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Lauren E. Dinsmore

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UNIVERSITY OF NORTHERN COLORADO

Greeley, Colorado

The Graduate School

PHYSIOLOGIC, PSYCHOLOGIC, AND OXIDATIVE STRESS RESPONSES TO
MULTIMODAL EXERCISE IN AN ENDOMETRIAL CANCER SURVIVOR
UNDERGOING HIGH-DOSE CHEMOTHERAPY: A CASE STUDY

A Thesis
Submitted in Partial Fulfillment
of the Requirements for the Degree of
Master of Science

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Exercise Science

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Entitled: *Physiologic, Psychologic, and Oxidative Stress Responses to Multimodal Exercise in an Endometrial Cancer Survivor Receiving High-Dose Chemotherapy: A Case Study*

has been approved as meeting the requirements for the Degree of Master of Science in the College of Natural and Health Sciences in The School of Sport and Exercise Science, Concentration of Exercise Science

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ABSTRACT

Dinsmore, Lauren E. *Physiologic, Psychologic, and Oxidative Stress Responses to Multimodal Exercise in an Endometrial Cancer Survivor Receiving High-Dose Chemotherapy: A Case Study* Unpublished Master of Science, University of Northern Colorado, 2010.

Exercise training, as a rehabilitative strategy, may be a vital factor in combatting the noxious toxicities related to cancer treatment. Research employing mixed modality exercise consistently demonstrates health benefits ranging from enhanced aerobic capacity and muscular strength to attenuated psychological distress. The primary aim of this case study was to examine the effects of exercise training on physiological and psychological parameters in an endometrial cancer survivor undergoing high-dose chemotherapy. Secondly, believed to play a role in toxicity development and progression, oxidative stress has yet to be studied in cancer survivors. The second aim of this case study was to determine the effects of exercise on a selection of blood parameters including reactive carbonyl derivatives, a marker of protein degradation. The case study subject was a 60-yr-old female, diagnosed with stage IIIC1 endometrial cancer, undergoing chemotherapy (paclitaxel and carboplatin, [PC]). Assessments (e.g., body composition, VO_2peak , 1-RM, pulmonary spirometry, fatigue and quality of life [QoL] indexes) were performed 1 day prior to the first PC cycle and again at 3- and 6-months. Exercise was performed 3 days/week (Tues, Thurs, and Sat) of each week for 21 weeks. Each 1 hour session consisted of treadmill walking and total body strength exercises. Blood pressure (BP), heart rate (HR), and ratings of perceived exertion (RPE) were

recorded during training sessions. Over 141 calendar days, the case study completed 63 exercise sessions (~45%). Physical characteristics remained relatively stable. $\text{VO}_{2\text{peak}}$ improved approx. 16% over the 6-month period (23.0 to 27.3 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Decrements in lung function were evidenced by spirometry parameters, FVC (-10%) and FEV_1 (-9%). Changes in global fatigue were not significant ($p=.17$) but affective and sensory subscales increased significantly between baseline and 3-months ($p=.05$). Subject-reported RPE scores during Phase I Nadir training were significantly lower than the prescribed range ($p=.008$). Also, Phase II Nadir scores were significantly lower than those reported in phase I ($p=.003$), suggesting the capacity to maintain exercise participation. Comparison of mean arterial pressure (MAP) between Phases I and II were not significantly different for Nadir ($p=.74$) or standard ($p=.12$) training. MAP was significantly reduced for Nadir compared to standard training ($p=.005$). ELISA results of oxidative stress markers illustrated a significant reduction of protein carbonyl concentration with programmed exercise ($p=.03$). Reduced protein oxidation may explicate the observed gains in muscular strength. Furthermore, results of complete hematology panels (e.g., WBC, RBC, HGB, and PLT) depicted a collective attenuation of treatment-related damage as per the recurring escalation toward initial (e.g., baseline) cellular concentrations. Multimodal exercise, as a remedial approach, appears to be well tolerated and appropriate for the preservation of physical and psychological capacities in an endometrial cancer survivor undergoing treatment.

TABLE OF CONTENTS

CHAPTER

I.	INTRODUCTION	1
	Statement of Purpose	5
	Research Hypotheses	5
II.	REVIEW OF LITERATURE	6
	Cancer Overview: Principles and Pathology	6
	Endometrial Cancer	12
	Principles of Chemotherapy and Radiation	17
	Antineoplastics and Toxicity Development.....	24
	Cancer-Associated Oxidative Stress	29
	Exercise Training and Attenuation of Treatment-Related Toxicities	36
III.	METHODOLOGY	47
	Experimental Design.....	47
	Participants.....	48
	Preliminary Paperwork	49
	Distribution and Interpretation of Psychological Indexes	50
	Assessment of Pulmonary Function.....	51
	Assessment of Muscular Strength.....	52
	Assessment of Cardiorespiratory Fitness.....	52
	Balance Assessment.....	53
	Development and Implementation of the Exercise Intervention	54
	Protein Carbonyl Determination & CBC Analysis	55
	Statistical Analysis.....	56
IV.	RESULTS	57
	Changes in Assessment Outcome Measures.....	57
	Changes in Training Load.....	63
	Changes in Subject Parameters.....	65
	Changes in Mean Arterial Pressure.....	67
	Changes in Blood Parameters	69
V.	DISCUSSION	72
	Conclusion	79

REFERENCES	82
APPENDIX A: RPE SCORES FOR A 21-WEEK EXERCISE INTERVENTION	97
APPENDIX B: COMPILED SUBJECT CHARTING SHEETS	99

LIST OF TABLES & FIGURES

Table 1: Physical Characteristics of Case Study	57
Table 2: Effects of Exercise Intervention on Muscular Strength	58
Figure 1: Changes in 1-RM from Baseline	59
Table 3: Effects of Exercise Intervention on Cardiorespiratory Fitness	60
Figure 2: Effects of Exercise Intervention on Spirometry Variables	61
Figure 3: Changes in Aerobic Capacity and Time to Fatigue	61
Table 4: Effects of Exercise Intervention on Psychologic Variables	62
Figure 4: Changes in Piper Subscales with Exercise Intervention	63
Table 5: Strength and Aerobic Training Loads	64
Figure 5: Changes in Imposed Training Loads over Time	65
Table 6: Effects of Exercise Intervention on RPE Scores	66
Figure 6: Changes in RPE Scores During Training Phases I and II	67
Table 7: Effects of Exercise Intervention on Cardiovascular Parameters	68
Figure 7: Changes in MAP during Nadir and Standard Training	68
Table 8: Effects of Exercise Intervention on Blood Parameters	70
Figure 8: Changes in Blood Parameters	71

CHAPTER I

INTRODUCTION

Owing to strides in disease management and early detection, the concept of cancer survivorship is no longer a fruitless endeavor but more often the anticipated outcome of clinician and patient alike. Alas, accompanying improved survivorship are the persistent toxicities related to treatment. Historically, patients receiving anticancer treatment have been advised to reduce physical activity and seek rest. Yet, there is growing evidence contesting obsolete rehabilitative strategies in order to avoid self-perpetuated conditions (e.g., fatigue). With attention directed at tackling corrosive toxicities, the pursuit for new remedial strategies is a welcomed challenge to prolong survival. Therapeutic aims focus on improving the *quality* and *quantity* of life after cancer diagnosis.

Cancer remains the second leading cause of death in the United States, as indicated by the National Cancer Institute (NCI, 2010a). Despite the high mortality rates associated with certain cancers, prospects for survival continue to improve. According to the American Cancer Society (ACS), the survivor population in the United States comprises approximately 12 million individuals. Globally, this number climbs to nearly 20 million, with about 285,000 people being added on an annual basis (ACS, 2009a).

While tumor biology has long been central to oncology research, patients' expectations for a better quality of life (QoL) drives research efforts to focus on enhanced survivorship care. By cancer site, there is a disproportion of available research.

Disparities are justified by a survivor population comprised of 50% breast and prostate diagnoses with colon, hematological, and endometrial malignancies each accounting for only about 10% (Hewitt, Greenfield & Stovall, 2005). Needless to say, the safe and efficacious management of cancer-related toxicities requires analysis and validation across cancer sites (Visovsky & Dvorak, 2005).

Outlined by Courneya and Friedenreich (2007), the *Cancer Control Framework* suggests specific disease-related stages exist along a “logical continuum” and illustrate the transition from prescreening to active treatment and survivorship care. Implications associated with a particular stage may be involved with and/or advance psychological and physiological impairment. Specifically, medical interventions that improve the outlook of surviving cancer are undertaken at the expense of treatment-induced toxicities. The most common treatment modalities (e.g., surgery, radiotherapy, and chemotherapy) elicit a wide range of well-documented toxicities that can generate persistent damage long after treatment is complete.

Systemic therapy (e.g., chemotherapy drugs) is associated with a range of chronic debilitations (Schneider, Dennehy & Carter, 2003). The cumulative nature of chemotherapeutic agents augments the severity and extent of toxicities. Irradiation therapy elicits significant damage similar to chemotherapy, especially amplified in targeted tissue. This development of toxicities following treatment is presumed to be induced by a state of amplified oxidative stress (Chen, Jungsuwadee, Vore, Butterfield & St Clair, 2007).

Prolonged, intensive treatments elicit whole-body toxicities and compromise the integrity of healthy tissue through the generation of free radicals (Lucia, Earnest & Pérez,

2003; Loft & Poulsen, 1996). Collective toxicities foster a degradation of physical and emotional functioning (Beesley, Eakin, Janda & Battistutta, 2008). With the deterioration of patients' psychologic well-being, cancer-related fatigue and waning QoL are amplified. As fatigue is activity-limiting by nature, somatic perceptions can remain for years.

According to Smets, Garssen, Schuster-Uitterhoeve and Haes (1993), the prevalence of fatigue, irrespective of disease site or stage, is approximately 70%, making to the most frequently reported symptom in cancer patients (Visovsky & Dvorak, 2005; Dimeo, 2001). A complex etiology complicates alleviation (Smets et al., 1993). The well-meaning advice to combat fatigue paradoxically compounds symptoms. As patients take on sedentary habits, fatigue is self-perpetuated through catabolic pathways and detraining (Courneya, 2003).

By contrast, participation in physical activity is gaining credibility as a restorative approach, boasting an antidote for a range of toxicities to enhance QoL and reduce fatigue (Schneider, Hsieh, Sprod, Carter & Hayward, 2007; Speck, Courneya, Mâsse, Duval & Schmitz, 2009). The explosion of novel research that has surfaced will ultimately affect medical practice to revolutionize techniques employed to prevent, attenuate, and restore treatment-induced tribulations.

Due to high diagnosis rates, the majority of research has investigated the effects of exercise in breast and prostate patients (Courneya, Friedenreich, Arthur & Bobick, 1999). In this population, exercise programming has led to conclusive improvements in psychologic status, subjective fatigue, and cardiorespiratory fitness level (Burnham & Wilcox, 2002; van Weert, Hoekstra-Weebers & Grol, 2005). It is not sensible to

extrapolate findings to all cancer sites and stages; however, the body of evidence continues to grow in support of exercise as a collective rehabilitative approach for cancer survivors (Dimeo, 2001; Schneider et al., 2003).

A review by Schmitz et al. (2010) examined available literature in support of both the efficacy and safety of exercise training in cancer survivors. Evidence was gathered from completed randomized controlled trials (RCT) and assessed for each cancer site. Cancers of the prostate and colon have been evaluated in 12 and 4 studies, respectively. The outcomes of exercise programming for survivors of hematologic malignancies either treated with hematopoietic stem cell transplantation (HSCT) or in the absence of HSCT, have been evaluated in 11 and 4 studies, respectively.

A severe deficit of exercise research in gynecological cancers is evidenced by a single completed RCT at the current time. While 5 studies have used mixed samples, incorporating a small number of gynecologic patients (n=5-15), only one intervention has exclusively assessed this specific population.

Considered a weight loss intervention, this gynecological RCT by von Gruenigen et al. (2008) was conducted in a sample of endometrial cancer survivors. Specified inclusion criteria required that subjects be of post-treatment status and overweight/obese classification. With the primary focus of this 6-month intervention on weight change, physical activity served as a secondary health outcome. Allocated pedometers, used in place of a structured exercise program, made conclusions in regard to the effects of physical activity seedy and unreliable.

Research has yet to evaluate the effects of a structured exercise program in endometrial cancer survivors. Moreover, most exercise studies conducted in oncology

research implement interventions after the completion of treatment. Along with the lack of research focused on exercise during treatment, even rarer is it to find a study that has collected baseline measures *prior* to antineoplastic treatment. Gathering baseline values for parameters of interest can only expand the understanding of toxicity development and the benefits of exercise.

Therefore, the purpose of this case study was to investigate the effects of exercise training on physical capacity and psychological functioning in an endometrial cancer survivor undergoing high-dose chemotherapy. Also, knowing that exercise regulates the generation of reactive oxygen species (ROS) in a range of chronic diseases, the second aim of this study was to determine the effects of exercise on reactive carbonyl derivatives, a marker of protein oxidative stress.

Statement of Purpose

To examine the effects of a 6-month multimodal exercise intervention on physiologic and psychologic functioning and a selection of blood markers in an endometrial cancer survivor receiving high-dose chemotherapy.

Research Hypotheses

- H1 Multimodal exercise will ameliorate cancer-related fatigue and preserve QoL over the course of high-dose chemotherapy cycles.
- H2 Aerobic capacity and muscular strength, as per $\text{VO}_{2\text{peak}}$ and 1-RM, respectively, will be sustained through an individualized exercise plan.
- H3 The training intervention will attenuate oxidative stress damage, as evidenced by a reduced protein carbonyl concentration.

CHAPTER II

REVIEW OF LITERATURE

Cancer Overview: Principles & Pathology

According to the National Coalition on Cancer Survivorship, a cancer survivor constitutes any person diagnosed with cancer, from the time of discovery and for the entirety of his or her life thereafter (Speck et al., 2009). Presently, this clinical population is comprised of 12 million individuals and continues to expand (Schmitz et al., 2010).

The growth is attributable to enhanced diagnostic tools and more effective antineoplastics. Moreover, as noted by the National Cancer Institute's *2009-2010 Cancer Trend Progress Report*, a reduction in disease incidence and death rate across all cancers has been reported since the turn of the twenty-first century (NCI, 2010a). In spite of continued progress, cancer will claim approximately 562,000 lives this year, making it the second most common cause of death in the United States (Mariotto et al., 2008). Of the 1.5 million diagnoses, leading tumor sites in men and women are prostate and breast, respectively (ACS, 2009a).

In recent decades, research contributions have enhanced the understanding of cancer to a new, unprecedented level. The primary focus of research has long been tumor biology and the associated intricacies, with less attention devoted to host biology and patient care. The evolving avenue of translational research relates molecular biology to

patient therapeutic and diagnostic care, uniting the human and animal research models (Song, Samulski & Van Dyke, 2008). Once diametrically separated, biological mechanisms can now be used by the clinician to improve disease evaluation and remedial management. Theories of cell cycle kinetics provide insight into disease origin and progression. The cell cycle is comprised of a series of precisely programmed events which regulate proliferation. When the distinct cycle phases, G₀, G₁, S, G₂, and M, occur in the anticipated procession, division occurs under appropriate circumstances in a timely manner (Weinberg, 2007). Because proteins act as modulators in growth and apoptotic pathways, disturbance of protein regulation can propagate deviant growth patterns and advance tumorigenesis (Macheda, Rogers & Best, 2005).

Errors in intrinsically normal molecular pathways remain central to cancer genesis. Signaling pathways involved in homeostasis, cellular proliferation and differentiation, and apoptosis demonstrate interconnectivity; aberrations in pathways concerned with basic and essential processes can promote disease phenotype (Weinberg, 2007). Under normal circumstances, abnormal or superfluous cells are managed through apoptotic pathways. Yet, deviations can instigate hyperproliferation (Schneider et al., 2003). The volume of mechanism-specific cell types augments the scope of obstacles posed by cancer. Often, the same mechanism responsible for cellular diversity dictates disease progression (Song et al., 2008).

In cancer cells, feedback mechanisms responsible for cellular turnover are disconcerted leading to the formation of irregular, undifferentiated masses of cells, or tumors. If not removed or destroyed, tumors have the potential for direct penetration of contiguous tissue. A metastatic disease has penetrated the lymphatic and blood vessels,

utilizing the bloodstream to colonize throughout the body. Invasion and metastasis allow cancer cells to leave the primary tumor site, inhabit distant tissues and spread throughout the body (Minn & Massagué, 2008). Tumor development relies on a constant supply of fuel in order to maintain cellular processes. Like normal cells, malignant cells employ shared metabolic pathways to sustain energy production.

A Duke University study by Sonveaux et al. (2008) elucidated upon the bioenergetic pathways exploited by cancerous tumors. Tumors, considered heterogeneous tissue, are comprised of oxygenated and hypoxic cellular regions. Both the oxygenated and hypoxic cells utilize glucose as the primary energy metabolite (Sonveaux et al., 2008). Glucose is reduced in a cascade of chemical reactions which constitutes glycolysis (Powers & Howley, 2007). Hypoxic and aerobic cells yield distinct glycolytic end-products, lactate and pyruvate, respectively. This favorable characteristic ensures energy substrates for the metabolically-discrete cells (Sonveaux et al., 2008). Researchers refer to this metabolic partnership as an “intratumoral metabolic symbiosis” (Semenza, 2008). This cyclic production-utilization drives tumorigenesis and progression.

The lactate produced in hypoxic cellular regions is taken up by aerobic cells and serves as a primary substrate for oxidative cancer cells. Hypoxic tumor cell activity is anaerobic due to limited oxygen availability and as a result, less energy is produced (Powers & Howley, 2007). To counteract the reduced rate of energy production, hypoxic cells augment glucose uptake to remain homeostatic (Macheda et al., 2005). Consequentially, healthy cells are starved of nutrients and will quickly become necrotic, allowing disease invasion and metastasis (Heiden, 2010).

The structure and activity of a cancer cell is highly unorganized in contrast to healthy cells (Schneider et al., 2003). A loss of cellular differentiation and atypical mitotic processes instigate failure of host tissue. The origins of malignancy are widespread. Etiological factors can range from exposure to chemical toxins to heritable traits and nutrition status. Carcinogenesis, or the process by which healthy cells become cancerous, is attributed to an array of established risk factors. Atypical cellular processes are instigated by carcinogen assault (Ehrman, Gordon, Visich & Keteyian, 2003). Since 1971, the International Agency for Research on Cancer (IARC) has evaluated 900 environmental factors to determine the carcinogenic potential of each. Approximately 400 agents have been deemed either carcinogenic, probably carcinogenic, or possibly carcinogenic (IACR, 2008).

