University of Alberta

Exercise Rehabilitation for Breast and Head and Neck Cancer Survivors

By

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Dedication

I would like to dedicate this work to the many cancer patients and survivors that I have had the privilege of working with during my career. You have provided me with the motivation to complete this work.

Abstract

The purpose of this dissertation was to provide an in-depth examination of exercise rehabilitation in two cancer survivor groups—breast cancer and head and neck cancer (HNC). These two cancer tumour groups were chosen for study as survivors of these cancers represent a large proportion of the oncology clinical caseload in physical therapy departments. A further objective of this dissertation was to provide research evidence to guide clinical exercise programming.

Study one is a systematic review and meta-analysis (SRMA) examining the effects of physical exercise for breast cancer patients and survivors. A comprehensive search identified 136 papers, of which 14 met all inclusion criteria. Exercise led to significant improvements in quality of life, physical functioning, peak oxygen consumption and fatigue. The preliminary evidence supports exercise as an effective intervention to improve quality of life, cardiorespiratory fitness, physical functioning, and fatigue in breast cancer patients and survivors.

The next section of the thesis contains three studies (case series, pilot study and randomized controlled trial) that form the main focus of the dissertation and examine exercise for shoulder dysfunction in HNC survivors. The case series study examined the potential benefit of progressive resistance exercise for shoulder dysfunction in a select group of survivors. The pilot study examined the feasibility of the exercise program and showed a high rate of adherence with the exercise program among head and neck cancer survivors. The randomized controlled trial demonstrated that the resistance exercise program was superior to standard physical therapy for improving shoulder pain and disability, upper extremity strength, and upper extremity endurance. Changes in neck

dissection impairment, fatigue, and quality of life favoured the PRET group but did not reach statistical significance.

In summary, the results of the SRMA provide justification for including clinical exercise programs in the rehabilitation of breast cancer survivors. The results of both the pilot and efficacy studies in HNC support the use of resistance exercise as an adjunct to standard physical therapy to reduce shoulder pain and disability. The findings of the studies with HNC survivors suggest a need for further research with a larger sample size.

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TABLE OF CONTENTS

APPENDICES

CHAPTER TWO

CHAPTER FIVE

LIST OF TABLES

CHAPTER FIVE

CHAPTER SIX

LIST OF FIGURES

I: CHAPTER ONE

INTRODUCTION

I-1. OVERVIEW OF THE DISSERTATION

Recent attention has been directed toward the role of exercise in the rehabilitation of cancer survivors. Exercise rehabilitation following medical treatment for other chronic diseases is associated with low complication rates and numerous positive effects (1-4). The high prevalence of disease and treatment-related side effects in cancer survivors has stimulated interest in the potential of exercise as a rehabilitation intervention. While some evidence suggests its benefit among cancer survivors, exercise is an uncommon component of care in the clinical setting. At present, there are many gaps in our knowledge on the benefits of exercise at different time points in the disease and treatment trajectory, and it is unclear if exercise interventions will prove equally beneficial for all cancer populations. The purpose of this dissertation was to provide an in-depth examination of exercise rehabilitation in two cancer survivor groups—breast cancer and head and neck cancer (HNC). A further objective of this dissertation was to provide research evidence to guide clinical exercise programming.

The first section of this introduction provides an overview of cancer statistics and the expanding study of cancer survivorship. The second section provides background information on the etiology, pathogenesis and treatments for breast and HNC tumour groups that lead into a review of the unique physical and functional issues for each cancer. The introduction concludes with a review of the role of exercise as a potential intervention in the rehabilitation of cancer survivors. The main body of the dissertation

consists of five chapters. Chapter Two is a systematic review and meta-analysis examining the effects of physical exercise for breast cancer patients and survivors. The next section of the dissertation, including Chapters Three to Five, reviews what is currently known about the role of physical exercise interventions in HNC survivors and concludes that, in contrast to the breast cancer tumour group, minimal research has been performed with the head and neck tumour group. This section contains three studies (case series, pilot study and randomized controlled trial) that form the main focus of the dissertation and examines exercise for shoulder dysfunction in HNC survivors. The first two papers present the findings from the initial development and testing of the progressive resistance exercise training regimen. The third paper examines the efficacy of the regimen in HNC survivors. Chapter Six reflects on the culmination of these concentrated studies, by discussing the issue of cancer exercise rehabilitation and offering recommendations for integrating exercise programming into clinical practice. Overall conclusions of this work, practical implications of these findings, and future directions are also discussed.

I.2. STATEMENT OF THE PROBLEM

I.2.1. Cancer Statistics and Survivorship

The overall estimate of new cases of cancer for the year 2007 is 1.44 million in the United States and 159,900 in Canada (5, 6). Lung, prostate and colorectal cancers represent the most common cancers in men, accounting for 49% of estimated cancer cases, while breast, lung and colorectal cancers account for 52% of estimated cancer cases in women (5). Lung cancer is the leading cause of death in both men and women.

In more recent years, mortality rates have declined in the four most common cancers with the exception of lung cancer in women. The improved death rate in male lung cancer is a result of a reduction in smoking rates among men. The improved death rates in breast, prostate and colorectal cancers largely reflect improvements in early detection and treatment (5). While cancer still accounts for more deaths than heart disease in individuals less than 85 years of age, fewer absolute cancer deaths were reported in each of the last two reporting years (5).

Today, many cancer survivors can expect to cross the five-year mark (7). The growing population of cancer survivors has stimulated interest in the recovery issues of those living with and beyond a cancer diagnosis (8). The National Coalition of Cancer Survivors, a cancer advocacy group founded in 1986, defined cancer survivorship as 'the experience of living with, through, and beyond a diagnosis of cancer' (9). An individual diagnosed with cancer is considered a survivor from the time of diagnosis through the balance of life. Three phases of survivorship have been proposed to assist in defining and delineating the effects of cancer and its treatment. *Acute survival* begins at the time of diagnosis and extends through the diagnostic and therapeutic time period of the disease (10). *Extended survival* is the period of remission or the period following the completion of primary treatment of the cancer, and *permanent survival* is the extended disease-free survival period when the probability of recurrence is low.

Cancer and its treatment can result in impairments and disabilities ranging from visible physical effects (e.g. mastectomy, laryngectomy) to less obvious effects such as pain and fatigue (11). Recent evidence suggests that survivors are unprepared to manage the chronic and often poorly understood effects that arise and persist after treatment of

cancer (8, 12). In an attempt to identify the health effects by their onset, definitions have been proposed for late and long term effects experienced by cancer survivors (10). *Long term effects* refer to complications or toxicities of treatment, such as pain and fatigue that begin during treatment and persist beyond the end of treatment. *Late effects* are unrecognized complications or toxicities that are absent or subclinical at the end of therapy, such as lymphedema, that become apparent months to years after the completion of treatment (10).

Rehabilitation programs have the potential to help cancer survivors manage late and long term effects, and regain and optimize physical, psychosocial, and vocational functioning following treatment for the disease (10). While programs such as cardiac rehabilitation are now established components of cardiac care, cancer rehabilitation programs have been slow to evolve (10). Unlike other disease states, there are over 200 different diseases called 'cancer', each with its own unique disease and treatment profile. Moreover, cancer rehabilitation is essentially a moving target as new treatments for the disease are introduced and tested in the clinical setting. Despite these challenges, the growing population of survivors has brought attention to the need for interventions to address the physical and psychological sequelae that result from cancer and its treatment.

Physical exercise has been gaining recognition as an intervention to promote health and well-being among cancer survivors. As with cardiac rehabilitation, research evidence is emerging to support physical exercise as a key component in the rehabilitation of cancer survivors. The *Physical Activity and Cancer Control* (PACC) framework was developed to organize and stimulate research in physical activity and cancer control. The PACC framework considers six possible time periods for

administering an exercise intervention across the cancer continuum (13). As the three phases of survivorship correspond well with the PACC cancer-related time periods that follow the diagnosis of cancer, both can be integrated in the development of a delivery model for cancer rehabilitation care.

Acute survivorship corresponds with the cancer control outcomes of treatment preparation/coping prior to treatment and treatment effectiveness/coping during treatment (13). In this phase, exercise may be prescribed to improve physical functioning prior to treatment and/or to prevent or attenuate functional decline during treatment. Extended survivorship corresponds with the regular medical follow-up period including cancer control outcomes of recovery and rehabilitation. Exercise during this phase may be prescribed to address treatment specific impairments and/or to improve overall fitness and functioning. Permanent survivorship is the disease-free survival period that includes the cancer control outcomes of disease prevention and health promotion. In this phase, exercise may be prescribed to address long-term effects of treatment and to prevent cancer recurrences, new cancers and other diseases.

Physical therapists and exercise professionals are well positioned to work collaboratively as leaders in the research and development of cancer exercise rehabilitation programs. The challenge to these professionals is to develop and implement evidence-based cancer rehabilitation interventions that address the changing needs of survivors through the transition from acute to permanent survivorship and that respond to the changing needs and presentation of survivors as treatments for cancer evolve over time (10).

I-3. REVIEW OF BREAST CANCER

Breast cancer is the most common cancer diagnosed in women in North America, accounting for approximately 26% of all new cancer cases. In 2007 it is estimated that 180,510 American women (5) and 22,300 Canadian women will develop breast cancer (14). The risk factors for breast cancer include female gender, increasing age, prior breast cancer and a family history of breast cancer. Other established risk factors are, for the most part, hormonally related and include early menarche and late menopause, first pregnancy after the age of 30 years, increasing body height and adiposity, physical inactivity and daily alcohol consumption (15).

With a current five-year survival rate of 88%, a substantial number of women in the North America are living with a history of breast cancer (6). Many of these breast cancer survivors will experience physical and psychological sequelae from their cancer and/or cancer treatment that will impact their function and quality of life.

I-3.1. Surgery

Treatment of breast cancer most often involves surgery. The surgical treatment of breast cancer is determined in part by the size of the tumour, the presence of multiple tumours within the breast, and the survivor's preferences. For invasive breast cancer, a modified radical mastectomy or breast-conserving surgical procedure is usually performed (16). Surgical removal of the axillary nodes still represents the gold standard for staging the axilla (17). The status of the axillary lymph nodes remains the single most important independent factor predicting outcome (17).

