A., Hsiang, D., Butler, J., & Mehta, R. (2005). Diffuse optics in breast cancer: Detecting tumors in pre-menopausal women and monitoring neoadjuvant chemotherapy. *Breast Cancer Research*, *7*(6), 279–285.

Van Beekvelt, M. C. P., Borghuis, M. S., Van Engelen, B. G. M., Wevers, R. A., & J M Colier, W. N. (2001). Adipose tissue thickness affects in vivo quantitative near-IR spectroscopy in human skeletal muscle. *Clinical Science*, *101*, 21–28.

Van Beekvelt, Mireille C. P., Colier, W. N. J. M., Wevers, R. A., & Van Engelen, B. G. M. (2001). Performance of near-infrared spectroscopy in measuring local O 2 consumption and blood flow in skeletal muscle. *J Appl Physiol*, *90*, 511–519.

Weitz, J., Antonescu, C. R., & Brennan, M. F. (2003). Localized extremity soft tissue sarcoma: Improved knowledge with unchanged survival over time. *Journal of Clinical Oncology*, *21*(14), 2719–2725.

Wolf, M., Ferrari, M., & Quaresima, V. (2007). Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. *Journal of Biomedical Optics*, *12*(6), 062104-1–062104-14.

Woll, P. J., Reichardt, P., Le Cesne, A., Bonvalot, S., Azzarelli, A., Hoekstra, H. J., Leahy, M., Van Coevorden, F., Verweij, J., Hogendoorn, P. C. W., Ouali, M., Marreaud, S., Bramwell, V. H. C., & Hohenberger, P. (2012). Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): A multicentre randomised controlled trial. *The Lancet Oncology*, *13*(10), 1045–1054.