There is evidence to support that most cancers have a strong environmental etiology. Doll and Peto (1981) evaluated a selection of lifestyle factors to determine the extent modification played in attenuating cancer incidence. Researchers speculated that 35% of cancer mortality in the United States could be prevented by alterations in diet, indicating that a considerable proportion of diagnoses could be avoided (Doll & Peto, 1981).

Nutritional status, physical activity, and body size all interact to regulate energy balance. There is substantial epidemiological evidence to support that excess weight and obesity (BMI >25) contributes to various endocrine and metabolic perturbations, which can trigger carcinogenesis (Fair & Montgomery, 2009). Specifically, adiposity, resulting from surfeit caloric intake relative to energy expenditure, produces a positive energy balance (PEB). It is posited that a PEB has potential to disrupt growth factors,

inflammatory markers, and hormones. It has been suggested that inflammatory signaling has etiological potential (Henderson & Bernstein, 2008). Energy imbalances can be piloted by a lack of participation in physical activity, as well. In fact, an inverse relationship has been postulated between physical activity and cancer incidence/mortality, supporting regular exercise as a means of reducing cancer risk (Michels & Willett, 2008).

It has been postulated that oxidative stress is implicated with cancer etiology (Loft & Poulsen, 1996). Oxidative stress reflects a state in which the generation of reactive oxygen species (ROS) exceeds adaptive capacities of the antioxidant defense system (Oberley, 2001). Produced as the byproduct of respiration and other biochemical reactions in which oxygen is involved, ROS fall under the intricate regulation of the antioxidant defense system. When properly managed, ROS maintain a breadth of physiological processes, including signal transduction and regulation of mitochondrial enzyme activity. With a reduction of antioxidant enzymes as per aging, Diabetes, ischemia/reperfusion injury, cancer, etc., the concentration of ROS can quickly climb to toxic levels (Valko et al., 2006).

Just as carcinogens can act upon any somatic cell, the risk of cancer threatens all individuals. Cancer risk can be evaluated as the probability of cancer development over the course of the entire lifetime (lifetime risk); men and women in the United States have a lifetime cancer risk of slightly less than 1 in 2 and a little more than 1 in 3, respectively (ACS, 2009a). Lifetime risk does not assess the risk of developing specific cancers. More often, risk is assessed based on the relationship strength between particular risk factors

and certain cancers (relative risk). Relative risk provides useful insight for the individual and is more appropriate for assessing the threat posed by a particular cancer.

Genetic mutations, capable of eliciting tumorigenesis, demand appropriate disease classification for accurate diagnosis and therapy prescription. Based on the location and tissue type affected, tumors are broadly categorized. Cancers arise in the form of solid tumors or serous and hematological malignancies.

Cancers involving solid tumor formation include carcinomas and sarcomas. Carcinomas, originating in the epithelial lining of various tissues, are extremely common and account for nearly 90% of all diagnoses. Only about 2% of cancers develop as sarcomas, or invasive tumors of the connective tissue, bone, muscle, cartilage, and fat (Schneider et al., 2003).

Serous cancers include leukemia, melanoma and lymphoma. Leukemia involves the abnormal production of white blood cells. Responsible for defense against pathogenic invasion, leukemia can leave the immune system compromised. Melanomas and lymphomas affect somatic melanocytes and lymphocytes, respectively (Schneider et al., 2003). Extensive histological evaluation of the tumor is obligatory in order to ascertain disease trajectory and accurately stage the disease.

In an effort to ease ambiguity in clinical staging and diagnosis, The American Joint Committee on Cancer (AJCC) manages revisions made to *The AJCC Cancer Staging Handbook*, which evaluates specific anatomic criteria to facilitate cancer stage identification. Considered by many to be the gold standard in oncology classification, the AJCC tumor node metastasis (TNM) system is used by physicians and health care professionals in order to construct universal descriptions of neoplastic diseases. A

standard classification system is essential to assigning treatment plans and the assessment of outcomes following disease management (Edge et al., 2010).

The anatomic criteria evaluated by the TNM system includes: primary tumor size and contiguous extension (T), presence/absence and extent of lymph node involvement (N), and presence/absence of distant metastasis (M). From a clinical evaluation of the TNM components, disease progression is assessed and an appropriate cancer stage determined (Schneider et al., 2003). AJCC and its collaborative organizations require sufficient time to evaluate newly acquired clinical data and judge potential benefits for improved prognosis (Edge et al., 2010). Even with periodic amendment to the staging system every 6-8 years, diagnoses based on thorough clinical assessment are not infallible.

The expanding population of cancer survivors poses the well-received challenge of addressing the individual needs of long-term survivors (Aziz & Rowland, 2003). The aim of continued care is based on patients' traits (e.g., age, gender, race), cancer type, existence of comorbidities, etc. Attention is now focused on strategies to transition the cancer survivor back into a disease-free life and the potential adjuvant strategies to foster this shift.

Endometrial Cancer

Cancers of the corpus uteri (body of the uterus) involve carcinomas and sarcomas of the endometrial epithelial lining. Sarcomas of the uterine stroma and muscle cells are less common and associated with poorer outlooks (ACS, 2009b). Endometrial cancer is the most prevalent female gynecological malignancy, accounting for 6% of all female cancers. Close behind cancers of the breast, lung, and colon, endometrial carcinoma is the

fourth most frequent killer of women in the United States (Rodriguez, 2001a; NCI, 2009; Dizon, 2010). The well-established warning sign associated with endometrial cancer, postmenopausal or abnormal bleeding, affords a high incidence of stage I diagnoses and frequent curable prognoses. The incidence of endometrial cancer has declined by approximately 0.5% each year since 1997 and the improvements in 5-year survival rates for local, regional, and distant cancers, 96%, 68%, and 24%, respectively, attest clinical strides (NCI, 2010a).

Adenocarcinoma, the most common form of endometrial carcinoma, affects the gland-forming cells of the endometrium. Adenocarcinoma subtypes are recognized via distinct pathological features. ‘Typical’ adenocarcinomas, known as endometrioid adenocarcinoma, account for 90% of endometrial cancers (Chu, Lin, & Rubin, 2008). More rare, ‘high risk’ adenocarcinomas include clear-cell adenocarcinoma and papillary serous adenocarcinoma which develop in 5% and 6% of all cases, respectively. These subtypes are poorly differentiated, highly aggressive, and metastasize rapidly. Five-year survival outlooks are very poor for high-risk carcinomas (Rodriguez, 2001b; ACS, 2009b).

Disease stage is highly predictive of survival. Accordingly, the staging prognostic criteria should be capable of scrutinizing between minute histological and pathological differences. Diagnostic tests, such as the uterine biopsy and endocervical dilatation and curettage (D&C), are performed to evaluate uterine pathology. D&C, considered the gold standard of diagnostic tools, can decipher glandular abnormalities in epithelium of a thickness <5mm (ACS, 2009b). The criterion, serum CA-125, is not readily assessed across all cancer diagnoses, but plays a crucial role in endometrial cancer. CA-125 levels

>20 U/ml are indicative of deep myometrial invasion and metastatic assault. The criteria of histologic subtype, grade of differentiation, and stage at presentation are the most influential for prognosis.

Whether a carcinoma is classified as having ‘high-risk’ or ‘typical’ histology is dependent on the degree of differentiation of gland-forming cells. Cancer grade is an evaluation of endometrial architectural and appearance of glands formed by malignant cells in relation to those formed by healthy endometrium.

“High grade” cancers are associated with a lack of cellular arrangement in which gland formation is not possible. Grade III cancers tend to be aggressive due to haphazard organization and rapid growth patterns. Typically, less than half of cancerous tissue is capable of forming glands leading to poor prognoses (NCI, 2009). Grades I and II show glandular growth patterns of >95% and 50-95%, respectively. Lower grades are typically associated with better outlooks and slower disease progression. Cancer grade is crucial in diagnostic staging, as it can be predictive of metastasis and nodal involvement (Rodriguez, 2001b; Chu et al., 2008).

Recently, staging of corpus uteri malignancies has changed to a surgical system, relying less upon the previously employed clinical staging. Tissue removed during surgical assessment (i.e. uterine biopsy and/or curettage) allows for evaluation of local, regional, and metastatic development; tissue evaluation is used to assign the appropriate stage. Implemented by the International Federation of Gynecology and Obstetrics (FIGO), surgical staging better assesses lymph node involvement and extrauterine metastasis (Creasman, 2009). For gynecological cancers, FIGO staging is often used in place of the AJCC system due to specific evaluation of uterine histopathology and

cytology. Five-year survival rates for stage I and II carcinomas are 83% and 73%, respectively. High-risk carcinomas, III and IV, reveal 5-year survival rates of 52% and 27%, respectively (Rodriguez, 2001b).

Endometrial cancer has been associated with a selection of etiological factors. Chronic estrogen exposure is a well-recognized risk factor in disease development. Adenocarcinomas that develop due to estrogen stimulation are classified as Type I (Chu et al., 2008). Pathologically discrete, type II cancer development is not attributable to prolonged hormone exposure, as indicated by rare serous carcinomas. Type II pathogenesis is not well characterized, suggesting an explanation for the associated poor survivorship (Rodriguez, 2001b).

Many modifiable factors (e.g., nutrition, exercise, etc.) augment risk of adenocarcinoma development. High fat diets in Western cultures evidence climbing rates of obesity. A prominent risk factor, obesity increases endometrial cancer incidence/mortality rates. Moreover, obese women have elevated circulating estrogens due to adipocyte conversion of androstenedione to estrone (Chu et al., 2008). In contrast to her healthy counterparts, an obese woman with an excess weight of 30 lb or 50 lb increases her risk of endometrial cancer by 3x and 10x, respectively.

Women who do not bear children during the lifespan (nulliparity) endure chronic, uninterrupted estrogen exposure, which can increase the risk of endometrial cancer 2- to 5-fold (Rodriguez, 2001a). In contrast, pregnancy is considered a progestational state, which reduces endometrial cancer risk. Similar to the biological effects elicited during pregnancy, progestin regimens elicit parallel effects and reduce cancer risk. Certain clinical conditions, diabetes mellitus and hypertension, predispose an individual to

endometrial cancer, as result of elevated endogenous estrogen (ACS, 2009a). A history of pelvic irradiation along with various imaging techniques (i.e. x-rays, radioactive scans) elevates the risk of cancer, as well.

The incidence of endometrial cancer increases linearly with age; unfortunately, advanced age is inversely related to 5-year survival rates. Endometrial cancer is most frequently diagnosed in Caucasians, attributable to exogenous estrogen therapy employed for menopausal syndrome. Estrogen exposure elicits hyper-proliferative activity in endometrial cells. Consequently, the likelihood of somatic mutations increases (Dizon, 2010). A woman ingesting standard doses of estrogen, without concurrent progestational agents, increases her risk of endometrial cancer 9.5x (Rodriguez, 2001a). Such etiological factors can ultimately influence the selection of appropriate treatment modalities.

The course of treatment undertaken is closely related to the tumor histopathology, as it explicates upon disease trajectory and prognosis. In 95% of all endometrial cancer cases, removal of the uterus with bilateral fallopian tubes and ovaries (e.g., total abdominal hysterectomy with bilateral salpingo oophorectomy [TAH-BSO]) serves as the primary surgical procedure. Tissues removed during TAH-BSO undergo cytologic evaluation in order to stage the cancer. Due to the poor differentiation and myometrial invasion associated with grade III malignancies, pelvic and para-aortic node sampling is recommended to assess the extent of metastasis. Removal of lymph nodes (lymphadenectomy) for comprehensive analysis will not only reveal disease progression but can arrest further metastasis. In early-stage cancers, combined TAH-BSO and lymphadenectomy treatments may serve as an adequate course of therapy to combat cancer growth (Rodriguez, 2001b).

Advanced or recurrent cancers often necessitate adjuvant therapies such as chemotherapy or whole pelvic irradiation. Poor prognoses commonly associated with late-stage carcinomas accentuate the need for innovative treatment options. Showing promise in the late stages of clinical trials, epothilones represent a new class of chemotherapeutic microtubule-stabilizing drugs classified as cytotoxic metabolites. Epothilones may be successful in treating advanced adenocarcinoma resistant to standard taxane and/or anthracycline therapies (Lee et al., 2009).

Endometrial cancer survivorship is highly related to staging at the time of disease presentation. Yet, while early-stage diagnoses lead to promising outlooks in about 75% of women, it is projected that cancer of the uterine corpus will claim approximately 7,800 lives this year (ACS, 2009a). Though mortality rates have stabilized since the early nineties, this trend does not demonstrate strides in survivorship made in other areas of oncology. Current statistics beg for advancement of diagnostic tools and medical treatments.

Principles of Chemotherapy & Radiation

The primary objective of antineoplastic drugs is to prevent or delay rapid growth patterns of cancer cells. An inability to manage the spread of disease can result in the unrelenting necrosis of healthy tissue and, ultimately, the failure of organ systems leading to death. The appropriate course of action is based on a patient's cancer type and the metastatic trajectory. Additional factors that affect treatment selection include the existence of comorbidities at the time of diagnosis or prior exposure to antineoplastics in those individuals with recurrent cancer or second neoplasms (Kumar et al., 2009).

Recurrent cancers treated previously using chemotherapeutic agents may be resistant to second-line chemotherapy (Dizon, 2010). The development of chemoresistance is often related to the overexpression of specific molecular targets. Two commonly susceptible targets, the ATP-binding cassette (ABC) transporter proteins and the P-glycoproteins, elicit unregulated gene expression (Leslie, Deeley & Cole, 2005). Constitutive expression of certain proteins can disrupt transport and apoptotic pathways. Chemoresistance is associated with reduced chemotherapeutic agent found in tumor cells due to low activity of transport proteins (Fojo & Menefee, 2007). As a result, proliferation continues.

The stage of cancer dictates the goal of treatment; common aims include curative intent, control, and palliation of the disease. Treatments with curative intent remove the tumor, anticipating that it will not return. While a curative outcome may be the objective, it is not a certainty (ACS, 2010). Early-stage cancers, without metastatic qualities, are more typically associated with curative intent therapies. Disease control often serves as a more practical aim. A disease-free life may not be feasible, yet the spread of cancer may be controlled and monitored (Lawrence, Ten Haken & Giaccia, 2008).

Palliative therapies are most often employed in patients' characteristic of inoperable cancer, advanced stage disease, and contraindicative comorbidities. The premise behind palliation is to relieve symptoms brought on by the disease to improve the patient's QoL. Designing treatment plans with each patient in mind is critical to ensure that therapy is precise, effective, and as minimally harmful to healthy tissues as possible.

Surgical removal of cancerous tissue serves as the most common primary treatment (Schneider et al., 2003). In an effort to reduce the size of the cancerous mass

prior to dissection, neoadjuvant treatments often precede surgery, with the intent of making subsequent treatments more effective. Following tumor excision, secondary treatments are commonly administered to destroy any residual malignant cells. Subsequent treatments are classified as adjuvant therapies (NCI, 2010c). While surgery is effective in removing the bulk of the cancer, adjuvant therapies are employed if there is a threat of metastasis.

Chemotherapy and radiotherapy are extensively employed as second-line treatment. More than 50% of cancer patients receive radiation during the course of their illness (Khan, 2003). Radiation energy is administered as either photons or particles. The interaction of radiation with biological material results in ionization. When ionizing radiation is absorbed by chromosomal DNA, cellular inactivation and death ultimately occur (Lawrence et al., 2008).

Much like surgical oncology, radiotherapy is considered a local treatment. Cells in the irradiated target tissue lose the ability to divide due to breaks in double-stranded DNA, making growth and replication impossible (NCI, 2009). This inhibition of the cell-cycle can lead to cellular apoptosis depending on the radiotherapy dosage.

Radiation therapy is typically administered either as an external high-energy photon beam or internally-positioned radioactive source (ACS, 2010). The particular technique employed is based on cancer location and stage. Variability of patient responses to treatment necessitates adjustable dosage schedules relative to each patient. Internal radiation (brachytherapy) involves placing the radiation source inside the body. Radioactive sources can be placed within the tumor itself as interstitial brachytherapy or

within the surgical cavities near the tumor as intra-cavitary brachytherapy. The radioactive source takes on a solid form as seeds, pellets, or capsules (NCI, 2010b).

Rapid, uncontrolled growth patterns make cancer cells extremely radiosensitive. This augmented sensitivity promotes susceptibility to genetic damage and apoptosis (ACS, 2010). Unfortunately, the effects of radiation are not limited to dividing cancer cells. Healthy cells undergoing mitosis in close proximity to target tissue can endure the therapy-induced damage (Lawrence et al., 2008). The side effects experienced amid radiation reflect healthy cell destruction. With each treatment, the body attempts to maintain energy balance between cancer cell destruction and the sparing of surrounding tissue.

Radiation tolerance varies for tissues throughout the body. The amount of radiation a particular tissue absorbs refers to the radiation dosage (ACS, 2010). In order to maximize cancer cell destruction with minimal damage to healthy tissue, doctors divide the total dosage into multiple, smaller fractions. Typically, fractional doses are administered daily for a specified amount of time, allowing for recovery in nearby healthy tissue (Food and Drug Administration [FDA], 2009).

Assessment of radiotherapy-induced damage between malignant and healthy cells is exemplary of the therapeutic ratio, which yields the risk: benefit profile (Bioce, 2009, March). The selected radiation dose should control tumor growth with negligible production of deleterious toxicities (Shafiq, Barton, Noble, Lemer & Donaldson, 2009).

Higher doses of radiotherapy are commonly administered to regions harboring the bulk of the tumor, while neighboring tissue, suspect of occult disease and nodal involvement, will receive abridged dosage to address the threat of metastasis. Curative

intent treatments often justify heightened dosage schedules encompassing enlarged anatomical areas. As a result extensive tissue is affected and organ preservation becomes a primary concern. Though radiation frequently contributes to curative outcomes, it can also drive the development of second or recurrent neoplasms (FDA, 2009).

In advanced, metastatic disease, chemotherapeutic agents are often used in lieu of or in combination with other treatment modalities. Regularly utilized to address the limited life expectancy associated with advanced cancer, chemotherapy refers to the systemic treatment of cancer; chemotherapeutic agents are most commonly administered via intravenous delivery (Schneider et al., 2003). The efficacy of chemotherapy regimens demand a comprehension of the molecular pathways and mechanisms involved in both malignant and normal cells. The field of cancer genetics elucidates upon the drug kinetics and the disciplines of pharmacokinetics and pharmacodynamics. Cancer genetics can be used to construct strategies that reduce interpatient variability and augment consistency of therapeutic effects. The absorptive and metabolic actions associated with a particular agent shed light on the clinical effects (e.g., efficacy and toxicity) elicited within the body (Takimoto & Chee, 2008).