Post surgical impairments from breast cancer may include decreased range of motion (ROM) and strength in the shoulder, pain and parasthesia in the surgical area, and

edema in the ipsilateral breast, chest wall and arm. A number of nerves in the chest wall region are vulnerable to injury during more extensive axillary dissection procedures and may result in limitations in range of motion and strength in the upper extremity, and changes in sensation in the upper arm and chest wall (16). In general, the nerve damage is temporary (neuropraxia/axonotmesis), with recovery of sensation and motor function over time. Axillary web syndrome (AWS), or axillary cording, is common sequela of axillary dissection contributing to limited shoulder ROM in the postoperative period (18). Visible and palpable cords develop in the axilla within the first 6 to 8 weeks after surgery. The cords extend from the axilla down the volar surface of the arm, are painful and usually self-limiting. This condition is hypothesized to occur from the disruption of the superficial lymphatic vessels and veins during axillary surgery (18). A recent prospective study reported a prevalence of AWS in 20% of patients who had undergone sentinel node biopsy and in 72% of patients who had received standard axillary node dissection (18).

Breast cancer surgical techniques continue to advance at a rapid pace, with breast conserving surgery and sentinel node biopsy decreasing the extent of and morbidities associated with breast cancer surgery. Compared to standard axillary lymph node dissection, sentinel node biopsy is associated with less subjective pain, lymphedema, numbness/parasthesias, and improved range of motion, arm strength and function (19, 20).

I-3.2. Radiation Therapy

Radiation therapy to the breast is administered to reduce the risk of in-breast tumour recurrence when breast-conserving surgery is performed. If cancerous cells are

found in any lymph nodes, radiation therapy may also include the axillary, sternoclavicular or internal mammary lymph nodes. Radiation therapy may be used to reduce the risk of local regional recurrence post mastectomy for individuals with large tumours, if lymphovascular invasion is present or if invasive cancer is found close to or at the deep tissue margin (21). Clinical trials are currently in progress to assess the relative benefit of partial-breast irradiation in reducing morbidity associated with radiation therapy. While there is considerable advantage in local regional control with the addition of radiation therapy to surgery, radiation therapy increases the risk of shoulder dysfunction, lymphedema and fatigue in breast cancer survivors (19, 22).

I-3.3. Systemic Therapy

Chemotherapy and endocrine therapy are types of systemic treatments used to address the presence of potential metastatic deposits in distant organs (23). Chemotherapy drugs are administered either orally or intravenously and may be administered preoperatively or as an adjuvant treatment following surgery. In breast cancer survivors with large tumours, the administration of primary systemic chemotherapy may serve to reduce the tumour and allow for breast conservation procedures (23). Endocrine therapies are an integral part of the management of hormone-dependent breast cancers (24). Endocrine therapy is a form of systemic therapy used to alter the effects of the female hormone estrogen (24). Endocrine therapy is typically prescribed after radiation and chemotherapy have been completed and has been shown to reduce the incidence of new primary cancers and the long-term risk of cancer recurrence (24).

Adjuvant treatments such as chemotherapy and radiation therapy may lead to decreased cardiopulmonary function, lowered strength and energy levels, nausea and vomiting, resulting in inactivity and deconditioning (25). Loss of lean body mass and weight gain are complications unique to the diagnosis and treatment of breast cancer (26). The treatment-related weight gain may negatively impact body image and increase the risk for lymphedema, cancer recurrence, and other diseases (26, 27). Breast cancer survivors report multiple physical symptoms in the transition period from active cancer treatment to recovery that contribute to decreased physical functioning and increased anxiety (27). Clearly, effective interventions are needed to address these side effects and, in particular, the associated physical and functional impairments.

I-4. REVIEW OF HEAD AND NECK CANCER

In North America, cancers of the head and neck account for 5% of all malignant tumours (28, 29). Greater than 80% of HNCs are squamous cell carcinomas. Other less common types of cancers that occur in the head and neck region include salivary gland and thyroid tumours, as well as sarcomas, lymphomas and melanomas. The most common areas of occurrence are in the larynx and oral cavity (29, 30). The incidence rate is almost twice as high in men as it is in women; however, the male/female ratio has been steadily closing due to the declining rates of tobacco consumption among men and increasing rates in young female smokers (31, 32). The mean age at diagnosis is 62 years, with more than 90% of cases over the age of 40 years (30, 33).

The etiology of most HNCs is related to lifestyle factors such as smoking tobacco and heavy alcohol consumption (29). The vast majority of survivors have a history of

cigarette, cigar or pipe smoking, marijuana or chewing tobacco use and/or alcohol abuse. The use of alcohol in conjunction with smoking is estimated to increase the risk of HNC by 2.5 times that of nonsmokers/nondrinkers (34). Additional risk factors for HNC include viruses, exposure to dust and chemicals, chronic candidal infection and nutritional and vitamin deficiencies. In the non-smoking population, the Human Papilloma Virus (HPV) has been found in up to 35% of HNC cases and is strongly associated with increased risk of cancer of the tonsil, while the Epstein-Barr virus is associated with an increased risk of nasopharyngeal carcinoma (35).

The prognosis for HNC is dependent on the stage at diagnosis and the site of the tumour (31, 35). The five-year survival rates for early stage (I and II) range from 60% to 95% (35) and late stage (III and IV) range from 0% to 50% (31). The overall survival rates for HNC have not changed in the last few decades; however, site-specific analysis has shown improvements in five-year survival for cancers of the nasopharynx, oropharynx and hypopharynx as well as for early stage salivary gland and late stage laryngeal cancers (36).

I-4.1. Surgery

Surgery remains a primary modality of therapy for early stage resectable tumours. For more advanced stage cancers, surgery is most often followed by radiotherapy. Surgery may result in disfigurement and impairments in speech and swallowing. Surgical treatment most often includes dissection of lymph nodes in the neck which is used for the purpose of tumour staging and/or for the treatment of lymph node metastases (37). Pain and dysfunction in the shoulder region are well documented complications of

neck dissection procedures and are a result of temporary damage to (neurapraxia/ axonotmesis), or resection of (neurectomy), the spinal accessory nerve (38-41).

I-4.2. Radiation Therapy

Radiation therapy is a loco-regional treatment modality that is an alternative to invasive surgery for many early stage cancers in the head and neck (42). Radiation therapy may also be used prior to surgery or as a modality alone or in combination with chemotherapy for unresectable tumours (42). The sequelae associated with radiation therapy include xerostomia (dry mouth), problems with eating, chewing and swallowing, neck tightness, trismus and dental problems (43, 44).

I-4.3. Chemotherapy

HNC is now more commonly treated with organ preserving neoadjuvant or concomitant chemoradiotherapy. While successfully avoiding the cosmetic deficits associated with surgery, acute toxicities from chemotherapy such as immunosuppression, nausea and mucositis are often severe (43). Long term side effects may include dry mouth, taste deficits, hearing loss and oesophageal stricture (43). Furthermore, the prolonged treatment course may result in profound deconditioning and fatigue (45). Taylor et al., (2004) in a study examining predictors of work-related disability reported that survivors who had undergone chemotherapy had three times the odds of being disabled when compared to survivors who did not undergo chemotherapy (45).

I-4.4. Quality of Life

Prior to cancer treatment, HNC survivors have a poorer quality of life than age matched controls in several domains including emotional, physical and social well-being (46). Furthermore, HNC survivors are often from socially deprived backgrounds (47).

Head and neck cancer and its treatment further impact the health related quality of life of these already vulnerable individuals (47). Fatigue, anxiety and depression are often side effects of HNC treatment (43). As HNC results in considerable impairment, survivors have very specific needs beyond those of most other people diagnosed with cancer (47).

I-5. EXERCISE ONCOLOGY

I-5.1. Definition of Exercise Terms

The term *exercise* in the clinical cancer setting encompasses a large range of potential interventions from range of motion exercises following surgery, to simple advice on increasing activity, to medically supervised aerobic exercise regimens. Proper use of the term *exercise* requires an understanding of the differences between therapeutic exercise, physical activity and physical exercise. Therapeutic exercise is defined as the *systematic performance of planned physical movements, postures or activities intended to alleviate or prevent impairments, improve function, minimize risk of injury and optimize overall health, fitness and well-being* (48). Therapeutic exercise is most often prescribed by a physical therapist to address specific physical and functional needs of the individual (49). Physical activity is defined as any bodily movement requiring the contraction of skeletal muscles that results in a substantial increase in energy expenditure over resting levels (50). Physical activity may include leisure-time physical activity and/or occupational and household physical activity. Physical exercise is defined as a form of leisure-time physical activity that is planned, structured, and usually performed on a repeated basis over an extended period of time (50). Physical exercise is prescribed specifically with the intent of improving fitness, performance, and/or health. A physical

exercise training prescription usually includes an activity mode (e.g., walking, swimming), volume (i.e., frequency, intensity, and duration), progression or periodization, and context (i.e., physical and social environment) (50). Physical fitness is defined as the ability to perform muscular work satisfactorily and includes components such as body composition, cardiorespiratory fitness, muscular fitness, and flexibility (50). Current public health guidelines recommend daily physical activity and/or formal physical exercise at a level that is equivalent to 30 minutes of brisk walking, five or more days per week (51).

There is obvious overlap in the areas of therapeutic, physical exercise and physical activity and the term *exercise* is used interchangeably. While an exercise intervention in a clinical population is often prescribed with a therapeutic intent, research examining physical exercise interventions has emerged that extends beyond the traditional therapeutic physical therapy focus to address outcomes of physical fitness and quality of life.

I-5.2. Review of Exercise Oncology Literature

Several studies have examined physical activity and exercise behaviour in the cancer population. This research has shown that the percentage of cancer survivors who exercise regularly is as low as 16-20% (52-54). In a cohort study of HNC survivors, only 30.5% and 8.5% were meeting public health guidelines for physical activity pre-treatment and after diagnosis respectively. A similar pattern of exercise behaviour has been shown in breast cancer survivors where cancer treatment has been found to have a significantly negative effect on exercise participation that is not completely recovered post-treatment (55, 56). These findings suggest that the majority of cancer survivors, including breast

and HNC survivors, are not likely exercising at a sufficient level to provide health benefits (52, 57).

Recently, observational data from the Nurse's Health Study demonstrated a protective association between increased physical activity following breast cancer diagnosis and recurrence, cancer-related mortality and overall mortality (58). A protective effect was shown for physical activity levels that met or exceeded the equivalent of four to five 30-minute sessions of brisk walking per week (9 or more metabolic equivalent task hours). Similar findings were reported in two studies examining physical activity and colorectal cancer (59, 60). While no studies have examined the association between physical activity and HNC mortality, overall, this research suggests a need for and potential benefit from interventions to promote physical activity and exercise across cancer-related time periods.

Over the past number of years, there has been increasing research evidence supporting the efficacy of exercise as an intervention both during and following cancer treatment. Four systematic reviews (61-64) and two meta-analyses (65, 66) have examined the effect of exercise as an intervention for cancer survivors (Table 1 and Table 2).

Oldervoll et al. (2004) performed a systematic review of randomized controlled trials in cancer survivors both during and after cancer treatment (61). The review included published studies written in the English language. The review focused on participant recruitment, compliance, content of the exercise programme and outcome measures. Twelve studies were included in the review. The authors reported that the most common tumour group studied was breast cancer (six studies) accounting for 62%

of randomized survivors. The authors found that, when reported, drop out rates in the trials were low and adherence to exercise was high both during treatment (72-86%) and following treatment (95%). Agreement to participate, however, ranged from 15-30% of eligible survivors, leading to questions regarding the generalizability of study findings. Aerobic exercise was the most common intervention (10 studies). The authors concluded that cancer survivors benefited from maintaining physical activity levels with promising effects on physiological and psychological outcomes. The authors recommended further research examining exercise regimens such as resistance exercise training and highlighted the need for follow-up data.

Douglas et al. (2005) performed a systematic review of intervention studies in cancer survivors (62). The review included published studies written in the English language. A focus of the review was to examine the benefit of supervised versus unsupervised exercise regimens. Twenty-one studies were included of which 11 were randomized controlled trials. Seven of the trials were performed with breast cancer survivors. Twelve studies specifically examined aerobic exercise interventions. Fifteen studies included supervised exercise interventions, five examined unsupervised (self-directed) and one study included both supervised and unsupervised intervention groups. The authors concluded that early evidence supports the inclusion of exercise programmes in the rehabilitation of cancer survivors. The authors recommended supervised exercise for survivors presenting with high body mass index, no previous exercise history and/or for those less active.

Galvao and Newton (2005) performed a systematic review of 26 intervention studies examining exercise in cancer survivors (63). The review included only published

studies indexed on the Medline data base, written in the English language. The review included 11 randomized controlled trials. The authors examined interventions both during and following cancer treatment and attempted to establish a training dose-response. Seventeen studies examined aerobic exercise interventions and 12 studies were performed with breast cancer survivors. The authors reported positive physiological and psychological benefits from exercise when undertaken during or after treatment. The authors were unable to determine the training dose-response of exercise as the studies included in the review did not consistently control for specific training variables (e.g. intensity) and as most study interventions were of an inadequate duration to detect changes in physiological responses. The authors reported early evidence suggesting benefit of resistance exercise training on disease and treatment-related side effects.

Knols et al. (2005) completed a systematic review of randomized and controlled trials examining physical exercise in cancer survivors both during and after treatment (64). Thirty-four trials (27 randomized) were included in the review. The authors examined studies both during and after cancer treatment and divided the studies into breast cancer, bone marrow/stem cell transplant and mixed solid tumour groups. Twenty-two trials examined exercise during cancer treatment and 12 trials examined exercise after cancer treatment. Sixteen studies were performed specifically with breast cancer survivors. The most common intervention was aerobic exercise which was the chosen intervention in 20 studies. The authors reported positive results both during and after cancer treatment for physiologic measures, objective performance indicators, self-reported functioning and symptoms, psychological well-being and quality of life (64). The authors highlighted the need for studies with larger sample sizes, appropriate

comparison groups, comparable outcome measures and greater attention to issues such as exercise adherence.

Stevinson et al, (2004) performed a meta-analysis of exercise interventions for all types of cancer (65). The review included both published and unpublished trials and there were no restrictions on language of publication. The authors examined the effect of exercise on breast and nonbreast cancer populations. Thirty-three controlled clinical trials were included, 27 of which were randomized controlled trials. Ten studies examined the effect of exercise with breast cancer survivors. Nineteen studies examined the effect of an aerobic exercise intervention and 10 studies examined combined aerobic and resistance exercise regimens. The meta-analysis provided evidence to support exercise to improve objective indicators of physical functioning (e.g. peak oxygen consumption, walk tests) in trials of both breast cancer and nonbreast cancer. The pooled standardized mean difference for the ten trials with breast cancer survivors showed a large improvement in physical functioning from the exercise intervention (ES: 0.96; 95% CI: 0.49, 1.43). For the nine trials that examined survivors with cancers other than breast, the pooled standardized mean difference was 0.55 (95% CI: 0.12, 0.97) indicating a moderate effect on physical functioning in favour of exercise. The authors reported a lack of follow-up data on the long term effects of exercise and on outcomes of recurrence and survival.

Schmitz et al, (2005) performed a qualitative and quantitative review of 32 controlled trials for all types of cancer (66). The review considered only published studies written in the English language. Twenty-seven of the 32 studies were randomized controlled trials. Twenty-three of the 32 trials examined exercise interventions for breast

cancer survivors and one pilot study (67) examined resistance exercise for HNC survivors. The authors examined the effect of exercise at two time points; during and following cancer treatment. Positive qualitative findings, supported by 3 or more high quality studies, were reported for cardiorespiratory fitness and quality of life following treatment and for physiological outcomes and symptoms during treatment. The quantitative findings showed a moderate effect from exercise on cardiorespiratory fitness. The weighted mean effect size (WMES) for cardiorespiratory fitness was reported as 0.51 (95% CI: 0.24, 0.78) and 0.65 (95% CI: 0.22, 1.09) during and after treatment respectively. A small to moderate effect was found for physiological outcomes (WMES = 0.28; 95% CI: 0.12, 0.44) and symptoms (WMES = 0.39; 95% CI: 0.17, 0.60) and a large effect was found for vigor post treatment (WMES = 0.82; 95% CI: 0.05, 1.60). The authors highlighted the need for further research to establish the range and magnitude of positive effects of exercise among cancer survivors.

I-5.3. Summary

In summary, while there is evidence to support exercise as an intervention for cancer patients and survivors, the evidence has been the result of trials performed primarily with breast cancer survivors. Based on the number of studies performed in the breast cancer area, the benefit of physical exercise focusing exclusively on randomized controlled trials in breast cancer warrants a comprehensive systematic review. In contrast, there is also a need for empirical research on the relative safety and efficacy of exercise for HNC survivors.

I-6. STUDY PURPOSES

The primary purposes of this dissertation were to: (a) perform a qualitative and quantitative evaluation of the evidence from randomized controlled trials examining the effectiveness of physical exercise interventions for breast cancer survivors, (b) develop and test the feasibility of a specialized progressive resistance exercise training (PRET) program for spinal accessory neurapraxia/neurectomy in post surgical head and neck survivors, (c) determine the efficacy of a moderate duration supervised PRET program on upper extremity strength, pain and disability, and quality of life in HNC survivors, (d) propose guidelines for the implementation of exercise rehabilitation in the clinical setting.

I-7. STUDY HYPOTHESES

I-7.1. For the systematic review/meta-analysis (SRMA), it was hypothesized that:

1. Restricting the SRMA to the clinically homogenous breast cancer population would allow for preliminary estimates on quantitative effects of the physical exercise interventions on objective physical measures, self-reported symptoms, and quality of life outcomes.
2. The inclusion of only randomized controlled trials in the SRMA would provide the best evidence to evaluate the efficacy of exercise interventions for breast cancer survivors.

I-7.2. For the head and neck feasibility study, it was hypothesized that:

1. Head and neck cancer survivors would be willing and able to participate in a 12-week resistance exercise program addressing shoulder dysfunction due to spinal accessory nerve damage.

2. The optimal time to administer the intervention would be as soon as possible after the surgery.

I-7.3. For the head and neck efficacy study, it was hypothesized that:

1. An appropriately prescribed upper body resistance training program using the principles of progressive overload would improve upper extremity strength and endurance.
2. Improvements in strength and endurance of the scapular muscles would result in a significant reduction in patient-rated shoulder pain and disability.

Table I-1. Systematic Reviews of Physical Activity in Cancer Survivors (Published by 2005)

Study author, year # RCTs	Selection Criteria	Tumor Groups included:	Exercise intervention	Specific focus of review	Results/ Key Findings
Oldervoll, 2004 12 RCTs	RCTs only: P: Cancer patients I: Physical exercise C: Not stated O: All outcomes	Breast: 6 Leukemia: 1 Prostate: 1 Stomach: 1 Mixed: 3	Aerobic: 10 studies Resistance exercise: 2 studies	Recruitment, compliance, intervention details & outcome measures	Agreement to participate: 15% to 30% Sample sizes: 21 to 155 participants Withdrawals: 0% to 34% Breast cancer: 62% of trials Conclusions/ recommendations: • Promising effects on physiological and psychological outcomes. Further research warranted.
Douglas, 2005 11RCTs/ 21 Trials	Intervention studies: P: Cancer patients I: Exercise C: Not stated O: All outcomes	Breast: 7 Leukemia: 1 Multiple Myeloma: 1 Prostate: 1 Mixed: 11	Aerobic: 12 studies Resistance: 2 studies Combined intervention: 7 studies	Supervised/ Unsupervised Recommendations for exercise programming	Supervised: 15 studies; Unsupervised: 5 studies; Supervised & Unsupervised: 1 study Conclusions/ recommendations: • 4+ days/ week; 35-60 minutes; Moderate intensity; Walking; Supervised exercise for less active; exercise started during treatment. • Exclude individuals with contraindications to exercise &/or co-morbidities.
Galvao & Newton, 2005 11RCTs/26 Trials	Published studies: P: Cancer patients I: Exercise C: Not stated O: All outcomes	Breast: 12 Colorectal: 1 Leukemia: 1 Prostate: 1 Stomach: 1 Mixed: 10	Aerobic: 17 studies Resistance: 2 studies Combined intervention: 7 studies	During and after treatment Dose-training response	Studies predominantly in breast cancer using cardiovascular training Conclusions/ recommendations: • Cardiovascular training 55-90% MHR or 40-85% MHRR, 3-5 days/ week, 20-60 minutes, continuous or intermittent; Resistance exercise 50-80% 1RM, 1-3 days/ week, 1-4 sets, number of repetitions not stated. Flexibility 2-3 days/ week, 10-30 seconds, 2-4 sets per muscle group, specific stretches & intensity not stated.