Cytotoxic drugs are classified into broad groups on the basis of chemical properties and structure. Common drug classes include, but are not limited to, platinum-based agents (e.g., Carboplatin) and antimicrotubule agents (e.g., Paclitaxel). Cancer site and stage, previous chemotherapy exposure, and contraindicative health conditions dictate which drug class/analog will be the most therapeutic (ACS, 2010).

Single-agent monotherapy has not historically revealed the efficacy of combination chemotherapy (DeVita & Chu, 2008). While each drug elicits a scope of

specific effects, the success of combinational therapy is attributable to interactions between antineoplastic agents. If considering combination chemotherapy, established optimal dosage schedules of each drug should be maintained (Weinberg, 2007). Because overlap of toxicity profiles has potential to induce lethal effects, all drug interactions and risks are evaluated.

Genetic variability accounts for the vast array of patient reactions to antitumor therapies. Tailoring a treatment approach to each patient is the central theme to the “art of medicine”. Discrepancies of responses to chemotherapy regimens may require manipulation of the dose intensity, or the amount of drug per unit time (DeVita & Chu, 2008). Dose intensity is established from the time allotted for administration. There is a well-established relationship between dose intensity and treatment outcome (Takimoto & Chee, 2008).

Summation dose intensity is used to predict treatment outcomes in combination therapies. As the number of antitumor agents administered at full therapeutic dose increases, the cure rate linearly rises (Berglund, Bolund, Fornander, Rutqvist & Sjoden, 1991). Coalescing mechanism-specific drugs often leads to augmented efficacy. Treatment outcomes are highly related to the patient’s capacity to tolerate a multi-agent course of therapy. While effective dose intensities lead to tumor destruction and optimistic prognoses, augmented delivery can elicit deleterious toxicities. Postponement of successive drug cycles is related to poor outlooks (Edge et al., 2010). A topic of concern, research addresses the need for effective combinational therapies with minimal side effects.

A NCI clinical trial evaluated the efficacy and toxicity between two of the most popular combination therapies, carboplatin and paclitaxel (collectively referred to as PC) versus Doxorubicin (Dox), cisplatin and paclitaxel. Despite the fact that Dox serves as an effective antitumor agent, its high toxicity profile deters many clinicians. Researchers conclude that administration of carboplatin with concurrent paclitaxel was just as effective at killing tumor cells with less destructive toxicities (DiSaia, 2008).

The efficacy of platinum-based Carboplatin is based on erroneous binding patterns of nucleic acid bases (Reed, 2008). Deterioration of the double stranded helix structure induces genetic damage to inhibit cellular reproduction (Ross, 1972). The effects of chemotherapeutic agents are not limited to malignant cells, as the “nonspecific” mechanism makes any rapidly proliferating cell a prospective target.

Paclitaxel and other antimicrotubule agents act upon fundamental organelles responsible for cellular division, transport, and signaling (Lee & Harris, 2008). The contrasting minus and plus end caps that compose microtubules govern the processes of treadmilling and dynamic instability (Nogales, 2001).

The success of antimicrotubule taxanes is based on the suppression of treadmilling and dynamic instability. As the drug binds to the microtubules, mitotic arrest is imminent (Lee & Harris, 2008). Loss of microtubule functionality serves as a conduit for malignant cell malfunction and demise. Varied treatment modalities can ultimately compromise the integrity of healthy tissue as evidenced by the corrosive toxicities associated with failing somatic systems.

Antineoplastics and Toxicity Development

Anticancer treatments aim to destroy cancer cells while preserving functionality of healthy tissue. Yet, physiological alterations are not limited to malignant cells and the consequential toxicities reflect a collective cellular disruption. The severity of side effects is based on treatment modality, dosage, and patient tolerance (ACS, 2010). Quantitative analysis, via Nadir, is common practice for hematological evaluation. The value of the subjective perceptions should not be negated, however, as they afford relevant information in regard to patient response to and tolerance of a particular treatment (Lucia et al., 2003). Psychological perceptions of fatigue and depression often mask the primary cellular disturbance.

The impairment of somatic processes emerges as acute or chronic effects (Schneider et al., 2003). Acute side effects are characteristic of somatic tissue that relies on rapid self-renewal. Because radiation-induced apoptosis occurs during mitotic division, cell loss is amplified in tissues with rapid turnover (e.g., skin and mucosal surfaces). Proliferation is heightened in response to the treatment-induced cell loss in an effort to stabilize mitotic/apoptotic pathways. The immediate effects of radiation typically resolve within 1 to 2 weeks of treatment completion (Vargo, Smith & Stubblefield, 2008). Acute responses not well-tolerated have potential to progress into chronic effects.

Many antitumor therapies demonstrate cumulative effects over time. While this characteristic facilitates constructive eradication of disease, it also augments the severity and extent of toxicities. Chronic toxicities gradually develop over the course of treatment and endure after completion, giving way to lingering complaints of sustained fatigue,

neuropathy, etc. The adverse effects of chemotherapy reflect the nature of its systemic drug action. While toxicities develop throughout somatic systems, local skin reactions at the injection site are common. Irritants induce a transitory inflammation within the vein of administration, subsiding shortly thereafter. Symptoms of tenderness, warmth, and redness are indicative of the local response (The Scott Hamilton CARES Initiative [CARES], 2005).

Myelosuppression, a prominent side effect paralleled in chemotherapy and radiation, has serious consequences on the functionality of the immune system (Schneider et al., 2003). The rapid cellular turnover of hematopoietic tissue makes bone marrow a primary target for chemotherapeutic-induced toxicities (Dimeo, 2001). Ultimately, declines in red and white blood cells disrupt aerobic metabolism and immunocompetence (Nieman, 2003).

Moreover, low levels of neutrophils (neutropenia) compromise the ability to combat pathogenic invasion, piloting the development of flu-like symptoms, weakness, and fatigue. Decrements in blood cells and impaired pathogenic defense are noncumulative. A conventional 3-week dosing schedule is based on the standard recovery from neutropenia within 15-21 days of administration (Vargo et al., 2008).

Specific drug interactions augment myelosuppressive toxicities; administration of cisplatin prior to paclitaxel leads to a 33% reduction in paclitaxel clearance from plasma (Wilkes & Barton-Burke, 2008). Accordingly, clinicians administer paclitaxel *prior* to the platinum analog, cisplatin. Adjustments in dosing schedule controls for a portion of side effect severity.

A loss of bone marrow functionality also facilitates anemic conditions. Low levels of hematocrit and hemoglobin compromise the oxygen-carrying capacity. Chemotherapy-induced anemia is related to an impairment of tissue perfusion (Vargo et al., 2008). Compensatory changes are apparent in the form of reduced cardiopulmonary status (e.g., maximal oxygen uptake). Reduced blood oxygenation elicits an impairment of oxygen utilization for ATP synthesis. As a result, energy is obtained through less-efficient anaerobic pathways. Overwhelmed aerobic transport systems perpetuate complaints of fatigue and weakness during low-intensity activities associated with daily living.

Energy and strength deficits are further amplified through gastrointestinal toxicity-derived malnutrition. Nutrient deficiencies, arising from reduced absorptive capacity, reflect energy balance disruption. The acute side effects of chemotherapy, loss of appetite, vomiting, and nausea, drive this process. Compromised intestinal absorption, due to stenosis, ulceration, and fibrosis, can provoke depressed levels of essential elements such as magnesium, calcium, and sodium. As a result, secondary nephrotoxicities can progress from impaired renal function.

Chemotherapy stimulates a wide array of neurotoxicities within the central nervous system. Many platinum analogs elicit sensory nerve damage; the cultivation of peripheral neuropathy arises from heavy metal accumulation within the neuron cell body. Ataxia and weakness are manifest immediately following treatment, progressing into severe sensory deficits over the course of treatment (Wilkes & Barton-Burke, 2008).

Distractibility, memory loss, and the inability to multitask typify only some of the cognitive impairments resulting from chemotherapy; the collective cognitive impairments are often termed, “chemobrain” (Chen et al., 2007). Vestibular setbacks in coordination

and balance reveal further impairment of neural control. Such perturbations within the central nervous system are etiological in the genesis of cancer-related fatigue (Nerenz, Leventhal & Love, 1982).

Mucositis, ulceration, and related tissue damage evidence chemotherapy-induced alteration to mucosal membranes throughout the body. Symptomatic of pulmonary fibrosis, dyspnea develops due to the administration of various alkylating agents. Pulmonary toxicities reflect damage sustained by microscopic alveoli and transpire as inflammation and diminished tissue compliance (Riverside Regional Medical Center [RRMC], 2007).

Potent vesicants, anthracyclines cause severe tissue necrosis when extravasated outside of the vein (CARES, 2005). Moreover, anthracycline therapy elicits direct damage to cardiac tissue. Acute cardiotoxicities emerge as disruptions in EKG waves during and/or immediately following administration. The cumulative nature of cytostatic agents augments the threat of late cardiomyopathies and tachycardia (Ross, 1972; Yahalom & Portlock, 2008).

Though by means of disparate mechanisms, radiotherapy elicits several analogous toxicities with chemotherapy. The extent to which adverse effects develop is dependent upon the total radiation administered as well as length of exposure and number of sessions. The development of toxicities is often dictated by tumor location and associated irradiation target area (Khan, 2003).

A spectrum of cardiovascular complications is associated with mediastinal irradiation and incidental cardiac damage. Pericarditis, inflammation of the sac enclosing the heart, is a common complication following radiotherapy to the chest (Adams et al.,

2003). With diminished tissue capillarization within the target area, blood perfusion and oxygen delivery become compromised. Radiotherapy-induced fibrosis can alter the ventilation-perfusion ratio, eliciting inflammatory distress in the form of pneumonitis (RRMC, 2007).

There is a prevalence of skin reactions of the irradiation target area. Localized lesions and infections may develop following treatment. Edema, hemorrhaging, and inflammation of musculoskeletal and connective tissues cause myofibril disruption and progress deficits in muscle integrity and force production (Schneider et al., 2003).

The risk of second neoplasms following irradiation is a principal concern shared by clinicians and patients alike. Such news can be devastating, having severe implications on psychological well-being (Bioce, 2009, March). Despite its frequent therapeutic use and established efficacy, a growing research base supports the potential of successive malignancy development. Lethal dose radiotherapy induces effective cell kill kinetics; yet, the administration of sublethal radiation can have tumor promoting effects (Kumar et al., 2009). Moreover, when administered over prolonged periods of time, sublethal dosing can elicit effects similar to those seen in atomic bomb survivors (Thompson et al., 1994).

Kumar et al. (2009) demonstrated that a person's relative risk (RR) of developing a second neoplasm increases linearly with time since exposure. With latency periods of 13-18, 24-29, and >30 years since initial exposure, a person's RR is augmented 25%, 47%, and 123%, respectively. The absolute risk of radiation exposure-induced cancers is 1 in 74 people. Not surprisingly, second cancers predominately develop within the field of initial exposure. Clinicians often suggest that patients receiving radiotherapy attend counseling to psychologically prepare for the prospective late effects associated with

primary treatment. The debilitating effects of treatment become more pronounced as toxicities impinge on multiple body systems. Curative therapies, irradiation and chemotherapy, elicit toxicities in a broad scope of body systems and severity can be further amplified on the basis of premorbid conditions, age, treatment modality, etc. (Schmitz et al., 2010). Collective toxicities foster fatigue and psychological distress in the form of depression and anxiety (Speck et al., 2009).

When compounded, these issues compromise patients' QoL (Beesley et al., 2008). Due to the multifactorial origin of cancer-related fatigue it is not feasible to ascertain a distinct cause (Lucia et al., 2003). The accrual of toxicities over the course of treatment advances the destructive side effects; severity of fatigue can be paradoxically amplified through sedentary habits due to catabolism and waning functional capacity (Dimeo, 2001).

Cancer-Associated Oxidative Stress

Critical in a multitude of life processes, adequate supplies of oxygen bring about inherent physiological benefits, but, conversely, have the capacity to yield destructive by-products (e.g., free radicals), inducing a state of oxidative stress (Loft & Poulsen, 1996). It has been postulated that oxidative stress is implicated with both the malignant phenotype and pathogenesis of cancer (Loft & Poulsen, 1996; Toyokuni, Okamoto, Yodoi & Hiai, 1995). Oxidative stress refers to a state in which the generation of free radicals exceeds the capacities of the body's antioxidant (AOX) defense system (Oberley, 2001). Free radicals refer to reactive oxygen species (ROS), which educe both deleterious and favorable effects in biological systems (Valko et al., 2006). A byproduct of respiration, as well as various other biochemical reactions, ROS action depends on the

intricate regulation of the AOX system. With appropriate management, ROS maintain a breadth of physiological processes, including signal transduction and regulation of mitochondrial enzyme activity (Toyokuni et al., 1995).

The characteristic volatility of ROS molecules demands precise control. It is the unpaired electrons of these molecules that provoke a considerable degree of reactivity in ROS. As ROS “pull” electrons from surrounding biomolecules (e.g., DNA, protein, lipids) to fill an incomplete valence, new free radicals are formed, propagating a chain reaction (Valko et al., 2006). A toxic scenario can develop through depressed AOX levels due to aging, cancer, ischemia/reperfusion injury, etc., along with sustained production of ROS (Valko et al., 2006). If the noxious effects of ROS cannot be managed, destruction as per oxidative stress is imminent.

Oxidative stress reflects excessive free radical disruption on biological molecules. Nucleic acid damage/alteration, protein degradation, and peroxidation of lipid membranes educe dysfunction throughout somatic tissue. Base pair transversions of the DNA helix induce alteration to genetic framework, which may be fundamental in oxidative stress-related oncogenesis (Loft & Poulsen, 1996).

Patients receiving anticancer treatments experience a breadth of deleterious toxicities. Oxidative stress serves as one of the primary mechanisms by which chemotherapy and radiation induce damage in nontargeted tissue (Chen et al., 2007). The administration of platinum-based drugs and alkylating agents has a well-recognized association with oxidative stress-mediated damage of healthy tissue. Moreover, according to the FDA, 56 of the 132 approved antitumor agents currently used in cancer treatment are implicated in oxidative stress (Johnson, Williams & Pazdur, 2003).

Treatment-related increases in ROS induce protein damage through the upregulation of the ubiquitin-proteasome pathway (Laviano, Meguid, Preziosa & Fanelli, 2007). This degradation of amino acids can ultimately lead to cachexia of skeletal muscle, a common side effect of cancer treatment (Valko et al., 2006). Increased ROS production leads to the compromise of contractile function and an alteration of mechanisms controlling force development (Toyokuni et al., 1995). Strength deficits related to oxidative stress-induced cachexia can be propagated as patients reduce physical activity and seek periods of rest (Lucia et al., 2003).

While the origin of cognitive declines in the central nervous system remain somewhat elusive, emerging research supports the mechanistic involvement of oxidative stress (Chen et al., 2007). ATP-dependent transporters at the blood-brain barrier (BBB) prevent the free movement of substances into certain areas of the brain.

The proposed mechanism of ROS-induced damage relies on the unrestricted movement of a particular cytokine across the BBB (Ehrman et al., 2003). Following the administration of chemotherapy, circulating tumor necrosis factor alpha (TNF- α) crosses the BBB, triggering the local production of this cytokine in the brain. TNF- α , in turn, induces nitric oxide synthase, responsible for the generation of RNS and subsequent cognitive toxicities (Abd & El-Sawalhi, 2004).

Of paramount concern, cardiotoxicities can significantly compromise the integrity of the heart. The mitochondria-dense composition (approx. 40% cardiomyocyte volume) of cardiac tissue makes the heart especially vulnerable to oxidative stress. Due to the “leakage” of electrons from the electron transport chain (ETC), mitochondria serve as a primary site for ROS production. Induced disruption of normal metabolic processes

augments the threat of late cardiomyopathies and tachycardia (Ross, 1972; Yahalom & Portlock, 2008).

The theory of oxidative stress-induced oncogenesis continues to gain support, as researchers begin to shed light upon the proposed mechanisms (Loft & Poulsen, 1996). An association between anticancer treatment and oxidative stress is well evidenced in the literature (Oberley, 2001). Accordingly, the evolution and pathogenesis of treatment-related toxicities are attributable, in part, to augmented ROS activity. With an understanding of the mechanisms involved in toxicity development, research efforts focus on potential approaches to ameliorate ROS-related toxicities.

AOX mechanisms generally counteract ROS production, maintaining homeostasis within these parallel, yet diametrically opposed, pathways. AOX defense is often compromised in those individuals combatting chronic medical conditions (e.g., cancer, hypertension, muscular dystrophy, etc.). To protect against free radical damage of healthy tissue, patients are frequently encouraged to augment AOX intake.

According to D'Andrea (2005), advice to seek AOX supplementation is convoluted in cancer patients receiving radiotherapy, suggesting that “supplements do more harm than good”. Because ionizing radiation relies on free radical generation as a means for cancer cell destruction, AOX supplementation may reduce the efficacy of therapy. Furthermore, it's been suggested that antioxidants may collectively protect healthy and malignant cells.

A recent publication by Ross (2010) challenges conclusions drawn by D'Andrea (2005). In an attempt to redress the stance taken on AOX supplementation in cancer survivors, the original work is described as a “selective and distorted report”. Misleading,

over simplistic conclusions are attributed to premeditated research outcomes. Scientific fallacy is indicated by the use of research that neither demonstrates objective improvement, nor proposed harm in consequence of AOX ingestion. With only a brief discussion of two non-enzymatic vitamins (e.g., Vitamin E and C), the article lacks conclusive evidence to recommend the blanket rejection of AOX supplementation in patients receiving cytotoxic therapy.

Due to a lack of explicate guidelines, the American Cancer Society does not currently recommend heightened AOX intake for those patients receiving cytotoxics, as many dietary supplements (e.g., daily multi-vitamin) already contain levels of antioxidants above the recommended daily intake (Doyle et al., 2006). The effects of specific antioxidant types/dosing on various types of cancer require further elucidation. Until agreement is met in regard to AOX supplementation, the most probable benefits will be achieved through a balanced diet, consisting of approximately 100% of daily values of micronutrients (Doyle et al., 2006).