Table I-1 (continued). Systematic Reviews of Physical Activity in Cancer Survivors (Published by 2005)

Study author, year # RCTs	Selection Criteria	Tumor Groups included:	Exercise intervention	Specific focus of review	Results/ Key Findings
Knols, 2005 27 RCTs/ 34 trials	Controlled trials: P: Cancer patients I: Physical exercise C: Not stated O: Specific Physical & QoL No language restrictions	Breast: 16 Colon: 1 Head & Neck: 1 Leukemia: 1 Multiple Myeloma: 1 Prostate: 1 Stomach: 1 Mixed: 12	Aerobic: 20 studies Resistance: 3 studies Combined intervention: 11 studies	Divided into breast, BMT/PSCT, mixed solid tumors During and after cancer treatment	Trials were of moderate methodological quality Breast during treatment: 9 trials Breast post treatment: 7 studies Exercise post BMT or PSCT: 8 trials Mixed solid tumors during treatment: 5 trials Mixed solid tumors after treatment: 5 trials Conclusions/ recommendations: • Cancer patients may benefit from physical exercise during and after cancer treatment

Table I-2. Meta-Analyses Performed Examining Physical Activity in Cancer Survivors (Published by 2005)

Study author, year # RCTs	Selection Criteria	Cancer Tumor Groups included:	Exercise intervention	Specific focus of review	Results/ Key Findings
Stevinson, 2004 25 RCTs /33 Trials	Controlled Trials: P: Cancer patients all stages I: Exercise: any type to C: Control/ Comparison O: All outcomes Published & unpublished, no language restrictions	Breast: 10 Colorectal: 1; Lung: 1; Multiple Myeloma: 1; Prostate: 3; Stomach: 1; Leukemia: 1 Mixed: 7	Aerobic exercise: 19 studies; Resistance: 3 studies Combined aerobic & resistance: 10 studies Team sport: 1 study	Data presented as exercise effect in breast cancer versus nonbreast cancer	Physical Function: Effect size: 0.96 for breast cancer & 0.55 for nonbreast cancers No increases in fatigue as a result of exercise participation
Schmitz, 2005 27 RCTs/32 Trials	Controlled trials: P: Adult cancer patients all stages I: Exercise C: Comparison group O: All outcomes Published, English language only	Breast: 23 Lung: 4 Colon: 3 Ovarian: 2 Stomach: 1 Prostate: 2 Lymphoma: 3 Other: 8	Aerobic component: 29 studies Only nonaerobic exercise: 2 studies Not specified: 1 study	Timing of intervention: Acute: 1 buffering; 17 coping Post Treatment: 13 Health prom: 5 Survival: 2 Mixed: 6	Cardiorespiratory fitness: Effect size: 0.51 during treatment & 0.65 after treatment Symptoms/ physiological outcomes during treatment: Effect size: 0.28 Vigor post treatment: Effect size: 0.83

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II: CHAPTER TWO

"Effects of Exercise on Breast Cancer Patients and Survivors: a Systematic Review and Meta-Analysis"

McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. (2006), Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. Reprinted from *CMAJ Canadian Medical Association Journal*. 17: 34-41, by permission of the publisher.

II-1. INTRODUCTION

Among females living in Western countries, breast cancer is an important disease in terms of incidence and mortality (1-3). Improvement in survival over the past twenty years has resulted in a substantial number of breast cancer survivors, many of whom will have a normal life expectancy (3). Increasingly, cancer care is being directed towards developing interventions to improve overall quality of life (QoL) as well as longevity (4).

Physical exercise has consistently been identified as a central element of rehabilitation for many chronic diseases(5-8) and has been successful in improving quality of life and reducing all cause mortality (9). Recent observational evidence suggests that moderate levels of physical activity may even reduce the risk of death from breast cancer (10), and therefore, exercise may prove to be a valuable intervention to improve not only quality of life but overall survival.

The effectiveness of exercise interventions in cancer patients and survivors has been assessed in both qualitative systematic reviews and meta-analyses that included all types of cancers and all types of trial designs (i.e., nonrandomized and/or uncontrolled trials)(11-13). It is well-known, however, that cancer survivor groups are clinically heterogeneous in terms of their demographic profile (e.g., age, sex distribution), behavioral profile (e.g., smoking status, drinking status, obesity rates), disease pathophysiology, treatment protocols, and symptoms and side effects. Consequently, the wisdom of summarizing the effects of exercise interventions across such disparate groups is questionable. It is clear from previous reviews that the vast majority of exercise intervention research has been conducted in breast cancer patients and survivors. Therefore, there is now sufficient research to restrict a meta-analysis to this cancer

survivor group. It is also well-known that the inclusion of nonrandomized and/or uncontrolled trials provides an overestimation of the effect of an intervention. It is recommended that meta-analyses be restricted to RCTs if possible (14). Here, we present the first systematic quantitative review of the effects of exercise interventions in breast cancer patients and survivors restricted solely to randomized controlled trials.

II-2. METHODS

The following electronic databases were searched to March 2005: Cochrane library, MEDLINE, EMBASE, CANCERLIT, CINAHL, PSYCHLIT, PEDRO and Sport The breast cancer specialised register maintained by the Cochrane Breast Cancer Group was also searched (Details of search strategies used by the group for the identification of studies are outlined in the group's Cochrane Library module). Search terms related to breast cancer (e.g. breast neoplasms, mastectomy, axillary dissection), exercise (e.g. exercise, physical activity, sport) and publication type (e.g. random allocation, clinical trial) were used. The search strategy used for MEDLINE is provided, as an example, in Appendix 1. Modification of this search strategy was performed as necessary for each database. Non-English language publications were included. In order to locate unpublished research, we reviewed proceedings from major cancer and sport medicine meetings, clinical practice guidelines for breast cancer and searched websites housing clinical trial details, theses or dissertations. In addition, we hand-searched the reference lists of all potentially relevant studies and contacted experts and authors of previous studies to identify relevant articles.

II-2.1. Inclusion criteria

Studies were considered eligible for inclusion if they were randomized controlled trials (RCTs) comparing exercise to a placebo, controlled comparison or standard care. For the purposes of the review, exercise was defined as a form of leisure-time physical activity that was performed on a repeated basis, over an extended period of time, with the intention of improving fitness, performance, or health (15). Studies with an additional treatment arm/combined intervention (i.e. exercise with diet modification) were included only if the effects of exercise could be isolated. Exercise studies that included cancers other than breast cancer were excluded unless separate data were available for the breast cancer subgroup. Therapeutic exercise regimens addressing only specific impairments related to the shoulder and/or arm were excluded.

Inclusion in this review was restricted to trials of women with early to later stage (Stage 0-III) breast cancer who had undergone breast cancer surgery with or without adjuvant cancer therapy. Studies were required to include one of the following primary outcomes of interest: quality of life (QoL), cardiorespiratory fitness, or physical functioning. Secondary outcomes of interest included fatigue and body composition (body weight/ body mass index). Information was sought on complications (adverse events) resulting from the exercise intervention. *A priori*, we decided to exclude any reports that were available in abstract form only.

II-2.2. Study selection, data abstraction, and assessment of quality

Two independent reviewers (MLM, KLC) screened the titles and abstracts of identified studies for eligibility. Papers deemed potentially relevant were obtained and the full papers were reviewed for inclusion, again by the two independent reviewers.

Information on patients, methods, interventions, outcomes, and adverse events were abstracted from the original reports onto specially designed, pre-tested paper forms by the two independent reviewers. All disagreements were resolved by consensus.

The methodological quality of each RCT was assessed using the following criteria: 1) Was there adequate concealment of allocation?; 2) Was the method of randomization well described and appropriate?; 3) Was the outcome assessment described as blinded?; 4) Was there a description of withdrawals and dropouts?; 5) Was the method of blinding of the assessment of outcomes well described and appropriate?; 6) Was the analysis intention-to-treat?; 7) Were withdrawals/ dropouts < 10%; 8) Was the adherence to the exercise intervention (attendance/ completion of exercise session) > 70%?. All items were scored as positive (+), negative (-) or unclear (?). High quality was defined as fulfilling 4 or more of the 8 quality criteria.

II-2.3. Statistical Analysis

All data were entered into Review Manager Software (version 4.2.3, Update Software, Oxford, United Kingdom). Results of studies were pooled, if appropriate, using random effects models after consideration of heterogeneity between the trials. For continuous outcomes, individual and pooled statistics were calculated as weighted mean differences (WMD) when data were on a uniform scale and standardized mean differences (SMD) with 95% confidence intervals (95% CI) were calculated when data were on different scales. The estimated effect size was calculated for outcomes that were reported in three or more studies. For dichotomous variables, individual and pooled statistics were calculated as odds ratios (OR) with 95% CI. Heterogeneity was tested using a chi-squared test that considered a p-value of less than 0.10 to indicate significant

heterogeneity between the trials. When heterogeneity was evident, and could be explained by clinical dissimilarities, trials were not pooled.

II-3. RESULTS

II-3.1. Search and Selection of Studies

The search identified 140 papers, of which 25 were considered potentially relevant (16-40). Independent review of these 25 papers led to the inclusion of 14 studies involving 717 participants (16-20, 25, 26, 30-32, 34-37). Study methodology varied significantly, particularly with regards to timing of the exercise intervention, the chosen exercise regimen and outcomes reported (see Table 1). Kappa statistics for agreement on inclusion of trials and quality score were 0.8 and 0.92 respectively.

The median score for methodological quality of all included studies was 3 with a range of 0 to 7 (Table 2). Using a cutoff point of 4 out of 8 criteria, 4 of the 14 studies were considered high quality (18, 19, 30, 37). The most common methodological shortcomings in the studies involved were the following:

- No blinding of outcome assessment (12 studies scored "negative" or "unclear")
- Inadequate method of blinding outcome assessment (12 studies scored "negative" or "unclear")
- Inadequate concealment of allocation (11 studies scored "negative" or "unclear")

II-3.2. Quality of Life

Three studies involving 194 patients compared exercise to control (17, 18, 37). Exercise was superior to control (usual care) for both the Functional Assessment of Cancer Therapy - General (FACT-G) and Functional Assessment of Cancer Therapy -

Breast (FACT-B) QoL scales. Pooled data from three studies demonstrated that exercise led to significant improvements in QoL for both the FACT-G (WMD = 4.58; 95% CI: 0.35, 8.8) and FACT-B (WMD = 6.62; 95% CI: 1.21, 12.03) (see Figure 1).

II-3.3. Cardiorespiratory Fitness

Cardiorespiratory fitness was reported as an outcome in nine studies (17-20, 25, 31, 32, 34, 37) involving 473 patients. Due to significant heterogeneity between the nine trials, data were not combined and are reported only by specific outcome measurement (Table 3). Three of the studies(18-20) that reported peak oxygen consumption in ml/kg/min from symptom-limited graded exercise tests were successfully combined. The pooled results from these three studies showed a significant improvement in peak oxygen consumption with exercise (WMD: 3.39; 95% CI: 1.67, 5.10).

II-3.4. Physical Functioning

Four studies (17, 18, 26, 37) involving 208 patients reported physical functioning or physical well-being components of QoL. Two studies(17, 18) reported the physical well-being subscale of the FACT QoL scale and two studies(26, 37) reported results from the physical functioning subscale of the SF-36. The pooled results from showed a statistically significant increase in physical functioning/well-being from exercise (SMD: 0.84; 95% CI: 0.36, 1.32).

II-3.5. Fatigue

Six studies (16-18, 20, 30, 34) involving 319 patients assessed the effect of exercise on symptoms of fatigue. One study(18) measured fatigue using the Fatigue Scale of the Functional Assessment of Cancer Therapy QoL scale (FACT-F), four studies (16, 17, 20, 30) measured fatigue using the revised Piper Fatigue Scale and one study

used a visual analogue scale for fatigue (34). Though all studies demonstrated improvements in symptoms of fatigue with exercise, only the two studies(18, 34) reported statistically significant improvements in fatigue from exercise. The two studies(18, 34) were also the only studies carried out following cancer treatment. The pooled results from all six studies (Figure 2) showed that exercise significantly improved symptoms of fatigue (SMD: 0.46; 95% CI: 0.23, 0.70). The pooled results from the four studies (16, 17, 20, 30) carried out during adjuvant cancer treatment showed a nonsignificant effect on fatigue (SMD 0.28; 95% CI: -0.02, 0.57).

II-3.6. Body composition

Four studies(18, 20, 35, 37) monitored body weight and four studies(18, 20, 34, 35) reported body mass index (BMI) as an outcome. The pooled results from the four studies showed a nonsignificant reduction in body weight (WMD: -0.03 kg; 95% CI: -0.44, 0.38). The individual study results as well as the pooled results for BMI showed non-significant reductions in favour of exercise (WMD: -0.02; 95% CI: -0.09, 0.05).

II-3.7. Adverse events

Adverse events were reported in four studies (18-20, 36). One study (36) reported back injury (n = 4) and shoulder tendonitis (n = 1) related to participation in the resistance exercise intervention during the first six months of the trial. Injuries to the back (n = 4), wrist (n =1), lower leg and ankle (n = 5) and rotator cuff (n = 1) related to study participation were also reported in months 7 to 12 of the same trial. In another study, shoulder tendonitis (n = 1) and a worsening of fatigue (n = 2) were reported as adverse outcomes related to study participation (20). Two studies also reported cases of lymphedema occurring in exercise participants (18, 19). There was a non-significant

difference in the occurrence of lymphedema between exercise and control interventions in the individual studies and when data was pooled (OR: 4.91; 95% CI: 0.52, 36.25).

II-4 DISCUSSION

This review summarizes the best available evidence regarding the effects of exercise on QoL and physical outcomes for breast cancer patients and survivors.

II-4.1. Quality of life and Physical Functioning

Only three studies provided adequate data to assess QoL. The statistically significant increase of > 4.0 points on the FACT scale represents a clinically meaningful improvement in QoL from exercise (41). Additionally, analyses of the physical functioning and physical well-being subscales of QoL indicated large improvements (effect size = 0.84) from exercise.

II-4.2. Cardiorespiratory Fitness

The pooled results of three studies examining peak oxygen consumption from symptom-limited graded exercise testing showed an improvement of 3.39 ml/kg/min or almost one metabolic equivalent (MET) improvement in fitness (42). Each 1 MET increment in fitness has been found to correspond to a 12 percent improvement in survival in men (42). As cardiorespiratory fitness is an important predictor of all-cause mortality in women(9), it is likely that an improvement of this magnitude would have similar implications in women; however, the duration of these studies was insufficient to provide this evidence.

II-4.3. Fatigue

The pooled results of the six studies examining the effect of exercise on symptoms of fatigue showed a moderate-to-large effect (effect size: 0.72); however, statistically significant improvements in symptoms of fatigue were reported in only two studies (18, 34). Both studies examined exercise following primary cancer treatment (18, 34). During adjuvant cancer treatment, the effect of exercise on fatigue is less clear. The evidence suggests that exercise has a nonsignificant and potentially small effect on symptoms of fatigue for women undergoing adjuvant cancer treatment. Despite statistical nonsignificance in the four studies, all point estimates were in favour of exercise suggesting the need for more research prior to rejecting this effect.

II-4.4. Body composition

There was no statistically or clinically significant change in body weight or body mass index as a result of the exercise trials included in this review. It is not known, however, if positive changes in body composition occurred as a result of the exercise intervention due to lack of studies using direct measures of tissue-and body composition. As an example, Schmitz et al (2005) examined body composition by means of dual X-ray absorptiometry and reported positive changes in lean body mass as well as significant decreases in percent body fat in favour of the exercise intervention (Table 3) (35). As well, Schwartz et al (unpublished data) assessed bone density of the lumbar spine using dual X-ray absorptiometry and reported that subjects participating in weight bearing aerobic exercise had significantly less bone density loss than controls (Table 3)(36). The findings suggest that positive changes in body composition may occur despite nonsignificant changes in body weight and body mass index.

II-4.5. Methodological Quality

The studies included in this review were of variable quality, with only four studies considered of high quality. Our conclusions are tempered by this fact. Clearly, further progress must be made to improve research quality. Future trials should focus on adequate randomization, concealment of allocation and blinding of outcome assessors throughout the study.

A noteworthy feature of trials included in this review was the wide variability in study execution. Many different exercise regimens were prescribed. The diversity in exercise prescription is not surprising, however, given the lack of consensus on the optimal exercise prescription for this patient population. Conversely, the wide variety in study outcomes and measurement methods is surprising. This variation precluded pooling studies and made overall conclusions regarding the relative effectiveness of exercise difficult. The short duration or complete lack of follow-up data examining the effect of exercise on QoL and rehabilitative outcomes in the long-term is also noted. Moreover, data are lacking to support the use of exercise in preventing cancer recurrence and improving overall survival.

A further limitation of this meta-analysis is the non-specificity with respect to the timing of the exercise intervention. Clinical heterogeneity was evident particularly in trials carried out during adjuvant cancer treatment. This resulted from trials conducted during different adjuvant cancer treatments and/or trials in which the participants were undergoing one of a variety of adjuvant treatments (e.g. chemotherapy, radiation therapy and hormonal therapy).

Finally, poor adverse event reporting in most of the studies limits any conclusions

about the relative safety of exercise, and the small sample sizes provide insufficient power to detect meaningful differences in rates of rare adverse events. For example, lymphedema is a potential side effect of cancer treatment and represents a barrier to exercise for some individuals(4), and yet none of the included studies formally monitored for this side effect.

II-5. CONCLUSIONS AND FUTURE RESEARCH

The evidence suggests that exercise is an effective intervention to improve QoL, cardiorespiratory fitness, physical functioning and symptoms of fatigue in breast cancer patients and survivors. While these preliminary results are promising, the findings are based on a relatively small number of trials with significant methodological weaknesses. Furthermore, at present, there is no evidence to support the use of current exercise regimens to reduce body weight or body mass index. Based on our findings, we make the following research recommendations:

1) Methodologically rigorous studies designed to examine different exercise regimens (e.g. comparing moderate vs. low-intensity) are needed in order to better understand of the role of physical exercise among breast cancer patients and survivors.

2) The exercise prescription should be reported in detail (frequency, intensity, time and type of exercise) to allow for determination of exercise dose-response. To this end, adherence to exercise should be reported for both completion of exercise sessions (attendance) and exercise prescription (intensity and duration). Furthermore, monitoring of activity in the comparison group(s) is necessary to assess potential contamination.

3) Consensus is required on standardized methods of assessing physical fitness

and body composition to allow for pooling of data and for comparisons across studies.

4) Future trials should formally monitor for, and report the incidence of potential adverse events such as lymphedema.