There is a growing body of research to support exercise training as a potential strategy in the management of ROS-induced toxicities. Following a single bout of exercise, a transient upregulation of total antioxidant capacity is demonstrated by acute increases in enzymatic AOX, superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT). In order to achieve enduring AOX enhancement, more chronic stimulation (e.g., exercise training) may be necessary (Finaud, Lac & Filaire, 2006). Paradoxical to the proposed benefits of exercise, contracting skeletal muscle also generates free radicals through a transient amplification of oxygen flux within the mitochondria and consequential electron leakage (Clanton, Zuo & Klawitter, 1999).

High levels of free radicals due to prolonged or intense exercise lead to the oxidative damage of cellular constituents (Powers & Jackson, 2008). Yet, a low-to-moderate production of oxidants serves various cellular regulatory roles. According to Finaud et al. (2006), positive adaptations of AOX pathways lead to less oxidative stress following moderate intensity exercise training.

Conversely, the accumulation of intense exercise may trigger free radical generation and consequential cellular damage and injury. To ensure attainment of proposed benefits demands an understanding of training principles (e.g., frequency, intensity, duration, and progression) to establish exercise dose. Moreover, to establish appropriate prescriptive exercise for cancer survivors, exercise parameters must be understood with respect to this clinical population (Schneider et al., 2003).

Exercise induces transient but significant changes in immune response, which could have severe implications for patients undergoing anticancer treatment due to pre-existing immunodepression. The J-Curve Model illustrates the relationship between exercise dose and immune function (Nieman, 1994). Notable benefits of moderate intensity training are evidenced by the preservation of AOX status, which supports immune cell (e.g., T-cells, NK cells) functionality (Gleeson, 2007; Schneider et al., 2003).

ROS-related perturbations of protein metabolism evolve during and following treatment, leading to skeletal muscle wasting (e.g., cachexia), which is perpetuated by reduced physical activity (Al-Majid & Walters, 2008). Circulating ROS disrupt cytokine signaling, which promotes protein degradation through ubiquitin-proteasome pathways (Laviano et al., 2007). Cancer-related cachexia is associated with augmented levels of

malondialdehyde, a marker of phospholipid peroxidation and total body oxidative stress. The degenerative loss of muscle mass and strength associated with sarcopenia is attributed to analogous etiological mechanisms (Meng & Ju, 2010). Alleviation of cancer-related cachexia through exercise training demands further clarification of AOX mechanisms.

Based on the research of Fisher-Wellman, Bell and Bloomer (2009), exercise training serves as a remedial approach in the attenuation of oxidative stress within various chronic conditions. The impact of exercise has been well established in an array of chronic diseases, yet there is a deficit of research investigating the effects of exercise on AOX/ROS status specifically in the cancer population.

In patients of coronary heart disease and conjunctive heart failure, the upregulation of AOX defense following exercise training is evidenced by heightened activity of enzymatic antioxidants (e.g., SOD, GXP, and CAT) and a reduces lipid peroxidation of cellular membranes (Linke, Adams & Schulze, 2005; Leaf, Kleinman, Hamilton & Deitrick, 1999). Similar findings have been established in diabetic populations and patients with cardiovascular disease (Fisher-Wellman et al., 2009).

At this point, one animal-model study has investigated the effects of training in attenuating treatment toxicities; conclusions supported exercise as an amelioration approach in tumor-bearing mice (Kanter, Hamlin, Unverferth, Davis & Merola, 1985). Kanter et al. (1985) assessed the effects of a 21-week swim intervention on AOX enzymes and cardiotoxicity in mice receiving doxorubicin (DOX). Mice were randomized into either a swim-trained or sedentary control group; all mice received intravenous DOX biweekly over the course of the study. Results indicated severe

cardiotoxicity in sedentary drug-treated mice. In comparison, swim-trained animals receiving the same DOX dosage revealed attenuated damage. Measured at 9 and 21 weeks, concentrations of SOD, GXP, and CAT in the liver, heart, and blood were all significantly elevated in trained animals ($p<0.01$), demonstrating an upregulation of AOX defense.

ROS-associated toxicities develop during treatment and, at times, progress long after completion; the noxious effects can ultimately compromise various dimensions of patients' lives. It has been proposed that exercise may attenuate toxicity through an upregulation of AOX enzymes. Augmented AOX activity enhances the body's capacity to combat free radicals and recover from inflicted damage. While other chronic diseases indicate a range of benefits relating to habitual exercise, additional research is necessary before claims can be extrapolated to cancer.

Exercise Training and Attenuation of Treatment-Related Toxicities

The projected 5-year survival rate across all cancers and disease stages has climbed to 66% (ACS, 2009a). Improved prognosis and survivorship now demand a shift in research efforts. Now regarded as a potential primary, secondary, and adjuvant treatment, exercise boasts restorative properties for an array of toxicities, enhancing the quality and quantity of life (Courneya, 2003; Speck et al., 2009).

In spite of the recognized prognostic and therapeutic value, cardiopulmonary exercise testing in the field of oncology has been limited, as skeptics deliberate upon the safety and practicability in this clinical population (Jones et al., 2007). An investigation performed by Jones (2010) reveals exercise testing as feasible and appropriate in cancer populations when symptom-limited protocols account for any contraindications.

Advantageous to the clinical oncologist, exercise testing allows for an objective evaluation of functional capacity to provide an array of prognostic and therapeutic information pertaining to disease management.

Exercise interventions evidence reduced fatigue and enhanced QoL and functional capacity (Burnham & Wilcox, 2002; Schneider et al., 2007). Given the multitude of physiologic and psychological effects, current research advocates regular physical activity as a lifestyle change to enhance the health status of cancer survivors (Lucia et al., 2003; U.S. Department of Health and Human Services, 2008).

The effect of individualized exercise on cancer-related parameters, fatigue, QoL, and functional capacity, remains central to current investigation. Grueling treatment regimens may be curative over time but at the expense of patients' physical capacity and psychological and cognitive functioning. The most frequently reported symptom, cancer-related fatigue, pervades and intensifies as treatment continues and ultimately compromises QoL and survivability (Durak, Lilly & Hackworth, 1999; Visovsky & Dvorak, 2005).

Early approaches addressing somatic perceptions of fatigue were empiric, leading to self-perpetuated symptomology. Recommendations to reduce physical activity augment catabolic pathways, inducing acute muscle deconditioning and cachexia. While many etiological mechanisms exist to explain pathologic fatigue, it is the metabolic distress due to inactivity and treatment-induced alteration of energetic pathways that bring about the customary lack of energy in performing everyday tasks (Dimeo, 2001; Dimeo, Schwartz, Wesel, Voigt & Thiel, 2008).

Conclusions drawn from a systematic review by Smets et al. (1993) depict a wide ranging prevalence of fatigue, varying by cancer site, disease stage, and treatment modality. As a population, irrespective of the abovementioned characteristics, fatigue affects approximately 70% of all patients, and remains the symptom most frequently reported (Visovsky & Dvorak, 2005; Dimeo, 2001). A multidimensional etiology makes alleviation of cancer-related fatigue complex (Smets et al., 1993).

Dimeo et al. (2008) studied the effects of a 3-week combined exercise intervention in 32 cancer patients, post high-dose chemotherapy. The subject population was consisted of mixed diagnoses including solid tumors (e.g., breast, bladder, prostate, testicle, and cervix), Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and myelodysplastic syndrome. Subjects performed treadmill walking ($80 \pm 5\%$ HRR) and resistance exercises of large muscle groups. Significant improvements in functional status were documented as per the workload achieved at anaerobic threshold ($p < 0.0001$). Moreover, global fatigue scores decreased by 25%, indicative of reduced psychological distress. Enhanced functional capacity was associated with reductions in complaints of fatigue during normal daily activities, owing to improvement in blood oxygen transport as well as capillary and mitochondrial density (Lucia et al., 2003; Dimeo et al., 2008).

Results are consistent with those found in a 1997 pilot study, in which the correlative relationship between physical deficits and psychological distress was assessed in 78 cancer patients of solid tumors or hematological malignancies (Dimeo et al., 1997). Subjects with impaired physical performance indicated significantly higher scores for mental distress ($p < 0.005$).

In addition, a strong correlation between fatigue and depression ($r = 0.68$) further elucidates upon emergence patterns of psychological impairments, which could provide insight for rehabilitative strategies (Dimeo et al., 1997, 2008). With up to 30% of cancer patients complaining of persistent adverse effects long after treatment, novel remedial approaches are welcome (Berglund et al., 1991).

Exercise augments the work performed by the cardiac and respiratory systems. As a result, adaptive changes occur in plasma volume, lung ventilation and perfusion, and oxidative enzyme concentration. Such adaptations elicit ATP production through more energy efficient oxidative pathways due to improvements in oxygen carrying-capacity, transport and delivery to working muscles. According to Schneider et al. (2003), the physiological benefits of exercise oppose toxicities generated during antitumor treatment. This 'mirror effect' minimizes cancer related fatigue through improved cardiovascular efficiency.

The manifestation and progression of fatigue during treatment highlights the cumulative nature of treatment modalities. Because the intensity of fatigue can endure long after cessation of treatment, research efforts are now evaluating rehabilitative exercise programs undertaken amid treatment, in order to determine if persistent effects are better eluded. Adamsen et al. (2006) designed a multi-modal exercise program to investigate its impact within a sample of 66 cancer patients undergoing cytostatic treatment. Because there is evidence to support that fatigue and physical impairment develop irrespective of cancer type, subject population was inclusive, comprising six different hematological malignancies and thirteen types of solid (oncological) tumors

(Smets et al., 1993; Lucia et al., 2003). Few studies have been carried out to allow generalizability across comprehensive cancer sites.

The 6-week study consisted of resistance and cardiovascular training, as well as relaxation and body awareness training. High-intensity exercises, resistance training and cycle ergometry, were performed at 85-95% 1RM and 60-100% heart rate max, respectively. Low-intensity exercises focused on balance, coordination, tension reduction and relaxation. Nonconsecutive days were allotted between high- and low-intensity workouts.

In order to assess the effects of training, two physiological tests (1RM & VO₂max) and two psychological questionnaires (MOS SF-36 & QLQ-C30) were conducted at baseline and again after six weeks of training. Upon completion, there were significant improvements in aerobic capacity ($p < 0.001$). For all subjects, the average percent change in maximal oxygen consumption was +16%. Augmented strength gains led to significant improvements in leg press (+46%), chest press (+41%), and lat pull down (+36%) resistance exercises.

Along with augmented functional capacity, questionnaire data revealed significant improvement in the level of vitality ($p = 0.002$), perceptions of health ($p = 0.009$), and alleviation of fatigue ($p = 0.008$). With regards to the improvements achieved in physical and psychological status, no significant difference existed between oncological and hematological patients. This study encourages participation in exercise for those receiving adjuvant therapies, as it manages the treatment-related symptoms, enhancing psychological well-being and physiological capacity.

In agreement with Adamsen et al. (2006), Courneya et al. (2007) evaluated the effects of exercise in a sample of breast cancer patients receiving adjuvant chemotherapy. Divergent from universal participation in multimodal exercise, subjects were randomly assigned to one of three groups: usual care (UC), supervised resistance exercise (RET), or supervised aerobic exercise (AET). This three-armed, randomized trial sought to determine if a particular exercise component (resistance vs. aerobic) led to more significant beneficial effects in patients receiving cytostatic treatment.

The relative dose intensities (RDI) were higher in both exercise groups (RET, 89%; AET, 87%), when compared to subjects receiving standard care (UC, 84%). Findings indicate that the true dosing schedule administered to the exercise groups was closer to the pre-established regimen. Ultimately, reductions in RDI, because of delays in delivery or reduced dose, can have implications on disease prognosis (ACS, 2010; Dizon, 2010).

When compared to those receiving standard care, both exercise groups showed improvement of psychological parameters: QoL, depression, self-esteem and anxiety. The alteration of physiological parameters is specific to modality of exercise performed. Resistance exercise led to enhanced physical functioning related to muscular strength ($p<0.001$), and lean body mass ($p=0.015$), whereas aerobic exercise improved the outcome measures of aerobic fitness ($p=0.006$) and percent body fat ($p=0.076$). Researchers advocate a ‘whole body’ approach of exercise programming, employing resistance and aerobic components for more complete benefits (Courneya et al., 2007; Schneider et al., 2003).

Moderate intensity, multidimensional training is a recurrent design employed in oncology studies. Yet, investigation of either aerobic exercise or resistance training has revealed related benefits to those found in combined studies (Burnham & Wilcox, 2002). The outcome measures common to aerobic exercise studies include aerobic capacity, depression, anxiety, QoL, fatigue, and emotional distress (Visovsky & Dvorak, 2005).

Dimeo, Rumberger & Keul (1998) suggested aerobic exercise as a potential therapeutic intervention for cancer-related fatigue. Subjects (n=5) in this study performed treadmill walking each day for six weeks to determine the effects on fatigue and functional status. The training speed employed corresponded to a lactate concentration of $3 \pm 0.5 \text{ mmol} \cdot \text{L}^{-1}$ and was increased with evidenced training adaptation (e.g., reduced exercise HR and $[\text{LA}] < 2.5 \text{ mmol} \cdot \text{L}^{-1}$).

Following reassessment, there was significant improvement in physical performance as depicted by training distance/session as well as calculated $[\text{LA}]$ and submaximal HR at a specified workload. In addition, reductions in subjective fatigue scores allowed all subjects to return to normal daily activities without limitations.

The professed merit of aerobic exercise is evidenced by the heightened physical status and attenuated fatigue. The effect of aerobic training on psychologic and physiological parameters was also assessed by Durnham and Wilcox (2002), with emphasis on variable intensity aerobic exercise. Low- and moderate-intensity exercise, distinguished by the percentage of heart rate reserve (HRR), was performed at 25-35% HRR and 40-50% HRR, respectively.

Upon completion of the ten week study, no significant difference in physical parameters, aerobic capacity and body fat percentages, existed between the exercise

groups; as a result, final analysis was performed on combined exercise groups versus controls. Resembling the conclusions drawn by Dimeo et al. (1998), physical functioning and QoL status improved ($p < 0.001$) in the exercise group versus sedentary controls. A significant reduction in body fat percentage ($p < 0.001$) illustrates the benefits related to body composition resulting from exercise participation.

Research suggests that regular physical activity is protective against a host of chronic diseases (Nieman, 2003). Specifically, habitual exercise is associated with reduced cancer risk, owing to the stabilization of energy balance and circulating hormone levels following activity (Fair & Montgomery, 2009). As a primary intervention, exercise boasts a 20-40% reduction in cancer incidence (Holmes, Chen, Feskanich, Kroenke & Colditz, 2005).

According to an updated meta-analysis by Speck et al. (2009), the remedial properties of exercise for cancer survivors continue to gain interest and support, as the volume of literature has more than doubled in the past five years. Exercise as an adjuvant, rehabilitative strategy has been recognized as feasible and valuable in supervised settings (Schneider et al., 2007; Viscosky & Dvorak, 2005). Moreover, the multitude of physiological adaptations attenuates the corrosive toxicities related to treatment. Specifically, improved somatic parameters and physical functioning indicate favorable health outcomes. Inclusive benefits are attained through individualized regimens, involving aerobic and strength components (Jones et al., 2007; Ingram & Visovsky, 2007).

Historically, the preponderance of exercise studies has targeted breast cancer survivors, making extrapolation to all cancer sites and stages impractical (Courneya et al.,

1999). Growing evidence is becoming available to support exercise participation across cancer sites (Dimeo et al., 2008; Klika, Callahan & Golik, 2008). In a recent publication, Schmitz et al. (2010) outlined current research evaluating the effects of exercise training by cancer site. The lack of studies across cancer sites demands that progress be made. Currently, efficacy of exercise programming for cancers of the prostate and colon have been evaluated in 12 and 4 studies, respectively. Outcomes of exercise interventions for hematologic malignancies either treated with hematopoietic stem cell transplantation (HSCT) or in the absence of HSCT, have been evaluated in 11 and 4 studies, respectively.

The most prominent deficiency of exercise research is apparent in gynecological cancers. While 5 mixed sample studies have included a small proportion of gynecologic patients (n=5-15), only one intervention has exclusively assessed this specific population. Conclusions drawn from mixed sample studies indicate enhanced psychological functioning (e.g., QoL, self-efficacy, and wellbeing), reduced fatigue, and improvements in cardiorespiratory fitness following a structured exercise intervention (Berglund, Bolund, Gustafsson & Sjoden, 1994; Courneya et al., 2003; Hartvig, Aulin, Wallenberg & Wagenius, 2006; Thorsen et al., 2005; van Weert et al., 2005). No specific assumptions were made about exercise with regard to cancer type.

Undertaken by von Gruenigen et al. (2008), the current solitary gynecologic study is considered a weight loss intervention, with the primary endpoint of weight change. The study sought to assess the effects of a lifestyle intervention in 45 early-stage, overweight and obese endometrial cancer survivors. Subjects were randomized to either a 6-month lifestyle intervention (LI) or usual care (UC) control group. Parameters to be examined

included weight change, physical activity, and dietary intake. Subjects in the LI group attended group and individualized counseling sessions with a registered dietician and psychologist. Topics discussed in group sessions included weight loss readiness, exercise, and portion control. In regard to exercise, subjects were coached to gradually increase walking and other routine physical activities. Progress was monitored via a pedometer.

Upon completion, changes in body mass for LI and UC were -3.5kg and +1.4kg, respectively. Though reduced in LI subjects, caloric intake was not significantly different from the control group. Enhanced exercise participation in the LI group was evidenced by the increase of 17 MET/week compared to the UC group ($p=0.025$). Because exercise was performed on subjects' own accord, measureable effects were limited to changes in steps/day, as dictated by the pedometer.

Thus, it was not possible to quantify time and intensity. Lack of a structured exercise intervention and reliance on self-reported exercise participation (Leisure Score Index) highlight research gaps. Because weight change served as the primary endpoint, with changes in physical activity considered secondary health outcomes, the feasibility and effectiveness of this intervention, in regard to exercise effects, is suspect.

Research investigating the effects of exercise in gynecological cancer survivors is scant. Further evidence is needed to validate specific health outcomes (e.g., QoL, fatigue, and functional capacity). In addition, the effects of exercise at various time points on the cancer continuum should be investigated to determine potential risks and benefits (Courneya & Friedenreich, 2007). Secondary conditions such as lymphedema are the unfortunate consequence of cancer and its treatment. In view of the complexities

associated with lower limb lymphedema and its management, additional research is warranted to determine if exercise is feasible and appropriate under such circumstances.