Table II-1: Characteristics of Randomized Controlled Trials Examining the Effectiveness of Exercise for Breast Cancer

Study (year/ country)	Features	Participants	Intervention	Key Endpoints	Comments
Battagliani 2004 United States	**Supervised exercise** during adjuvant radiotherapy or chemotherapy	20 women with mean age (SD) of 57 (± 20) years	Mixed aerobic & resistance exercise; 2x/ week for 15 weeks @ 40-60% predicted exercise capacity; percentage of 1RM not stated; 60 minutes per session	Lean body mass VO_{2peak} U/E & L/E strength: 1 RM Fatigue	Incomplete data for lean body mass, VO_{2peak} and strength measures Adherence: not reported
Campbell 2004 United Kingdom	**Supervised exercise** during adjuvant radiotherapy or chemotherapy	19 women with mean age (SD)of 47.5 (± 8) years	Mixed aerobic & resistance exercise; 2x/week for 12 weeks @ 60-75% HR maximum; 10-20 minutes per session	QOL 12 minute walk test	Adherence: exercise attendance 70%
Courneya 2003 Canada	**Supervised exercise** post treatment x 1 year	52 postmenopausal women with mean age of 59 (± 6) years	Aerobic exercise (upright or recumbent cycle ergometer); 3x/week for 15 weeks @ 70-75% $VO_{2peak;}$ progressive 15-35 minutes per session	QOL VO_{2peak} Body weight Body composition (BMI & SSF)	Adherence: exercise attendance 98%
Crowley 2003 United States	**Home based exercise** during specific adjuvant chemotherapy with adriamycin & cyclophosphamide	22 women with age range of 35-60 years	Mixed aerobic (walking) & resistance (tubing); 3-5x /week for 13 weeks @ 60% of HR maximum; duration of exercise per session unclear	QOL VO_{2peak} U/E & L/E strength: 1 RM	Unable to use some relevant endpoints as data presented in graph form. Adherence: exercise completion not reported
Drouin 2002 United States	**Home based exercise** during adjuvant radiation therapy	23 women Age: 50 (± 8.2) years	Aerobic (self-monitored walking program with HR monitor); 3-5x/week for 7 weeks at 50-70% of HR maximum for 20-45 minutes per session.	QOL VO_{2peak} Body weight Body composition (BMI & SSF)	Adherence: exercise completion not reported

Table II-1 continued: Characteristics of Randomized Controlled Trials Examining the Effectiveness of Exercise for Breast Cancer

Study (year/ country)	Features	Participants	Intervention	Key Endpoints	Comments
MacVicar 1989 United States	**Supervised exercise** during adjuvant chemotherapy/ hormonal therapy	45 women Age: 45 (± 9.9) years	Aerobic (interval training on a stationary cycle ergometer); 3x /week for 10 weeks at 60-85% of HRR, duration progressively increased.	VO_{2peak} **Analysis:** without intention to treat analysis.	Adherence to exercise not reported
McKenzie 2003 (23) Canada	**Supervised exercise** post treatment with mean 6.5 (± 9) years from treatment	14 women with unilateral arm lymphedema Age: 56 (±9) years	Aerobic (arm ergometer) & resistance exercise; 3x/week for 8 weeks with progressive increase in intensity 8-25 watts (aerobic) & 2-3 sets of 10 repetitions of unreported weight (resistance); 5-20 minutes (aerobic) & not stated (resistance)	QOL UE (volume & circumference) **Analysis:** all subjects included in analysis	One subject in exercise allowed to join control group Adherence to exercise not reported
Mock 2005 United States	**Home-based exercise** during adjuvant radiotherapy or chemotherapy	119 sedentary women Age: 52 (±9) years	Aerobic (walking) 5-6x /week for 6 weeks (radiation therapy) or 3-6 months (chemotherapy) at 50-70% max HR & RPE, progressive increase in time from 15 to 30 minutes	QOL 12 minute walk test	12 minute walk test & physical functioning data as not reported by randomized group -Adherence: exercise completion 72%
Mustian 2003 United States	**Supervised Exercise** post treatment within 3 years from diagnosis	27 women; mean age (SD): 52 (±9) years	Tai Chi Chuan; 3x/week for 12 weeks for 60 minutes	6 minute walk test Muscular fitness (dynamometer & hand grip) Body composition (bioelectrical impedance)	Adherence: exercise attendance 72%
Nieman 1995 United States	**Supervised exercise** post treatment; mean 3.0 (±1.2) years from diagnosis	16women Age: range 35-72 years	Mixed aerobic (walking) & resistance (weights) training (2 sets of 12 repetitions for 7 exercises); 3x/week for 8 weeks at 75% max. Intensity not stated for resistance. Exercise duration: 60 minutes (30 minutes aerobic & 30 minutes resistance)	6-minute walk test L/E strength	Adherence: exercise attendance 87%

Table II-1 continued: Characteristics of Randomized Controlled Trials Examining the Effectiveness of Exercise for Breast Cancer

Study	Features	Participants	Intervention	Key Endpoints	Comments
Pinto 2005 United States	**Home based exercise** post treatment within 5 years from diagnosis	86 sedentary women Age: 53.1 (±10) years	Aerobic exercise: 2x/ week progressed to 5x/ week over 12 weeks @ 55% to 65% max HR; 10 minutes progressed to 30 minutes per session	One mile walk test BMI Percent body fat (sum of skin folds) Fatigue	Adherence: unclear
Schmitz 2005 United States	**Supervised exercise (13 weeks) then self-directed exercise (13 weeks)** post treatment 4 to 36 months.	85 women Age: 53.0 (8.2) years	Resistance exercise 2x/ week for 26 weeks; LE based on 8RM & UE starting at lightest weight; systematically progressed 1 set to 3 sets of 8-10 repetitions.	U/E & L/E strength Body weight BMI DEXA: Lean mass & body fat	Incomplete data for strength measures. Adherence: exercise attendance 92%
Schwartz (in press) United States	**Home based exercise** during adjuvant chemotherapy 3 groups: aerobic, resistance and control	66 women Age: 48.2 years (10.5)	1) Aerobic (walking/ jogging): 4 days/week for 6 months symptom-limited moderate intensity for 15-30 minutes 2) Resistance exercise: 4 days/ week for 6 months progressive resistance using bands and tubing; 2 sets of 8-10 repetitions of 4 UE and 4 LE exercises	12 minute walk test U/E & L/E strength Bone mineral density (spine)	Adherence: unclear
Segal 2001 Canada	**Supervised & Self-directed exercise groups** during adjuvant treatment (chemotherapy, radiation therapy or hormonal therapy) -3 groups: supervised, self-directed and control	123 women Age: 50.9 (8.7)	1) Supervised aerobic exercise (SE): supervised 3x/week & 2x/wk self-directed at 50-60% of estimated VO_{2peak} progressive increase in % $VO_{2peak;}$ duration not stated 2) Self Directed (SD) aerobic exercise: 5x/week @ 50-60% of estimated $VO_{2peak;}$ progressive increase in % $VO_{2peak;}$ duration of exercise not stated.	QOL Estimated VO_{2peak} (submaximal test) Body weight	Adherence: attendance/ completion 72%

HR, heart rate; QOL, quality of life measure; VO_{2peak}, peak oxygen consumption measured using an incremental exercise test (aerobic fitness); BMI, body mass index (kg/m^2); SSF, sum of skin folds (mm); U/E, upper extremity; L/E, lower extremity; RM, repetition maximum for muscular strength; DEXA: dual-energy x-ray absorptiometry.

Table II-2: Methodological Quality Assessment of Randomized Controlled Trials on the Effectiveness of Exercise Interventions for Breast Cancer

Study	1	2	3	4	5	6	7	8	Total/ 8
Battagliani, 2004	?	+	-	-	?	+	+	-	3
Campbell, 2004	?	+	-	-	+	-	-	+	3
Courneya, 2003	+	+	+	+	+	-	+	+	7
Crowley, 2002	+	+	+	+	+	-	+	?	6
Drouin, 2002	?	+	-	-	?	-	+	?	2
MacVicar, 1989	?	-	?	?	-	-	-	?	0
McKenzie, 2003	?	-	-	-	+	+	+	?	3
Mock, 2005	+	+	-	-	+	+	-	+	5
Mustain, 2003	?	-	?	?	+	-	-	+	2
Nieman, 1995	?	-	-	-	+	-	-	+	2
Pinto, 2005	?	-	-	-	+	+	+	?	3
Schmidtz, 2005	?	+	-	-	+	-	-	+	3
Schwartz (unpublished)	-	-	-	-	-	+	+	?	2
Segal, 2001	?	+	-	-	+	+	-	+	4
# studies meeting criterion	**3**	**8**	**2**	**2**	**10**	**6**	**7**	**7**	

1) Adequate allocation concealment; 2) Adequate method of randomization; 3) Blinded outcome assessment; 4) Adequate method of blinding; 5) Description of withdrawals/ dropouts; 6) Intention to treat analysis; 7) Withdrawals & dropouts < 10%; 8) Adherence: reported attendance/ completion of exercise sessions > 70%. + = positive; - = negative; ? = unclear.

Table II-3: Evidence of Effects of Exercise on Cardiorespiratory Fitness, Body Composition and Physical Functioning Outcomes

Outcome	**Unit**	**# studies**	**N**	**WMD (units) (95% CI)**	**P-value**	**SMD (Effect Size) (95% CI)**	**P-Value**
Cardiorespiratory Fitness							
VO_{2peak} absolute	L/min	2	95	0.30 (0.2, 0.41)	0.00001*	Not estimated	
VO_{2peak} relative	mL/kg/min	3	95	3.39 (1.67, 5.1)	0.0001*	1.14 (0.47, 1.81)	0.0009*
Predicted VO_2 (submaximal tests)	mL/kg/min	2	150	0.99 (-0.21, 2.18)	0.07	Not estimated	
6-minute walk test (goal more distance)	metres	2	39	35 (12.6, 58.1)	0.002*	Not estimated	
12-minute walk test (goal more distance)	metres	1	19	101 (62.5, 140.4)	0.00001*	Not estimated	
1 mile walk test (goal less time)	minutes	1	86	-1.31 (-0.42, -0.20)	0.004*	Not estimated	
Body Composition							
Weight (goal to reduce)	Kg	4	277	-0.03 (-0.44, 0.38)	0.88	-0.07 (-0.36, 0.21)	0.61
Body Mass Index (goal to reduce)	Kg/m^2	4	240	-0.02 (-0.09, 0.05)	0.58	-0.12 (-0.38, 0.13)	0.35
Percent Body Fat (goal to reduce)	Percent	1	81	-1.38 (-1.57, -1.19)	0.03	Not estimated	
Lean Body Mass (goal to gain or avoid muscle loss)	Kg	1	81	0.86 (0.76, 0.96)	0.008	Not estimated	
Bone density (goal to gain or avoid loss)	Percent	1	66	3.79 (-2.55, -4.17)	0.02	Not estimated	
Physical Functioning	Subscales	4	208	Not estimated	-	0.84 (0.36, 1.32)	0.0006