CHAPTER III

METHODOLOGY

Experimental Design

The purpose of this case study is to determine whether an exercise undertaken by a late-stage endometrial cancer survivor receiving high-dose chemotherapy is feasible and appropriate. More specifically, this in-depth analysis investigates the effects of a multimodal exercise intervention on a selection of physiologic and psychological parameters. Oxidative stress was also assessed through a hematological assay of reactive carbonyl species concentration. Baseline measures were gathered prior to the start of exercise, with Nadir blood draws obtained throughout the intervention every third week, which was 10 days following a chemotherapy treatment. Initial patient screening was conducted, which included the assessment of physical capacity, as per peak aerobic capacity (VO_{2peak}) and one repetition maximum (1-RM), and an evaluation of psychosocial status (e.g., QoL, depression, and fatigue).

From results gathered during the assessment, an exercise regimen was designed and implemented by a trained Cancer Exercise Specialist at the Rocky Mountain Cancer Rehabilitation Institute (RMCRI) at the University of Northern Colorado in Greeley, Colorado. At 3- and 6-months, assessment procedures were again performed to track progress and modify exercise, if necessary. An hour in length, supervised exercise

sessions were held on Tuesday, Thursday, and Saturday of each week. It was assumed that the subject would not participate in additional exercise beside that indicated by the intervention. Each workout incorporated a combination of strength and aerobic components. Blood pressure was measured both prior to and upon completion of each training session, with heart rate (HR) and ratings of perceived exertion (RPE) measured throughout the protocol. Within the exercise logbook, there was allotted space to make additional notes of progress, perceptions, lab results, etc.

Participant

Due to the nature of case study research, a single subject was recruited for this study. The basis for employing case study methodology was to perform a comprehensive analysis in an area currently lacking conclusive research. A faculty member at an institution for higher education, the female subject was 60 years of age at the start of this case study and had given written consent to participate in this study. An irregular Pap test in December of 2009 led clinicians to order an endometrial biopsy, which revealed the endometrial adenocarcinoma. The tumor was moderately differentiated and 4.9 cm³ in size with pelvic nodal involvement. There were no para-aortic nodes affected at the time of discovery.

Tumor staging was complicated by a 1994 diagnosis of cervical cancer which, at the time, was handled by performing a curative-intent hysterectomy to remove the tumor and reduce the chance of recurrence. Oncologists responsible for discovering the most recent tumor, however, deemed the primary cancer had been misdiagnosed. What was determined cancer of the cervix was, in fact, cancer of the endometrium. At the beginning of this investigation, the cancer stage was deemed, 'unspecified'.

To make matters more complex, the subject had received a lifetime dose of ionizing radiation in 1997 (3 successive days, internal brachytherapy; 25 treatments/5wk, external beam) in an effort to treat and cure the primary neoplasm. Radiation treatment for the recurrent cancer would likely provoke lethal implications. As a result, the selected course of action was 6 conventional chemotherapy treatments of paclitaxel and carboplatin through intravenous delivery. The initial assessment and baseline hematological analysis were performed a day prior to the first chemotherapy cycle. Dosage schedule involved a target AUC of 5.0-7.5 every 3 third week. Sequential infusion of paclitaxel *then* carboplatin effectively disrupts tumor kinetics by means of covalent DNA binding, as evidenced by an impediment of tumor growth.

Preliminary Paperwork

The subject was given explicit detail of the study's purpose and procedures, as outlined in the informed consent, and asked to complete the following pre-screening paperwork: cancer history, complete medical history, cardiovascular disease risk assessment and lifestyle/activity evaluation. All prescreening paperwork collected from the subject was reviewed and verified upon arrival for the initial assessment. From the medical and cancer histories, any concurrent comorbidity could be evaluated so as to assess possible limitations and considerations relevant to the exercise prescription. The subject's lifestyle, with regard to activity level, dietary intake, and regular tobacco and alcohol use, was illuminated through responses on the lifestyle/activity evaluation. Initial values for blood pressure (BP), HR, and oxygen saturation (PO₂) were determined. Height and weight were measured and recorded, as this information would be necessary for completing a portion of the assessment protocols. Any relevant morbidity (coexisting

medical conditions, all OTC and R_x medications, etc.) that could potentially be contraindicated to participation in this study were assessed prior to the start of exercise.

Distribution and Interpretation of Psychological Indexes

Prior to the initial assessment, along with each reassessment thereafter, the following psychological indexes were completed in their entirety: Piper Fatigue Scale, Beck Depression Inventory, and Ferrans & Powers Quality of Life Index Cancer Version III. Results from the Piper Fatigue Inventory yield a global score, which indicates the overall extent of cancer-related fatigue (CRF). Values calculated for behavioral, affective, sensory, and cognitive/mood subscales can demonstrate specific dimensions of a patient's life most afflicted by CRF. Collectively, the 4 subscales compose the 22-item inventory. Possible scores for each subscale range from 0 to 10. Total fatigue scores also range from 0 to 10 and are computed by determining the average of all subscales. A total score of 0 is indicative of a cancer survivor with no perceptions of fatigue. Scores ranging from 1-3, 4-6, and 7+ indicate mild, moderate and severe fatigue, respectively (Piper et al., 1998).

Depression, a common side effect following antineoplastic treatment, was assessed using the Beck Depression Inventory. Each of the 21 items on the Beck scale is comprised of 4 declarative statements corresponding to values ranging from 0 to 3. 0-value statements reflect the most extreme *negative* position. Contrary assertions, valued as 3, indicate the most extreme *positive* statement. Numerical values, 1 and 2, signify some degree of neutrality though one end of the spectrum may be favored. Values for all 22 items are added; scores range from 0 to 63 with 0 indicative of no depression and >40 reflecting extreme depression (Salkind, 1969).

Utilizing Ferrans & Powers Quality of Life Index Cancer Version III, QoL was assessed at baseline, 3-, and 6-months. This 66-question index evaluates a) subject satisfaction with and b) importance placed on the following dimensions of inquiry: social, psychological, family, and health. This Ferrans & Powers assessment has an impressive internal reliability ($\alpha=0.95$) and validity ($r = 0.80$). High total scores reflect agreement between the satisfaction with and importance placed on each dimension, which ultimately corresponds to an appropriate state of well-being (Ferrans & Powers, 1985).

Assessment of Pulmonary Function

Pulmonary function was assessed by means of a FlowmateTM (Spirometrics, Grey, ME) spirometer. Predicted normal values were based on the subject's physical characteristics: height, weight, age, race, and tobacco use. The subject was given detailed instructions on performing the test. The rationale and clinical value of spirometry analysis were also discussed. In order to be considered a valid assessment of lung function, the forced expiratory volume (FEV_1) of two consecutively performed tests had to be within 0.2 L of each other. If a third maneuver was required and, still, the criterion wasn't met, results were not interpreted. On the final printout, expected and measured values of forced vital capacity (FVC) were also provided, which portrayed the total volume of air expired during the maximal forced exhalation effort.

Variance between the predicted norm and the measured value was used to identify and quantify functional abnormalities; specifically, the ratio FEV_1/FVC can detect impairments of the respiratory system. Ratios of >0.7 are considered normal; deviations, in the form of reduced FVC and total ratio value <0.7 , are deemed as restrictive and obstructive ventilatory impairments, respectively.

Assessment of Muscular Strength

Muscular strength was assessed using 1-repetition maximum (1-RM) testing protocol for the following exercises: lat pull-down, leg press, chest press, and shoulder press. All protocols were carried out using the Cybex® Eagle Single Station Pin Selection Series. An expertise in the field of exercise physiology as well as a history as a collegiate athlete fostered the subject's familiarity with 1-RM testing. For the purpose of warming-up musculature, a "very light" weight was selected that could be lifted for 5 to 10 repetitions. Weight was added in approximately 5 to 10 pounds increments, and 2 additional sets were performed of 3 to 5 repetitions. With the slow augmentation of weight, the load begins to approach that of the first maximal attempt. Two additional sets of 1 repetition were performed. Between all lifts, 1 minute rest intervals were allotted, to allow sufficient recovery (Warpeha, 2010). Weight was increased in 2.5 lb. intervals until failure. The last successful attempt was deemed the 1-RM weight. The warm-up and gradual progression was repeated for each exercise.

Assessment of Cardiorespiratory Fitness

The RMCRI treadmill protocol was used to evaluate the subject's cardiorespiratory fitness (CRF). Adapted in 2010, this treadmill test was designed with the cancer survivor in mind, and is to be carried out in this clinical population. All details of testing protocol were given to the subject. Contraindications against performing the test were considered. With no pre-existing comorbidities of concern, the test was initiated. Using the MedGraphics® Diagnostics System and BreezeSuite™ computer software, RMCRI protocols were programmed into and stored on the hard drive, allowing researchers to monitor vitals (e.g., BP, HR, and RPE) during the test without the added

hassle of manually adjusting workloads. Stages were 1 minute in length with intensity adjusted as a means of belt speed, incline, or both each successive minute. Stage 1 walking speed was 1.0 mph, increasing by 0.5 mph until stage 6. Stages 1 through 4 maintained a constant grade of 0.0%. The first modification to grade was made at stage 5; this 2.0% incline was maintained through stage 6. From stage 7 until stage 21 or volitional fatigue, grade and belt speed increased 1.0% and 0.1 mph, respectively.

HR and PO_2 were recorded every minute with BP and RPE recorded every third minute until test completion. The stage attained at test termination corresponded with a $\text{VO}_{2\text{peak}}$ based on age, gender, and handrail use. Finally, the CRF classification corresponding to the aerobic capacity ($\text{mL/kg}^{-1}/\text{min}^{-1}$) was determined.

Balance Assessment

The modified Clinical Test for Sensory Interaction on Balance (mCTSIB) was employed to assess deficits in balance. This test has the capacity to discriminate between normal and abnormal balance performance but cannot detect specific patterns of sensory dysfunction. Results of mCTSIB testing may elucidate upon the development of vestibular setbacks related to cancer treatment. Each phase of this 4-part protocol is 30 seconds in length. The progression of testing phases includes: 1) eyes open, firm surface 2) eyes closed, firm surface 3) eyes open, foam pad 4) eyes closed, foam pad. Each stage corresponds to a numerical score of 30. Thus, a perfect score of 120/120 indicates that a subject maintained his or her balance during the entirety of all 4 stages. Incomplete stages are assigned a score of 0. Staggering, requiring spotter assistance, etc serve as grounds for test termination. Finally, the total score was calculated and balance classification determined.

Exercise Intervention: Development and Implementation

Outcomes of the initial assessment were used to develop an exercise prescription with the primary objective of maintaining physiological and psychological functioning while the subject underwent chemotherapy. The secondary endpoint, reactive carbonyl derivative response, was assessed to determine if exercise could alleviate oxidative stress-related damage. The subject underwent 6 cycles of PC while involved in the study.

Supervised training was carried out on 3 non-consecutive days per week for 6 months. Multidimensional exercise was performed for approximately an hour. Sessions consisted of moderate intensity aerobic, strength, and balance components for 25, 30, and 5 minutes, respectively. Initially, muscular strength exercises consisted of 2 sets of 10 repetitions, performed at 70-75% of estimated 1-RM. Exercises included: leg press, leg curl, leg extension, chest press, lat-pull down, and shoulder press. All exercises were completed on the Cybex® Eagle Single Station Pin Selection Series, just as they had been for assessment procedures. Prior to each exercise session, researchers reviewed a series of 10 questions to document any changes in medication, health status, pain/soreness resulting from previous workout, etc. Responses could highlight a need to reduce training intensity.

Using the modified 0-10 Borg RPE scale, subject-dictated perceptions of intensity were used to adjust the weight when necessary. RPE values <4 were used to increase the weight for the next workout; reduced RPE values were indicative of positive training adaptations. When appropriate, the progression of augmenting weight occurred in 2.5 pound increments. The initial target RPE range was 6 to 8, which was used as an

indicator of moderate intensity in this study. HR and PO₂ data were collected after completing both sets of a given exercise, and RPE values were assessed after each set.

Due to side effect development 3 to 4 days after the administration of chemotherapy, the intensity of training was reduced to 30-35% 1-RM. Repetitions and sets were held constant at this reduced percentage of maximum effort. In order to attribute physiological changes to the designed intervention, the subject was directed to refrain from additional physical activity, apart from normal living, while participating in the study.

Protein Carbonyl Determination & CBC Analysis

Blood samples were obtained at the Cancer Center at Northern Colorado Medical Center 10 days following each chemotherapy treatment (Nadir). Blood was placed into one of two tubes: either a 3 mL purple top tube, indicating the presence of ethylenediamine tetraacetic acid (EDTA) or a 5 mL red top tube without the anticoagulant. Samples collected at the hospital were placed on ice and returned to the biochemistry laboratory at UNC for centrifugation and further analysis. Test tubes were brought to room temperature prior to separation to ensure samples were adequately thawed. Tubes were spun for 10 minutes at 3,000 revolutions per minute (rpm). Using a micropipette, supernatant serum was removed from the sample lacking anticoagulant and evenly distributed into two 100 µL snap tubes. Tubes were immediately frozen as -20°C for later analysis. Extraction procedures were repeated for the blood sample with EDTA; plasma was also stored at -20°C.

OxiSelect™ Protein Carbonyl ELISA techniques were carried out for the detection and quantification of oxidative stress in collected blood samples (Cell Biolabs,

Inc., San Diego, CA). The amount of protein carbonyls in collected samples were determined by comparing the absorbance to that of known BSA standards. Methods were carried out as specified by the OxiSelect™ product manual; detailed procedures can be viewed at www.cellbiolabs.com. Results of complete blood counts (CBC), attained during Nadir blood draws, were reviewed and included in the results section. No additional analysis was employed for this portion of hematological parameters.

Statistical Analysis

Graphical analyses of outcome measures were primarily used to assess trends in the data. In some cases, Wilcoxon Signed Ranks was used to determine if significant changes had occurred in any of the assessment outcome measures. Statistical analyses were performed using GraphPad Prism Version 5 for Windows (GraphPad Software, San Diego CA). For all analyses, a *p*-value of 0.05 was considered statistically significant

CHAPTER IV

RESULTS

Change in Assessment Outcome Measures

Physical characteristics are presented in Table II. The initial assessment was performed on January 20, 2010 with first and second assessments performed at 3 months (April 1, 2010) and 6 months (June 25, 2010), respectively. Six cycles of chemotherapy were administered over the course of the study. Dates of treatment included January 21, February 12, March 5, April 8, April 30, and May 21, 2010. Physical characteristics measured at each assessment time point are presented in Table II. Height and leg circumferences remained stable over the course of the study, with 7% increases in both weight (166 to 178 lb) and BMI (27.6 to 29.6). At the start of this intervention, staging criteria for the endometrial adenocarcinoma was unspecified. On June 20, 2010, clinicians determined the TNM criteria: T3, N1, and M0. The tumor was staged as IIIC1.

Table 1. *Physical Characteristics of Case Study*

Physical Characteristic	Baseline	3-Month	6-Month	% Δ_{i-f}
Height (in)	65	65	65	-
Weight (lb)	166	172	178	+7%
Body Mass Index (BMI)	27.6	28.6	29.6	+7%
Thigh Circumference (in)	20	20	20	-
Lower Leg Circumference (in)	15	16	15	-

Strength and aerobic assessment data are presented in Tables 3 and 4, respectively. Wilcoxon Signed Ranks statistical analysis revealed no significant difference in the 1-RM weight for any of the strength exercises ($p=.25$, each). Trends in muscular strength are depicted in Figure 1. Between initial and 6-month assessments, total gains of 17%, 21%, and 9% were determined for the lat pulldown (95 to 115 lb), shoulder press (55 to 70 lb), and leg press (225 to 245 lb), respectively. The weight lifted for the chest press decreased approx. 17% between baseline and final assessment time points (90 to 75 lb). Collectively, the total percent change in upper and lower body strength was +21% and +9%, respectively.

Table 2. *Effects of Exercise Intervention on Muscular Strength*

Exercise	Baseline	3-Month	6-Month
Lat Pulldown	95	107.5	115
Chest Press	90	80	75
Shoulder Press	55	60	70
Leg Press	225	235	245

Note. All values are presented as weight in pounds (lb)

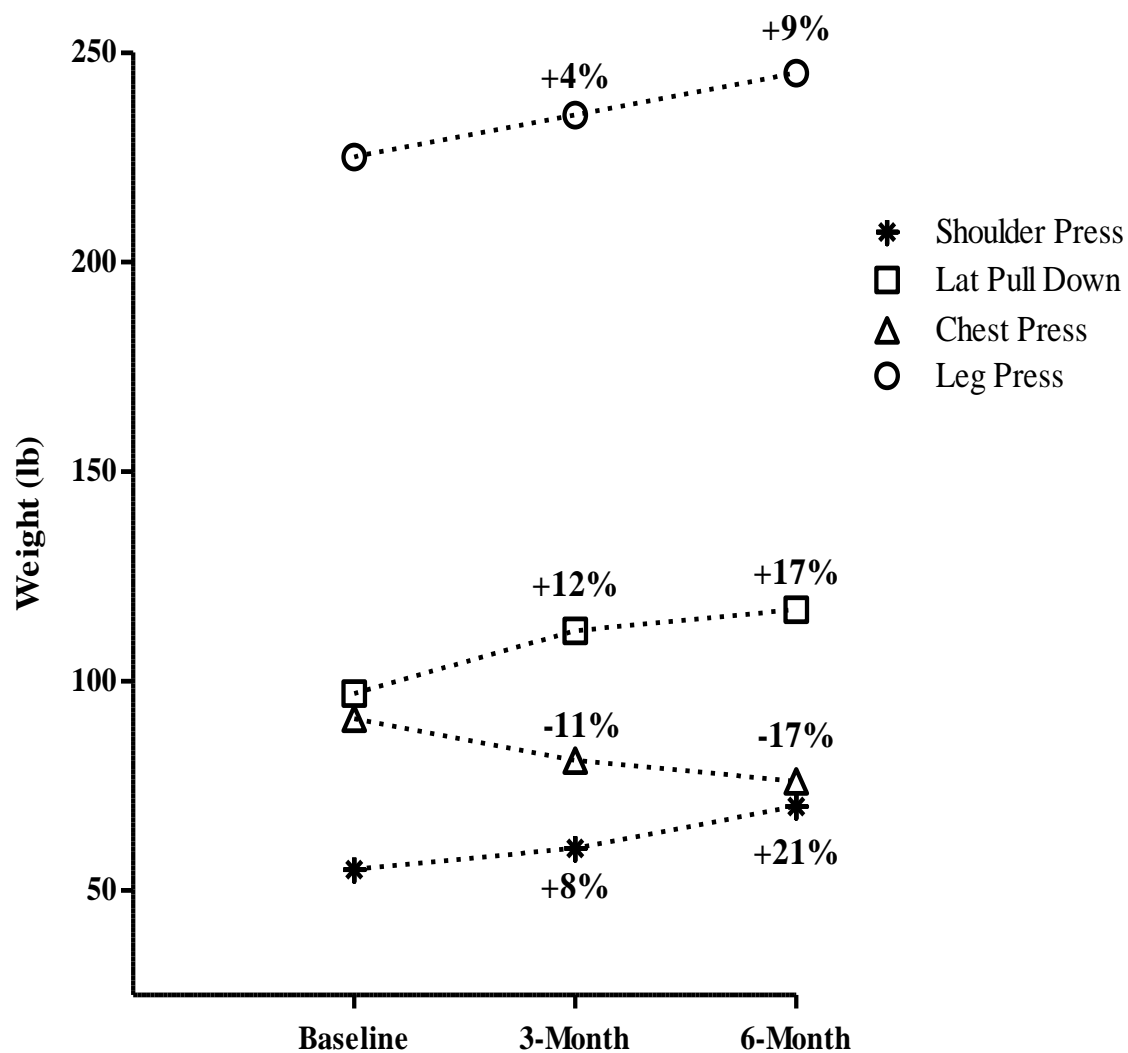


Figure 1. *Changes in 1-RM from Baseline*

Cardiorespiratory fitness parameters assessed during the intervention included: treadmill (TM) time to volitional fatigue, aerobic capacity ($\text{VO}_{2\text{peak}}$), and spirometry parameters, forced expiratory volume (FEV_1) and forced ventilatory capacity (FVC). As evaluated by time to fatigue, performance on the RMCRI Treadmill Test improved 30% between initial and final assessments (12.0 to 14.0 min). Directly related to TM time, $\text{VO}_{2\text{peak}}$ improved 16% between the baseline and 6-month assessments (23.0 to 27.3 $\text{mL/kg}^{-1}/\text{min}^{-1}$). Between the baseline and 6-month assessments, FVC and FVC_1 , evidenced declines of 9% and 10%, respectively.

Table 3. *Effects of Exercise Intervention on Cardiorespiratory Fitness*

Variable	Baseline	3-Month	6-Month
TM Time (min)	12.0	13.3	14.0
$\text{VO}_{2\text{peak}}$ ($\text{mL/kg}^{-1}/\text{min}^{-1}$)	23.0	26.2	27.3
FEV_1 (L/min^{-1})	3.43	3.24	3.07
FVC (L/min^{-1})	4.11	4.01	3.75

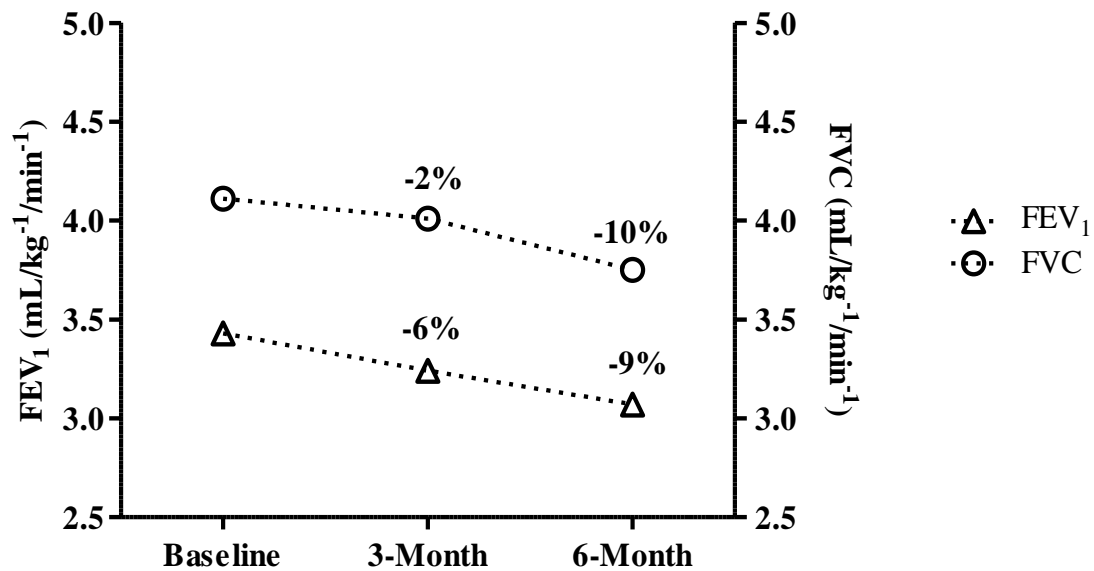


Figure 2. *Effects of Exercise Intervention on Spirometry Variables*

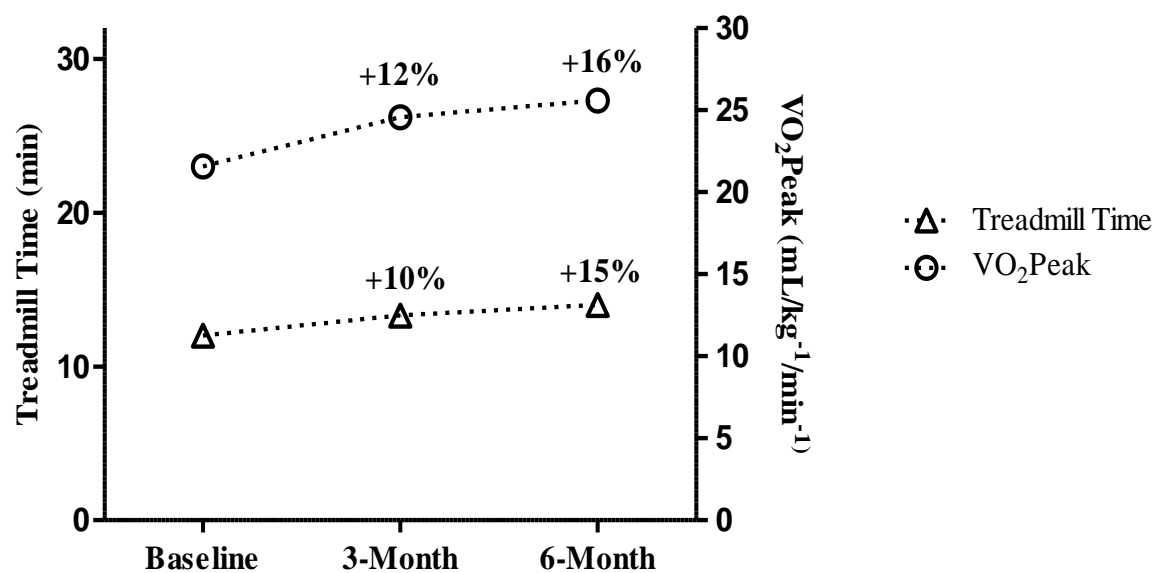


Figure 3. *Change in Aerobic Capacity and Time to Fatigue*

Total Piper fatigue, as well as subscale scores, can be found in Table 4. Wilcoxon Signed Ranks revealed no significant differences in total fatigue scores ($p=.17$), though scores increased 97% between the baseline and 3-month assessment. Changes in fatigue subscales (e.g., cognitive, sensory, affective, and behavioral) are depicted in Figure 4. A nonparametric Friedman Test indicated significant changes in affective and sensory fatigue subscales between the baseline and 3-month assessment ($p=.05$). No change in psychologic parameter, QoL, occurred over the course of the intervention.

Table 4. *Effects of Exercise Intervention on Patient-Rated Psychologic Variables*

Variable	Baseline	3-Month	6-Month
QoL	25	25	25
Total Fatigue	.04	1.2	1.2
Piper Subscales			
Behavioral	0	7	3
Affective	0	1	12*
Sensory	1	6	10*
Cognitive	0	2	3

Note. Piper fatigue scores range from 0 (no fatigue) to 10 (severe fatigue); * $p=.05$, significant difference between baseline and 3-month assessments

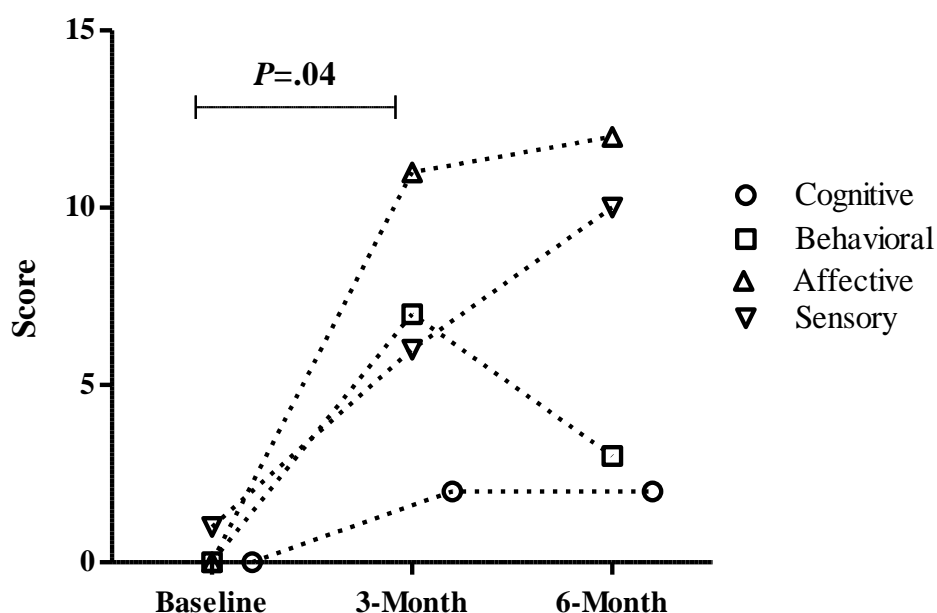


Figure 4. *Changes in Piper Subscales with Exercise Intervention*

Changes in Training Load

Training mode, duration of training session, RPE, and HRR, were prescribed and implemented from January 23, 2010 to June 17, 2010 (141 d). For the purposes of this study, the 141-day span was divided into two 3-month Phases, marked by the second assessment date. Prescribed training intensities for aerobic and strength components are portrayed in Table 5. Initial intensities set forth for strength and aerobic components were 70-75% 1-RM and 55-65% HRR, respectively. Training intensity bounds were adjusted as necessary throughout the study.

One complication occurred during the intervention. On February 16, 2010, extreme hypotension led to the following side effects: dizziness, light-headedness and weakness. The adverse effects were most likely propagated by the case study's

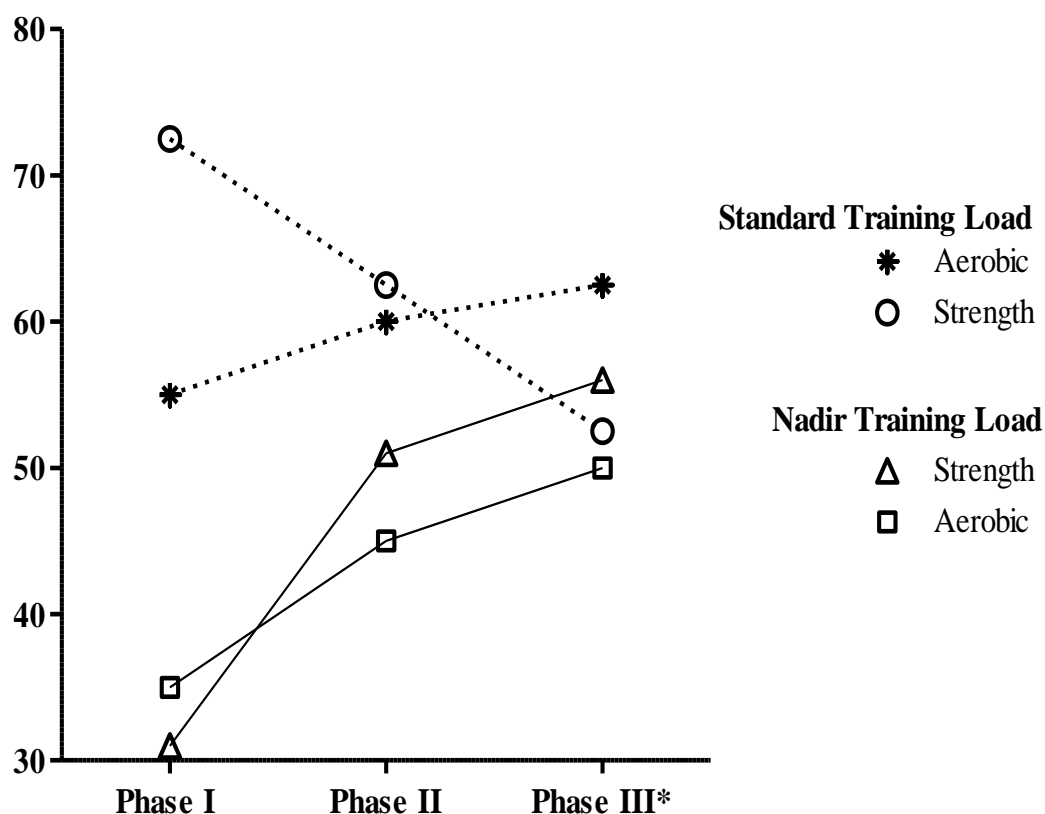
prescription blood pressure medication, Lisinopril. To avoid such events in the future, the training load was reduced to 30-35% 1-RM and 30-35% HRR for strength and aerobic components, respectively, the first week following treatment (Nadir training). For all other training sessions (Standard training), intensities were maintained.

Following the April 1, 2010 reassessment, 1-RM percentages were reduced approx. 14% for strength exercises (70-75 to 60-65% 1-RM). Phase II HRR was increased 12% (60-70% HRR). Training intensities employed during Nadir were augmented approximately 30% for both strength and aerobic components to address complaints of a “lack in difficulty”. Modifications made to training intensities over the course of the study are presented in Figure 5.

Table 5. *Strength and Aerobic Training Loads*

Component	Phase I		Phase II		Phase III	
	Standard	Nadir	Standard	Nadir	Standard	Nadir
Strength (% 1-RM)	70-75	30-35	60-65	45-50	50-55	45-50
Aerobic (% HRR)	55-65	30-35	60-70	40-50	60-70	40-50

Note. Phases I and II were undertaken in the time frame of this study; intensities set forth for Phase III depict projected training loads, had the study protocol continued.



Note. Phase III training loads were designed from 6-month assessment data. Proposed intensities would have been employed had the study continued on.

Figure 5. *Changes in Imposed Training Loads over Time*

Changes in Subjective Parameters

Table 6 presents RPE data compiled for Phases I and II of standard and Nadir training. The prescribed RPE range for each training phase can be found in Table 6 as well. As indicated in Figure 6, RPE scores did not differ significantly between standard training Phases I and II ($p=0.25$). However, scores differed significantly for Nadir training Phases I and II ($p=.003$). Significant variation from the prescribed RPE range was detected in Phase I Nadir training ($p=.008$). Comprehensive tables of all weekly RPE

scores are presented in APPENDIX A. All relevant subjective feedback was documented over the course of the study and recorded in RMCRI charting sheets. Charting sheets can be found in their entirety in APPENDIX B. Notes included: perceptions of exercise intensity, complaints of pain/lack of energy, results from medical scans/ prognostic changes, treatment side effects, etc. Charting sheets served as a subjective index to monitor psychological distress.

Table 6. *Effects of Exercise Intervention on RPE Scores*

Component	Phase I		Phase II	
	Standard	Nadir	Standard	Nadir
RPE Score	5.9 ± .53	6.4 ± .13**	5.8 ± .74	2.6 ± .56
R _x Range	6 - 8	3 - 4	5 - 7	3 - 4

Note. Values are means ± standard error; ** $p=.008$, significant difference from prescribed RPE range

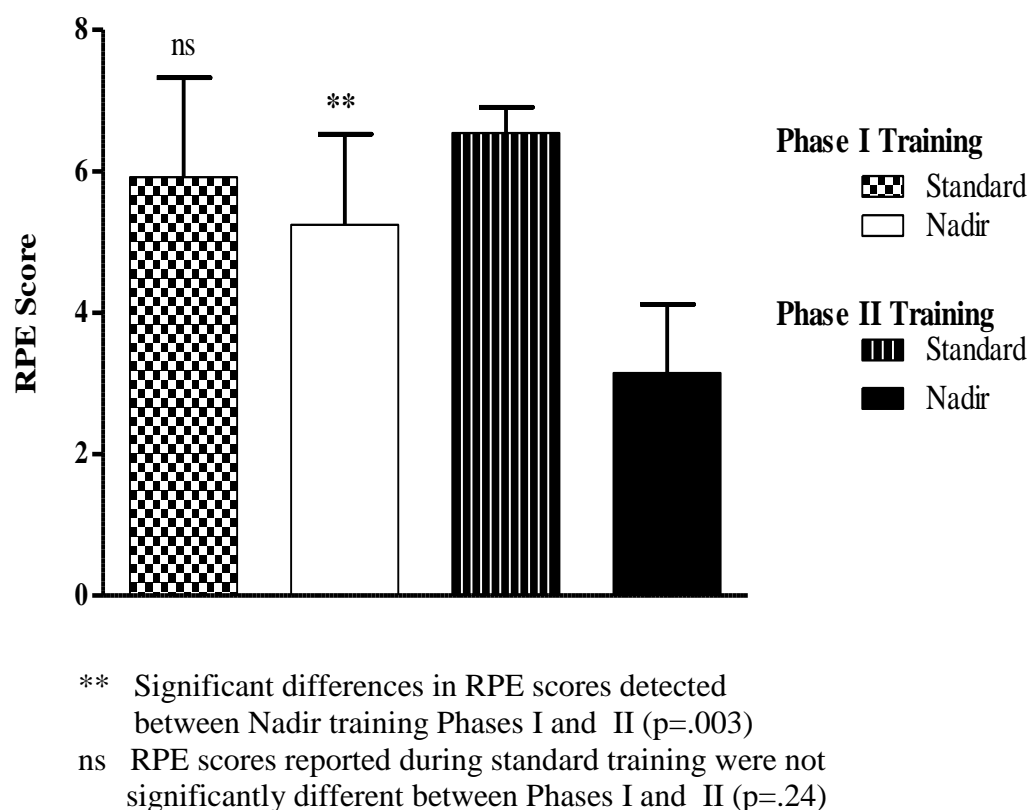


Figure 6. *Changes in RPE Scores during Training Phases I and II*

Changes in Mean Arterial Pressure

Blood pressure (BP) values were collected during each exercise session in order to monitor changes in cardiovascular function. From BP measurements, the mean arterial pressure (MAP) was calculated; values of MAP are presented in Table 7. Values of MAP were evaluated on the basis of overall change between training phases. Moreover, Nadir MAP was assessed for potential treatment-related side effects, specifically hypotension. There was no significant difference in MAP for Standard training I versus II ($p=0.12$). Once more, MAP values were not significantly different for Nadir training I versus II

($p=0.74$). Mean values of MAP for phases I and II of Standard training were combined (88.7 and 91.8); this was repeated for Nadir training phases (84.7 and 85.7). To assess differences in Standard versus Nadir MAP, combined-phase means were subjected to an unpaired t-test analysis. Results are presented in Figure 7. Standard training MAP was significantly higher than collected MAP values for Nadir training ($p=.005$).