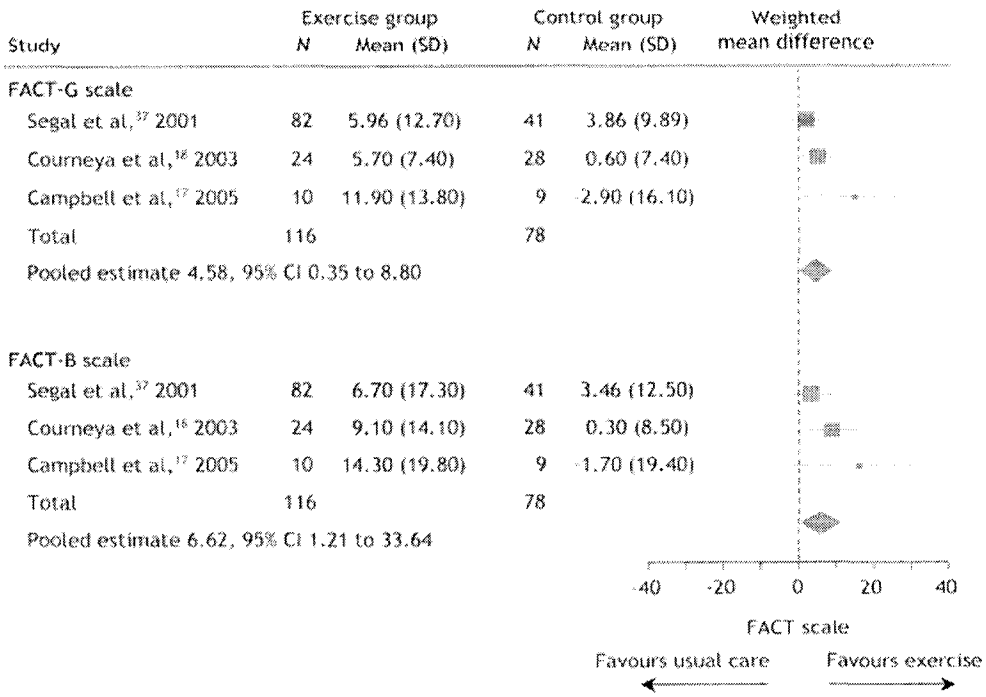

Figure II-1: Effect of Exercise on Quality of Life

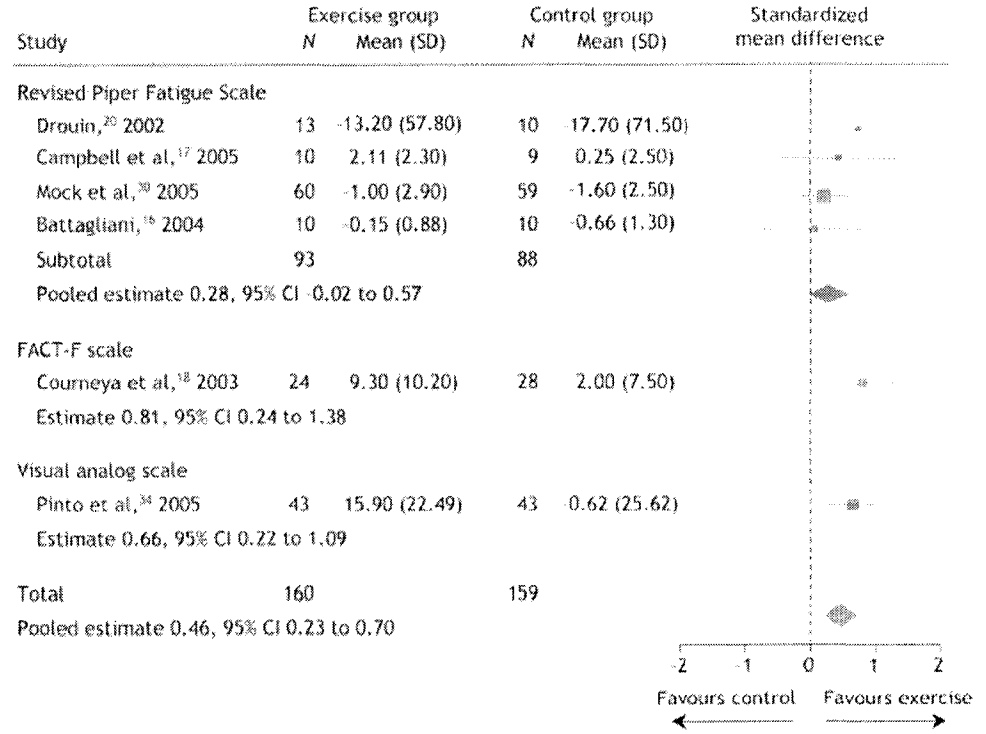

Figure II-2: Effect of Exercise on Fatigue

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III: CHAPTER THREE

"Resistance Exercise for Post Neck Dissection Shoulder Pain: Three Case Reports"

McNeely, M. L., M. Parliament, K. S. Courneya and M. Haykowsky (2004). Resistance exercise for post neck dissection shoulder pain: Three case reports. Reprinted from, *Physiotherapy Theory & Practice.* Vol. 20(1)(pp 41-56) by permission of the publisher.

III-1. INTRODUCTION

In North America, head and neck cancers account for 5% of all malignant tumours (1, 2). The majority of head and neck cancers are squamous cell in histology, and the most common areas of occurrence are in the larynx and oral cavity (1, 3). Though the primary goals of head and neck cancer treatment are cancer eradication, maintenance of normal function, and acceptable cosmetic appearance, patients often have considerable post treatment morbidity that heightens the impact of the disease (1, 4). Mastication, speech, respiration and cosmesis can all be radically altered by the cancer and/or cancer treatment (4, 5). A further set of problems may arise, however, when nodal dissection of the neck is performed in conjunction with surgical resection of the primary tumour site, a procedure necessary for the purpose of tumour staging and/ or for the treatment of lymph node metastases (3, 6). A well-documented complication of the neck dissection procedure is shoulder pain and dysfunction as a result of temporary damage to (neuropraxia/ axonotmesis), or resection of (neurectomy), the spinal accessory nerve (7-10).

The spinal accessory nerve, or cranial nerve XI, is the principal motor innervation to the trapezius muscle (8, 11-14). The trapezius provides passive support to the shoulder complex and is an important stabilizer of the scapula (8, 15, 16). Paralysis or weakness of the trapezius alters the alignment of the shoulder and disrupts the normal synchronous motion of the shoulder complex (8, 16, 17). The resulting dysfunction may remain a significant long-term problem (18). Months after the completion of cancer treatment, when other side effects have improved or resolved, the shoulder weakness and pain have

often deteriorated to a chronic state that includes glenohumeral joint restriction and marked deformity of the shoulder complex (8, 18, 19).

Previous investigations examining the incidence of shoulder morbidity following neck dissection have had variable findings (8, 15, 19). This variability may be due in part to differences in chosen outcome measures, and would be dependent on both the type of neck dissection performed and the resulting degree of nerve damage (8-10, 19). The presence of additional innervation, in approximately 20% of cases, from nerves other than the spinal accessory nerve, may also explain preservation of partial muscle function and thus inconsistent findings (11). The traditional radical neck dissection is associated with a reported incidence of shoulder pain and weakness in 60% to 100% of cases (15, 20). The high probability of shoulder impairment following radical neck dissection procedures is the primary reason for the preference of nerve-sparing procedures (7, 21). Preservation of the nerve does not, however, guarantee adequacy of its function, and the probability of post-operative trapezius paresis even after nerve-sparing procedures is still estimated to be between 20% and 60% (8, 15, 19).

Functionally, the impaired range of motion at the shoulder causes difficulty in simple tasks such as combing the hair, putting on clothing and reaching for objects overhead (12). Patients may complain that there is a loss of power in the arm and that it is easily fatigued with use (22). As a result, some patients are unable to continue with their usual household or recreational activities (2). Movement may exacerbate the pain, and patients with severe discomfort may require long-term use of narcotic analgesics (23). For patients whose job involves heavy manual work, the resulting disability may prevent return to the workplace (9, 21).

Various surgical procedures are available to correct or avoid shoulder problems (23, 24) due to chronic trapezius dysfunction; however, cancer patients, due to issues of age, activity levels, tissue fibrosis from combined surgery and radiotherapy, and recurrent malignancy are usually considered poor surgical candidates (18). For this reason, physiotherapy is generally recommended (8, 17, 18, 25), with treatment regimens varying from simple range of motion exercises to established physiotherapy programs (12, 16, 17, 25, 26). Initial treatment goals include preventing shoulder droop, reducing or eliminating pain, avoiding pectoralis muscle contracture, and improving scapular stabilization by strengthening alternative muscles to compensate for the loss of the trapezius (25).

The consensus among practitioners is that the quality and quantity of the physiotherapy intervention is a significant factor in retaining shoulder function and in preventing pain (18). Anecdotal evidence and results from early case studies suggest that this is the case, but since treatment is not standardized and research in the area is sparse, uncertainty remains. Gordon, Graham, Black and Miller (1977), for example, in a study examining spinal accessory nerve function following neck dissection techniques in the posterior triangle, noted improvement in 7 of 8 subjects receiving therapeutic exercise for the shoulder (26). Fialka and Vinzenz (1988) examined shoulder function after radical neck dissection, reporting positive results in the 18 study subjects who participated in a combined program of muscle stimulation, massage and therapeutic exercise (22). Johnson, Anseff and Saunders (1978) designed a resistance exercise program that focussed on the scapular retractors and elevators and noted improvements in posture, shoulder range of motion and function, and decreased pain (17). Herring, King and

Connelly (1987) described the use of an Isokinetic Dynanometer for strengthening of the shoulder in conjunction with a shoulder range of motion program (12). The strengthening program was progressed in terms of sets, range of motion, and speed of movement. The authors reported subjective improvements in symptoms and a reduction in overall rehabilitation time.

This article presents three case reports on a client management program that incorporated progressive resistance exercise training (PRET) to improve shoulder pain and function following neck dissection procedures.