Table 7. *Effects of Exercise Intervention on Cardiovascular Parameters*

Variable	Phase I ($n=10$)	Phase II ($n=11$)	p
Standard MAP (mmHg)	88.7 ± 0.86	91.8 ± 5.71	.12
Nadir MAP (mmHg)	84.7 ± 2.55	85.7 ± 1.36	.74

Note. Values are presented as means \pm standard error; n, number of weeks within each phase

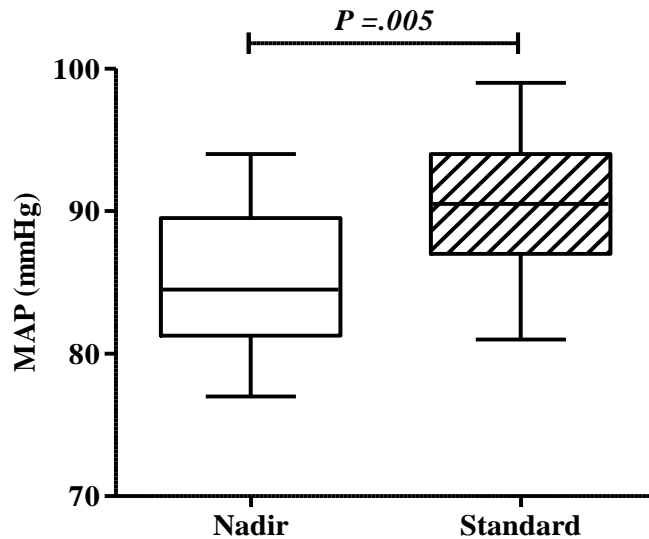


Figure 7. *Changes in MAP during Nadir and Standard Training*

Changes in Blood Parameters

Table 8 displays the results of complete blood counts (CBC) and an ELISA protein carbonyl assay. Protein carbonyl concentrations were measured only at Nadir time points, while the CBC parameters, white blood cells (WBC), red blood cells (RBC), hemoglobin (HGB), and platelets (PLT), were collected at Nadir time points (Nadir_#) as well as immediately prior to each treatment (Chemo_#). All parameters were measured prior to the first treatment, which served as a baseline from which subsequent data could be extrapolated and compared. Carbonyl concentrations were highest at baseline and gradually decreased between baseline and Nadir₂. Nadir₄ revealed a brief escalation of protein oxidation before resuming a downward trend. Wilcoxon Signed Ranks revealed a significant change in carbonyl concentrations across Nadir time points ($p=.03$). Nadir data evidenced compromised WBC concentrations, as depicted by the dramatic reduction in cell count; however, cell counts were resilient, as per the return toward baseline values, immediately prior to treatment. Platelets gradually decreased until Nadir₃, at which point the concentrations took on a trend much like that of the WBC, dropping during Nadir and increasing prior to treatment. HGB and RBC remained relatively stable. Trends for each parameter across time are presented in Figure 8. Each parameter is presented as a percentage of the baseline value.

Table 8. *Effects of Exercise Intervention on Blood Parameters*

Blood Draw	Date	WBC (10 ³ /μL)	RBC (10 ⁶ /μL)	HGB (g/dL)	PLT (10 ³ /μL)	PRT CRBYL (nmol/mg)
Baseline	Jan 21	6.5	4.05	11.8	242	6.13
Nadir ₁	Jan 21	3.7	4.07	11.7	220	5.65
Chemo ₂	Feb 12	7	4.25	12.2	207	
Nadir ₂	Feb 22	3	3.78	11	189	4.55
Chemo ₃	Mar 5	5.7	3.97	11.7	189	
Nadir ₃	Apr 2	4.2	3.86	11.7	244	
Chemo ₄ [*]	Apr 8	-	-	-	-	
Nadir ₄	Apr 20	3.4	3.82	11.4	153	5.65
Chemo ₅	Apr 29	5.8	3.74	11.4	219	
Nadir ₅	May 11	2.8	3.47	10.6	140	3.8
Chemo ₆	May 21	4.6	3.59	11.2	166	
Nadir ₆	June 3	2.5	3.34	10.6	107	1.47

* The hospital was unable to reproduce CBC results for Chemo₄

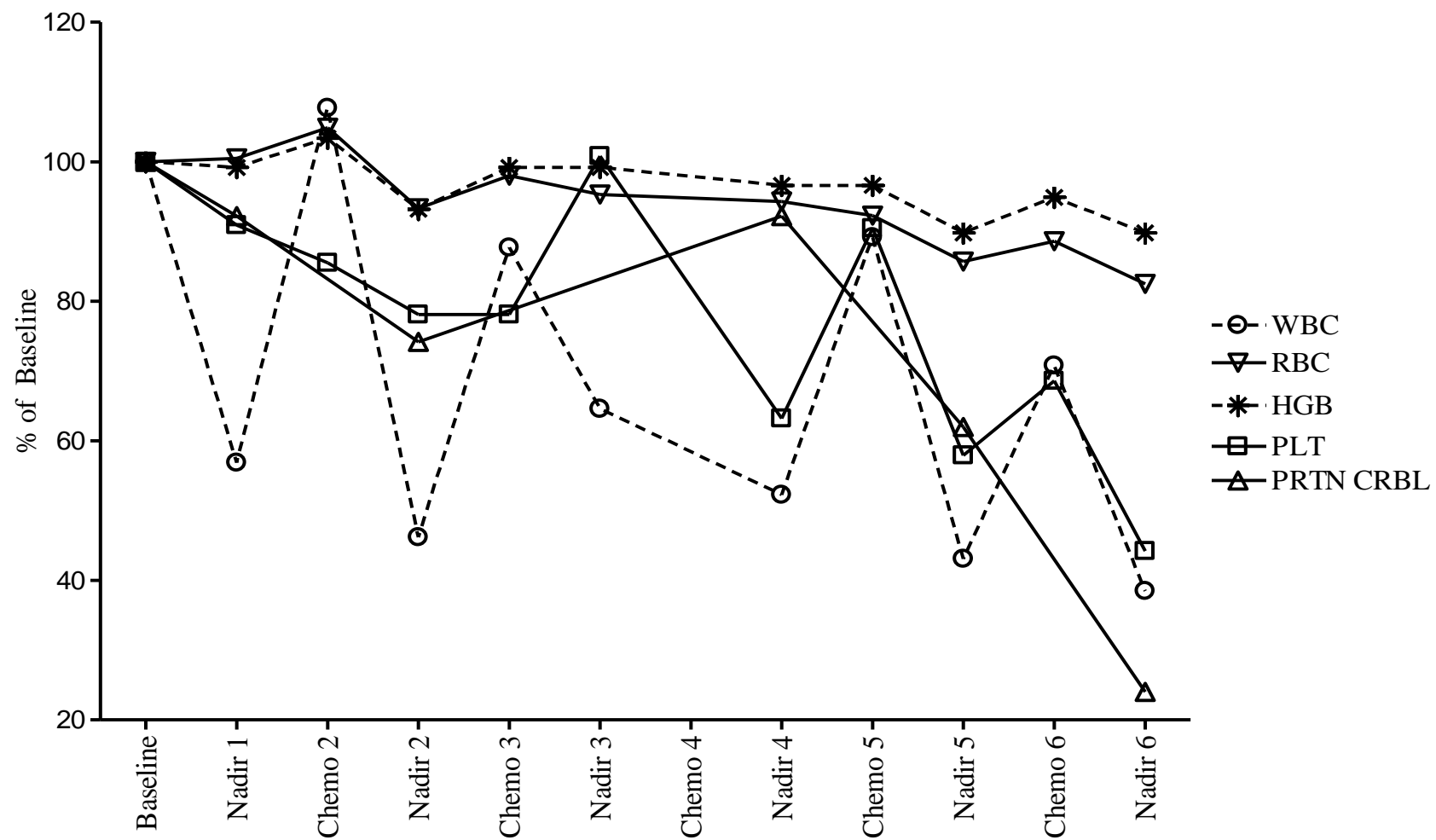


Figure 8. *Change in Blood Parameters*

CHAPTER V

DISCUSSION

Exercise as a remedial strategy continues to gain support, yet proposed benefits have primarily been investigated in only a selection of cancer populations, namely, cancers of the breast and prostate. This necessitates further exploration in order to extend inferences to all cancer types/stages. Markedly sparse is the research in gynecological populations. With this in mind, this case study sought to (a) to prescribe an individualized exercise intervention for a endometrial cancer survivor receiving high-dose chemotherapy, and (b) to determine the feasibility of this exercise program and the appropriate progression for its execution. Changes in physical and psychological functioning as well as oxidative stress status were described and assessed throughout the intervention.

Cancer patients are frequently subjected to prolonged inactivity, which may further promote treatment toxicities. Luckily, current trends encourage exercise, even at modest levels, as a means to promote health status in cancer survivors. Even with the recent explosion of research, exercise testing norms in cancer populations are limited. For this case study, assessment techniques and prescription development were based on the research of Schneider et al. (2003) at the Rocky Mountain Cancer Rehabilitation Institute (RMCRI). Immediately following her diagnosis, the highly motivated case study subject expressed a strong desire to take an active role in the recovery process, which should not

be considered uncommon, as many cancer survivors are capable of exercise participation and desire a way to reclaim self-efficacy (Dimeo et al., 1997). The subject demonstrated exemplary adherence over the 21-week study. In total, 63 training sessions were documented. Due to the closure of campus offices during weeks 9 and 10, the subject performed a modified, but comparable, training regimen during this time unaccompanied by the trainer. Excluding the aforementioned account, all training took place at RMCRI under the supervision of a trained Cancer Exercise Specialist.

At the Cancer Survivor Center for Health and Wellbeing in Aspen, Colorado, Klika et al. (2008) completed a case study to assess the exercise capacity of a breast cancer survivor during and following treatment. Unlike the multidimensional design used in our case study, this intervention was solely aerobic in nature. This study neglected to assess the effects of exercise on any psychological functioning. In our case study, the preservation of QoL and mitigation of fatigue served as primary outcome measures.

Furthermore, the subject participating in this study had a long history as an elite endurance athlete, limiting applicability of findings to highly-trained individuals with early stage breast cancer. The intervention was developed from exercise guidelines set forth by the United States Olympic Training Center; as a result, training was much more aggressive than is generally recommended for even the most ambitious cancer survivor. In fact, the case study became symptomatic of overtraining, which could have been instigated and/or perpetuated by continued treatment cycles.

Overtraining typically evolves as a result of poorly planned training along with excessive stressors (e.g., load, duration, etc.) and inadequate rest. This process is accelerated in patients receiving cancer treatment, as chemotherapy and radiation

generate parallel symptomology (e.g., mood disturbance, reduced physical capacity, muscle breakdown). With this in mind, our training intervention was designed to specifically avoid the development and perpetuation of these symptoms. This study demonstrated that a 6-month, combined exercise intervention maintained the physiologic and psychologic functioning in a late-stage endometrial cancer survivor receiving high-dose chemotherapy.

The single-sample design (e.g., N of 1, single-case research) led to positive and negative considerations. Though the depth to which a researcher can delve is limitless, statistical significance is rarely obtained from a sample size of one. With this in mind, graphical analysis was employed to assess trends in the data; nonparametric statistics were utilized only when appropriate. More important to case study research is the proposed clinical significance and application.

I failed to find another study that included *pre-treatment* baseline data. Assessing all variables prior to the first chemotherapy cycle highlights acute side effect development. Accordingly, the greatest change in global fatigue (+97%) occurred between the baseline and 3-month assessment, suggesting that the immediate effects of chemotherapy may be the most distressing. Extreme changes between the baseline and final assessments better demonstrate cumulative damage (e.g., chronic effects) of antineoplastic agents over time.

Even with the extreme percent change in fatigue, raw scores were not indicative of significant psychological distress ($p=.17$). Comparison of subject data with Piper standard norms indicated that the subject did not experience clinically significant levels of global fatigue at any point. Sensory and affective subscales, however, illustrated

marked distress based on the changes from baseline. Unlike behavioral and cognitive fatigue, sensory and affective subscales can have severe exercise-related implications. Spikes in sensory fatigue, specifically, are indicative of vestibular deficits associated with platinum-based analog administration. As a result, balance and coordination become compromised. Therefore it becomes imperative to include a greater amount of balance work than that prescribed to the subject participating in the case study undertaken by Klika et al. (2008).

QoL data collected over the course of this case study indicated the maintenance of psychological wellbeing, as hypothesized. Our findings are supported by preceding research, which also demonstrates a preservation of QoL through programmed exercise (Adamsen et al., 2006).

Physiological parameters measured during baseline, 3-month, and 6-month assessments remained stable over the 6 cycles of chemotherapy. Analysis of graphical trends illustrated near-linear improvements in both aerobic capacity ($\text{VO}_{2\text{peak}}$, $\text{mL}/\text{kg}^{-1}/\text{min}^{-1}$) and muscular strength (1-RM weight, lbs). However, Wilcoxon Signed Ranks analysis did not deem changes in physiologic variables to be significant.

Successive improvements did not translate directly to increased training load. In fact, modifications were more dependent on RPE scores and subjective feedback of the case study; a 10% reduction in the strength training load was imposed following both the 3-month and 6-month assessment. Aerobic training loads remained relatively unchanged over the course of the study. Through the tedious scrutiny of RPE scores and subjective complaints, training loads were adjusted to meet the needs of our subject, as the aim of this investigation was to create an exercise plan that could be maintained over time.

Because platinum-based drugs are known to affect cardiovascular function, mean arterial pressure (MAP) was used to evaluate changes in the systemic arterial pressure. Variations could indirectly indicate treatment-related alteration to systemic vascular resistance or cardiac output. Arterial pressure did not differ significantly between study Phases I and II for standard ($p=.12$) or Nadir ($p=.74$) training. Though standard training Phases I and II did not diverge significantly, arterial pressures were approximately 7 mmHg higher during Phase II. This response can be accounted for by the discontinued use of prescription medication, Lisinopril, following an early complication; the hypotensive response became compounded by the interaction of Lisinopril with carboplatin.

Training Phases I and II were combined and assessed over the 21-week study (Nadir I and II versus standard I and II). Nadir pulse pressure was significantly lower than standard training MAP ($p=.005$). This hypotensive response shortly after drug administration is characteristic of many platinum-based chemotherapy agents and highlights the importance of reduced training loads during Nadir.

Circumference measurements served as a tool for the evaluation of lymphedema development/progression. Lower limb circumference remained stable, as indicated by assessment data. Lymphedema in the lower extremities was a primary concern. In early March, deteriorating renal function required that a kidney stent be put in place to ensure unobstructed circulation to the lower extremities. Additionally, lymph node swelling blocked lymph flow into and out of the right leg which caused initial leg lymphedema. The swelling in the right leg was the symptom that alerted the medical team to find the endometrial cancer. With vasculature compromised in this region, the pressure needed to

ensure adequate circulation placed a great deal of stress on the heart. Lisinopril ingestion ameliorated this stress, and interestingly, the side effects of treatment induced similar actions, decreasing the blood pressure.

Treatment-related toxicities, cachexia, fatigue, and compromised QoL, are thought to be exacerbated through states of augmented oxidative stress. Reduced levels of oxidative stress may serve to alleviate toxicities brought on by treatment. Biochemical analysis of protein carbonyls indicated a significant reduction ($p=.03$) in protein oxidation from baseline assessment. Blood draws 1-3 illustrate a downward trend in carbonyl concentration (6.13, 5.65, and 4.55 nmol/mg). Each of the first 3 treatments were administered every third week as scheduled, and Nadir draws were collected 10 days after treatment.

Between the third and fourth treatment cycle, an additional 14 days elapsed due to vacation time and medical procedures unrelated to the cancer. It is likely that this extended span of time fostered tumor progression and may very well explain the restored increase in carbonyl concentrations between Nadir 3 and 4. Protein carbonyls measured between Nadir 4-6 recommenced a descending trend (5.65, 3.40, and 1.67 nmol/mg). Reduced protein degradation (likely associated with alleviated cancer cachexia) may explain sustained muscular strength.

Results from complete blood panels collected for each treatment and Nadir time point further elucidate changes within hematological parameters. As is typically the case, WBC concentrations revealed drastic reductions during Nadir (approx. 10 days post-chemo), before returning to heightened values immediately prior to treatment. While erratic, the up-and-down trend highlights a capacity to overcome treatment-facilitated

damage, likely heightened by exercise training. With compromised immune function common to those patients undergoing treatment, the time-dependent restitution of WBCs was fundamental in avoiding flu/cold viruses. Hemoglobin concentrations fluctuated very little over the course of the study. An essential transport protein, hemoglobin likely evaded significant destruction (e.g., oxidation) through exercise; this postulation is directly in line with the carbonyl assay results. While overall, blood counts regress over time, at no point did hematological values stall the administration of treatment. The ability to maintain the prescribed dosing schedule is directly related to the subject's continued optimistic prognosis.

Shortly after completing the sixth cycle of PC, the subject underwent medical imaging to evaluate the trajectory of the tumor. Results indicated that tumor growth had been halted; however, nodal involvement in the region meant that surgical removal would not serve as an effective means to ensure a cancer-free prognosis. The cancer was deemed controllable, but not likely curable.

As a result, PC will be administered continuously, approximately every fourth week in hope of controlling tumor growth. Chemotherapy used for non-curative intent is just as valuable, if not more so, in incurable cancers as it can impact survival by prolonging life. Oncologists hope to increase the span of time between cycles to limit the noxious drug effects. With this news, the capacity to attenuate psychological distress and maintain physical capacity has become more crucial than ever. The cumulative nature of chemotherapy drugs educes destruction systems throughout the body. This study has demonstrated that exercise training can attenuate the effects of treatment, and even lead to physiological and psychological improvements.

The significance of training load modification served as, perhaps, the most influential concept drawn from this case study. For patients receiving or expected to receive long bouts of treatment, the goal of exercise programming is a preservation of physical and psychological functioning. To offset the side effects of therapy and attenuate certain, unavoidable declines, training loads will likely be reduced. In this case study, the subject's ability to preserve muscular strength and cardiorespiratory fitness is likely due to modifications made to training intensity. The subject's unwavering resilience highlights sustained QoL and wellbeing. Taken together, exercise training appears to be a safe and effective means to improve the cancer survivorship outlook.

Conclusion

The growing cancer survivor population presents a welcomed challenge to health care providers and efforts that integrate nutrition and exercise as a means to enhance QoL continue to gain support. Exercise, both during and following treatment, is encouraged in order to attenuate the adverse effects brought on by antineoplastic drugs.

This case study demonstrated that multimodal exercise training of adaptable intensities is an effective strategy for maintaining physical and psychological function in a cancer survivor receiving palliative chemotherapy to control tumor growth. The preservation of physical capacity with concurrent reductions in psychological distress has been demonstrated in many other studies (Schneider et al., 2007; van Weert et al., 2005).

Collectively, upper and lower body strength improved over the course of the 6-month intervention. Aerobic capacity, as per VO_{2peak} , illustrated improvement as well. QoL remained stable and global fatigue scores were not indicative of psychological distress. Observed improvements may be attributable to modifications made to training

loads at various points during the study. Permitting necessary adjustments of training loads maintained the central objective of this case study, which was to construct a training program that could be continued over time. The significant reduction in protein carbonyls (e.g., protein oxidation) suggests a preservation of muscle integrity. Moreover, complete hematology panels (e.g., WBC, RBC, HGB, and PLT) revealed a collective resistance against treatment-related damage in the recurring escalation toward initial values. Owing to exercise training, a higher percentage of each baseline value was achieved than would have otherwise been observed had the subject remained sedentary over the course of the study.

The exercise design applied in this case study appears to have merit, which may assist health professionals seeking direction in the implantation of an exercise program for an endometrial cancer survivor. The outcomes of this case study emphasize that moderate to high intensity exercise are not beyond the realm of possibility for late-stage cancer survivors. Results from the baseline assessment should be assessed to establish initial exercise intensities. Preliminary intensities of 60-70% 1-RM and 60-70% HRR are appropriate for muscular strength and aerobic exercise, respectively. Establishing the intensity as a range of values allows for modification throughout the intervention. During Nadir, training loads should be reduced to avoid exacerbating noxious side effects during a period of low energy and compromised immunity. Nadir intensities of 40-50% 1-RM/HRR were well tolerated; even low- to moderate intensities illustrated sustained physiological capacity during a time in which our patient would have otherwise been inactive.

Exercise sessions should be approximately an hour in length in order to include all intervention components (e.g., strength, aerobic, balance). A training frequency of 3 days/week is recommended to allow for adequate recovery between workouts, while still providing ample stimuli to elicit physiological training effects. Patients should be monitored continuously as per RPE scores and subjective feedback. Fluctuations in subjective parameters may indicate the need for training load adjustment. The delineated exercise guidelines are recommended for achieving outstanding adherence and sustained physical and psychological capacities in endometrial cancer survivors.

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APPENDIX A

RPE SCORES FOR A 21-WEEK EXERCISE INTERVENTION

RPE Scores for a 21-Week Exercise Intervention

Week #	1†	2	3	4†	5	6	7†	8	9	10	11	12†	13	14	15†	16	17	18†	19	20	21
Chest Press	8.3	8.7	8.3	7.5	8.3	9	4.5	2.8	2.8	9	8.5	3.3	8.2	8	3.2	8.8	8.7	4.3	7.2	6.7	6
Military Press	9.2	7.8	8.3	9.3	6.7	7.8	8.2	9	9.4	10	10	4.2	7.7	6.8	3.3	6.8	7.3	7.2	7.7	7.5	7
Lat Pull	6	7.2	7.3	5	6.7	6.8	2.2	4	5	7	6.5	1.3	7	6.5	1.8	7	6.7	3.3	6.5	6.8	6.2
Leg Press	6.6	6.3	7.7	5.7	7.7	7	3.2	6	6.5	7.8	7	2.2	8.6	8.2	2.8	7	7.1	5.0	7.1	6.6	6.1
Leg Extension	5.2	5.5	6.5	6	6.5	6.2	3.2	3	3	6	7	2.5	6.3	6.3	2.3	5.7	6.5	2.9	6.3	6.5	7.1
Leg Curl	4.5	5.2	5.8	5	6.5	6	4.5	2.7	2.7	6	6	1.5	6.3	6	1.7	6	6	3.2	6.2	7.1	6.5
Tricep Extension	4.2	4.3	3	4	4.5	5	2.8	3	3.2	3.3	4	1.8	5.3	3	1.8	2	2.3	3.0	3.5	4.2	4.0

Values are means of RPE scores for each exercise in a given week;

† indicates first week after chemo (Nadir), reduced training loads for weeks 1, 4, 7, 12, 15, and 18

APPENDIX B
COMPILED SUBJECT CHARTING SHEETS

Rocky Mountain Cancer Rehabilitation Institute CHARTING SHEET

Name: [REDACTED]

Date	Time	Notes	Initials
		1st round of chemo on 1.21.10	
2.9.10		Rx written	LD FOR ALL
1.23.10		USED HANDRAILS DURING TREADMILL; CONSIDERATION FOR V _{0.2} PEAK VALUES TAKING 1/2 BP MED AFTER TRAINING SESSION DUE TO ↓BP AND DIZZINESS DURING TRAINING	
2.9.10		WEEK OF CHEMO: 4 DAYS/WEEK, 3 WITH TRAINER & 1 AT HOME. [10 MIN TM + 2 SETS/10 REPS LEG PRESS (160#)] 2 SETS/10 REPS BENCH PRESS (20#)	
2.12.10		CHEMO SESSION #2 OF 3	
2.13.10		LEG SWELLING IS REDUCED, ADD TRICEP EXERCISE TO RT PROTOCOL HAVING BURNING SENSATION IN ARCHES OF FEET	
2.16.10		BONE SORENESS, EXTREME FATIGUE, ENDED SESSION EARLY AND DROVE HER HOME	
		*HAD COMPANY IN TOWN OVER THE WEEKEND... TOO MUCH ACTIVITY FOLLOWING FRIDAY'S CHEMO IS PROBABLY TO BLAME	
2.18.10		DECIDED WEEK 1, POST TREATMENT WOULD REDUCE LB BY HALF TO AVOID ADVERSE EFFECTS SEEN 2/10.10, LESS SEVERE LEG PAIN TODAY	
2.20.10		RETURNED TO NORMAL PROTOCOL IN WEEK 2 ADDED FREE WEIGHT EXERCISE FOR TRICEPS	
2.23.10		LOW WBC/RBC INDICATED FROM BLOOD TESTS COMPLAINED OF ONLY MINOR LEG PAIN	
		NO LONGER TAKING BP MEDICATION, USING NITROGLYCERIN, DUE TO SIDE EFFECTS OF EXERCISE.	
2.25.10		SLIGHT (R) CALF PAIN BALANCE COURSE, ONLY USING ROPES. FIND THAT IRRITATION AND BURNING SENSATION OF ARCHES IS BROUGHT ON BY UNSTABLE OBJECTS THAT CAUSE CHAFFING	
2.27.10		9 MIN INTO TM, (R) CALF PAIN SWELLING OF (R) LEG DUE TO IMMOBILITY ON FRIDAY WHILE DOING WORK AND ATTENDING MEETINGS	
3.2.10		LEGS FEEL "TIRED", NOT PAINFUL TO START; 23 MIN INTO TM HOWEVER, SLIGHT PAIN IN (R) LEG	
3.5.10		3RD CHEMO ON FRIDAY (3.5.10) CHEMOTHERAPY → NO (-) RESPONSES TO RATE OF ADMINISTRATION/TH TIME, 7 HOURS (SHORTEST PROTOCOL OF THREE)	
3.10.10		WEEK 1, POST TREATMENT PROTOCOL (↓LB 1/2) FEELING GOOD AND NO LEG PAIN; SWELLING FROM EARLIER IN WEEK	

Date	Time	Notes	Initials
3.9.10		- TUESDAY FOLLOWING CHEMO: TIRED AND HAVING SPORADIC SHOOTING PAIN IN LOWER BODY, KNEE JOINT CAPSULES ACHY BUT NO LEG/CALF PAIN AS WAS OCCURRING PREVIOUSLY.	
		- DESCRIBED PROGRESSION OF SIDE EFFECTS AS PSYCHOLOGICAL FATIGUE FIRST (MONDAY) AND PHYSICAL DRAIN AND WEAKNESS SECOND (TUESDAY) WITH EACH PROCEEDING DAY SHOWING AN ELLEVATION OF SIDE EFFECTS; ALWAYS FEELS FINE SAT/SUN AFTER TREATMENT... "ON A HIGH THEN YOU COME DOWN ON MONDAY/TUESDAY"	
		- ALREADY HAS 2ND ROUND SCHEDULED, STARTING IN 3 WEEKS	
		VISITS ONCOLOGIST IN NE OVER SPRING BREAK FOR SCANS	
3.11.10		- FEELS GREAT THIS MORNING, NO LEG PAIN, AND CIRCUMFERENCE MEASUREMENTS ARE APPROX. SAME FOR BOTH LEGS (↓LYMPHADENIA)	
3.18.10		- SOMETHING IN LEG ON CAR TRIP TO MAHA, WAS BETTER ON THE WAY BACK DUE TO STOPS FOR WALK BREAKS	
		- TUMOR INCREASED IN SIZE, MEETING WITH KIDNEY SPECIALIA IN COMING WEEKS	
3.30.10		- REASSESSMENT SCHEDULED FOR 4.1.10	

Date	Time	Notes	Initials
4.1.10	2pm	FINISHED 3 MONTH REASSESSMENT + STARTED WRITING Rx.	LD
		- WILL BE HAVING SURGERY MONDAY OR TUESDAY FOR KIDNEY STENT MODIFICATION PRIOR TO 4TH ROUND OF CHEMO ON FRIDAY	
		- WILL CHECK WITH ONCOLOGIST TO SEE IF CONTINUING WITH TAXOL/CARBOPLATIN OR STARTING DOX/ALDOST.	
		- SAID SOMETIMES TAXOL REGIMEN DOESN'T WORK DURING FIRST ROUND, BUT DOES DURING 2ND... THIS WILL DICTATE WHICH ONE IS USED	
		- ORIGINAL RADIOLOGIST ON CASE SAID TUMOR DID <u>NOT</u> INCREASE IN SIZE. MRI AND CT SCAN WERE ORIGINALLY COMPARED; ONE GIVES MEASURE OF DENSITY AND OTHER GIVES REL. SIZE	
		"ALWAYS HAVE SUCCESSFUL BREAKS"... TOLD THAT HAD 6 MONTHS TO LIVE OVER XMAS AND THEN M.D. CORRECTED THAT AND NOW TUMOR DOUBLING AND CORRECTION OF LAB RESULTS."	
		- DOESN'T ENTIRELY BELIEVE THE CANCER IS THERE... FEELS GREAT, SAID COULD ACCEPT THE CANCER IF SHE FELT SICK.	LD

4.2.10	5pm	NEW 7.0HR: 50-05... 120-132 BPM DURING TREADMILL (WILL PRINT RX TOMORROW)	LD
4.3.10	12:30pm	NEW TREADMILL SETTINGS: 0.5% MAX ATTAINED, 3.5 MPH AT 0° INCLINE AND WEIGHT MACHINES AT 0.5% 1RM EXCEPT MILITARY PRESS, WHICH WILL BE PERFORMED AT 0.7% 1RM	
		- HAD MRI ON 4.2.10, RESULTS SHOW REDUCTION IN SIZE OF TUMOR! SIZE: 4.9cm SIZEp: 4.1cm, WILL BE REPEATING TAXOL/CARBOPLATIN REGIMEN FOR 2ND ROUND OF CHEMO.	LD
4.9.10		- HAD CHEMO ON THURSDAY (4.8.10) AND WILL BE TRAINING ON SATURDAY AT 8AM	
		- SURGERY WAS ON WEDNESDAY TUESDAY, WAS IN ON WEDNESDAY.	
		- DIDN'T TRAIN THIS WEEK.	
		- FINING OUT PSYCHOLOGICAL PAPERWORK TO ADD TO REASSESSMENT	
		- WEEK 1 POST-CHEMO: 1/2 0.5% 1RM TO COMBAT FATIGUE.	LD
4.10.10	QUICK TIMEUP RELAP	4.10.10 SPENT REPLACEMENT 4.8.10 CHEMO - START OF 2ND REGIMEN (1 OF 3 TREATMENTS) 4.10.10 DAY 1 BACK POST 2ND REGIMEN OF CHEMO	
		- MORE TIRED THAN USUAL TODAY 2 DAYS POST TREATMENT	
		- ARCHES BURNING DURING TREADMILL, SLEPT DURING BALANCE. WALKING AT INCREASED SPEED MAY CAUSE MORE RUBBING (FRICTION)	
4.13.10		- PAIN AT SITE OF TUMOR SINCE STARTING 2ND CHEMO REGIMEN (CHRONIC) CHEMO AFFECTING TUMOR?	
		- FEELS LIKE LEG CIRCULATION IS IMPROVING SINCE START OF 2ND REGIMEN DOESN'T FEEL LIKE LIMBS IS HEAVY AND IMMOBILE	

Date	Time	Notes	Initials
4.15	12pm	<ul style="list-style-type: none"> NEUROPATHY BEGINNING TO BE PREVALENT IN TOES AS WELL AS SOLES OF FEET CLIMPS FOR LONGER DURATION AS WELL; NOT JUST AT NIGHT ANYMORE ANY LONG DURATION STANDING AGGRAVATES IT. ALLVIATION WHEN WALK BAREFOOT ON CARPET AND UNO TILE. THE VARIETY OF TEMPERATURE/TEXTURE MAY HELP STIMULATE EXPOSED NERVES. NO LEG PAIN AT ALL WHILE WALKING. 	
4.20	9am	<ul style="list-style-type: none"> HAD COMPANY IN TOWN LAST WEEKEND, DID A LOT OF DRIVING. LEG HAS BEEN SWOLLEN MORE OF THE WEEK, MAKING IT FEEL HEAVY DURING TREADMILL FEEL TIRED TODAY, WEIGHTS "WERE HEAVIER THAN USUAL" HAD SIMPLE SUGARS PRIOR TO EXERCISE; COULD BE HYPOGLYCEMIC. 	
4.22	9am	<ul style="list-style-type: none"> "HEAVY LEG" OCCURRED AT 7 MIN MARK OF TREADMILL, MUCH EARLIER THAN USUAL. STILL FEELING FATIGUED. AC WAS NOT ON THIS MORNING, HEAT SEEMED TO PLAY INTO OVERALL STATUS OF FATIGUE NEUROPATHY DOESN'T SEEM TO BE AS PREVALENT ANY MORE IN PAST, WHEN LEG PAIN BEGAN DURING WALKING, WOULD PROGRESSIVELY GET WORSE BUT IT DOESN'T FOLLOW SAME TREND NOW. GETTING MASSAGE TODAY, WILL HOPEFULLY HELP WITH SWELLING AND PAIN! 	
5.1.10		WROTE UP WORKOUT FOR CLIENT TO PERFORM ON OWN, TRAINER OUT OF TOWN.	
5.11.10		NADIR BLOOD DRAWN, ALL COUNTS DOWN!	
5.14.10		MASSAGE. CA125 LEVELS PROGRESSED FROM 75 TO 80 TO 40 (WITH 35 BEING "NORMAL" HEALTHY)	
5.15.10		LOOKS PROMISING THAT ↓ TUMOR GROWTH AND SIZE.	
5.15.10		<ul style="list-style-type: none"> 13 MINUTES INTO TREADMILL WALKING, EXTREMELY PAINFUL AND HEAVY LEG. USUALLY CLIENT FEELS NO PAIN FOLLOWING MASSAGE LAST CHEMO (#6) NEXT THURSDAY 	
5.11.10		<ul style="list-style-type: none"> ADDED CRUNCHES TO SESSION MOWED LAWN, FELT GREAT DURING TRAINING 	
5.20.10		<ul style="list-style-type: none"> CHEMO #6 ON 5.21.10 MAY ADD BACK EXTENSIONS TO SESSIONS NEXT WEEK. WILL DO REASSESSMENT #2 AFTER LAST CHEMO; SCHEDULED FOR 7.1.10 	
5.21.10		<ul style="list-style-type: none"> WEEK AFTER CHEMO, 50% 1RM, NOT 50% TRAINING WEIGHT - ITS TOO LIGHT... ~ 30% 1RM "LOW INTENSITY" (60-75% 1RM) 	

Date	Time	Notes
6.3.10	9AM	NADIR AT NCMC, DID SERUM EXTRACTION AT GUNTER FLIGHT AFTER FOR ANTIOXIDANT CONTENT
6.19.10	11AM	<ul style="list-style-type: none"> 6.11-6.17 IN OMAHA FOR FOLLOWUP MRI FOLLOWING 2ND ROUND OF CHEMO → NO CHANGE IN TUMOR SIZE, WAS TOLD THAT THE CANCER IS CONTROLLABLE. GIVEN A 'STAGE III' DIAGNOSIS, WILL RECEIVE CHEMO SPORADICALLY (EVERY 4 WEEKS) FROM NOW ON. ON 6.8.10, TUESDAY FOLLOWING CHEMO (1ST CYCLE) DROPPED %IRM TO 55 WILL DO 2ND REASSESSMENT ON TUESDAY AT 9AM. #1-21 WEEKS FOR THERAPY DATA! WILL STILL TRAIN THOUGH TO HELP MAINTAIN FUN. CAP. AND QOL!

Date	Time	Notes	Initials
6.26.10	12PM	<ul style="list-style-type: none"> RX COMPLETED. CLIENT WANTS TO TRAIN AT 60%IRM UNTIL THE NEXT ROUND OF CHEMO (PROJECTED 7.12.10) THEN WE'LL PROP INTENSITY TO 50-55%IRM HAD TUBES PUT IN OF 6.25.10 TO DRAIN FLUID FROM EAR INFECTION GOING BACK ON MONDAY TO FINISH... PLATELETS ↓ AND LOTS OF BLEEDING. 	LD
7.24.10	11PM	<ul style="list-style-type: none"> NEW ENT DOCTOR SEEMS LIKE CLIENT IS DOING BETTER WITH EAR DROPS AND HEARING. WORKSHOP STARTED 7.26.10, DOESN'T SEEM OVERLY STRESSED WILL BE GOING TO OMAHA FOLLOWING WORKSHOP FOR NEXT ROUND OF CHEMO 	LD