III-2. CASE REPORTS

III-2.1. Case # 1

Diagnosis and Cancer treatment

A 52-year-old man was diagnosed with a squamous cell carcinoma of the base of the tongue. Surgery included a right extended hemiglossectomy, right lateral pharyngotomy, right radical neck dissection (sacrifice of spinal accessory nerve, sternocleidomastoid and internal jugular vein) and a left radial forearm free flap repair. He received 7 weeks of radiation therapy postoperatively. He was referred to physiotherapy in his final week of radiation therapy.

Physiotherapy Assessment

On initial assessment, the patient complained of a stiff, weak, right shoulder (dominant side) and a constant, toothache-like pain in the right upper scapular region. He had visible trapezius atrophy and a slight shoulder droop on the right side. The right scapula was resting in a depressed and protracted position on the chest wall. Active shoulder range of motion was limited in forward flexion, abduction and both rotations.

Passive range of motion was normal. Increased prominence ("winging") of the medial border of the scapula was apparent with forward flexion, and more pronounced with abduction in the coronal plane. The patient's goal was to regain adequate mobility of the shoulder to return to his previous occupation in manual labour.

Treatment Regimen

The patient requested a program that could be carried out in a fitness facility in his home town. A specific resistance training program for the shoulder was designed for him and was monitored by the personal fitness trainer at the facility. The exercise sessions were performed two or three days per week. Initially, all exercises were done in a supported position (supine or supported sitting) to assist in stabilizing the scapula. The chosen muscle groups to be strengthened were biceps, triceps, rhomboids, levator scapulae and latismus dorsi. Initially, free weights (1 kg to 2.5 kg) and resistive bands were used. The resistance was increased when all repetitions could be performed in the second set, and eventually, where possible, specific exercises were progressed to weight machines. Guidelines for progression of resistance included: maintaining appropriate posture and scapular position (no winging) during the specific exercise, no increased shoulder pain during the exercise session or in the following 24-hour period, and full recovery of secondary muscle soreness by the next training session. The program also included self-assisted shoulder range of motion exercises and stretching exercises for the pectoralis muscle group.

Outcome Measurements

Improvements were noted in both active shoulder range of motion and pain following the 6 months of resistance training (see Table 1). Improvements in pain and

function were measured using the shoulder pain and disability index (SPADI), an assessment questionnaire that was developed to measure the pain and disability associated with shoulder pathology (27). The SPADI is a self-administered index consisting of 13 items, divided into 2 sub-scales: pain and disability. The SPADI was not being used at the time of the patient's initial assessment and therefore was administered only at the 6-month follow-up. The patient had no reported complaints of pain at follow-up. Despite the absence of initial assessment information, it was apparent from both the SPADI and the follow-up physical assessment that, notwithstanding significant gains in strength, the patient continued to report functional limitation in tasks requiring the arm in an overhead position.

III-2.2. Case # 2

Diagnosis and cancer treatment

A 65-year-old man was initially diagnosed with adenocarcinoma of a left jugulodigastric lymph node from unknown primary. He was treated with preoperative radiation therapy followed by a left radical neck dissection (sacrifice of the spinal accessory nerve, sternocleidomastoid and internal jugular vein). Two years later, he was diagnosed with a squamous cell carcinoma of the right vocal cord, had a laryngectomy and right selective neck dissection with sparing of the spinal accessory nerve. He was referred to physiotherapy three months following his second surgery.

Physiotherapy Assessment

The patient complained of sharp pain with point tenderness at lateral third of the right clavicle. The pain had started when he was performing light maintenance work on his home and over a three-week period had progressed to an acutely painful state. On

examination, he had visible atrophy of the trapezius muscle bilaterally. Active range of motion was reduced on both sides (previous radical neck dissection on the left), with the right side more limited than the left. Passive range of motion was also limited bilaterally and adhesive capsulitis symptoms were apparent on the right side. Winging of the scapula was visible bilaterally with both forward flexion and abduction movements. The patient's main concern was the acute pain in the clavicle, which was limiting the functional use of his dominant arm. An x-ray was done, which showed a stress fracture at the site of the pain.

Treatment regime

Initially, treatment consisted of gentle joint mobilization and passive range of motion for both shoulders within a pain-free range. The patient was advised on appropriate posture, on resting positions, and was told to avoid heavy lifting. When the pain had diminished in acuity, isometric scapular stabilizing exercises were started. The PRET program (Table 2) was commenced three months later, when the clavicle had healed and the pain had resolved. The patient was progressed very slowly, starting with the lightest resistance (1 to 1.5 kg) and the lowest level of resistance band (red). The resistance was progressed when 25 repetitions could be performed in 1 set. When the resistance was increased the number of repetitions was decreased to ten and slowly progressed back up to 25 repetitions. Precaution was taken in progressing resistance due to the bilateral instability and potential risk of re-injury.

Outcome Measurements

A summary of the outcome measures is provided on Table 3. Significant improvements were noted in active range of motion and pain. Though the patient

continued to complain of occasional mild pain, the location was limited to the right neck and upper aspect of the right scapula. The pain in the right clavicle did not recur. Electromyographic and nerve conduction testing performed on follow-up, indicated recovery in only the superior and middle fibres of the right trapezius.

III-2.3. Case # 3

Diagnosis and Cancer Treatment

A 67-year-old man was diagnosed with squamous cell carcinoma at the base of the tongue with metastases to lymph nodes in the left neck region. He was treated with a hemiglossectomy, a left phayngectomy (with a left oropharyngeal radial forearm free flap repair) and a left radical neck dissection (sacrifice of the spinal accessory nerve, sternocleidomastoid and internal jugular vein). He received postoperative radiation therapy for five weeks. He was seen by physiotherapy initially during the course of his radiation therapy. At the time he presented with limited active range of motion into flexion and abduction on the left side. He had visible trapezius atrophy and winging of the scapula with both flexion and abduction. He had a measurable shoulder droop of 2 cm (measured from spinous process of the seventh cervical vertebra to the lateral aspect of the acromion) and had mild aching pain at the superomedial aspect of the left scapula. He attended physiotherapy twice a week for four weeks. He elected to discontinue physiotherapy at the end of his radiation treatment, as he felt he was doing well. He was provided with a home program at that time. The patient was referred back to physiotherapy six months later, with the diagnosis of radical neck syndrome.

Physiotherapy Assessment

The patient presented with marked atrophy of the left trapezius and his shoulder droop had progressed to 7 cm (Figure 1). His scapula was resting downward and laterally. He had limited range of motion both actively and passively, with severe limitation in active shoulder abduction. He stated that he was unable to use the arm (his dominant side) for functional activities due to pain and stiffness. His main concern was the constant aching pain in his left neck and shoulder region.

Treatment Regime

The patient was treated twice a week with passive range of motion, joint mobilization and stretching of the pectoralis major and minor muscles. Postural exercises and isometric scapular strengthening exercises were introduced in the second week of treatment and the PRET program was started after seven weeks. The resistance was started with a 1 kg weight and the lightest resistance band. Exercises were done in supine or supported sitting. The initial focus was on strengthening the rhomboids and levator scapula on the left side. The program was progressed to include strengthening of the biceps, triceps and shoulder external rotators.

Outcome Measurements

Table 4 provides information on initial and follow-up assessments. Improvements were made in active shoulder range of motion, with the most notable in shoulder elevation (shrugging). On the SPADI, both the pain and disability scores improved significantly.

III-3. DISCUSSION

Initial symptoms associated with trapezius palsy include pain, weakness and limitation in active shoulder movement (12, 19). The trapezius palsy, though compensated to some extent by the levator scapula, rhomboids and serratus anterior, results in weakness in shoulder shrugging, winging of the medial border of the scapula, and limitation in active shoulder abduction to 90 degrees (19, 28). Although passive range of motion is initially intact, adhesive capsulitis symptoms may begin to develop within a few weeks of surgery (16, 17, 19).

Establishing a diagnosis and determining an appropriate therapeutic intervention may be complicated if the shoulder dysfunction has progressed to a secondary shoulder impairment (15, 19). Loss of trapezius function removes the primary passive support for the shoulder, and consequently the entire shoulder girdle drops downward and forward as the trapezius becomes atrophic (8, 16, 25). The unopposed action of the serratus anterior may cause the scapula to deviate laterally and the inferior angle of scapula to rotate away from the spine. Long-term, this sloping, sagging posture may lead to pectoralis muscle contracture (28). The shoulder droop and the muscular imbalance around the shoulder alter the position of the glenoid fossa in relation to the direction of action of many of the shoulder muscles, and consequently, impair muscle force generation (25). Pain may occur with elevation of the arm above the head as the malalignment of the joint causes the humerus to impinge on the glenoid labrum (16). As well, the loss of passive support requires the sternoclavicular joint to bear the weight of the arm and, with repetitive activities or excessive force, anterior subluxation and/or eventually hypertrophy of the joint may occur (29). Alternatively, as observed in Case report #2, the clavicle may bear

the stress and fracture instead (30). When spinal accessory nerve damage is permanent, the laxity in the shoulder may eventually lead to a thoracic outlet syndrome and/or, as occurred with the patient in case report #3, progress to a radical neck syndrome (21).

Patients undergoing nerve-sparing procedures are also at risk for developing shoulder pain and dysfunction (10). Patten and Hillel (1993) reported nerve activity in 40% at one month, improving to 79% at 12 months and 85% at 18 months (19). Despite eventual recovery of the nerve, the authors found that 90% of subjects remained symptomatic. Interestingly, these symptoms were more characteristic of adhesive capsulitis than trapezius palsy, leading the authors to conclude that the effects were secondary and thus preventable.

Our case series demonstrates the use of progressive resistance exercise in patients presenting with trapezius muscle dysfunction due to spinal accessory nerve damage. As there were individual differences in both pain symptoms and shoulder function in the three cases, the design of the physiotherapy program was based on the patient's health status, shoulder presentation and in conjunction with the patient's overall goal. The goal of the PRET program was to restore and/ or optimize the strength and alignment of the shoulder. The specific exercises were carefully selected to ensure that the shoulder region was in a stable position for proper muscle action. The exercises were started with the lowest resistance and progressed within the patient's own tolerance. The treatment period was extended (minimum of 12 weeks) to allow adequate time to observe a physical response. The PRET program was considered a key component of the overall rehabilitation of the shoulder; however, we conclude that an intervention consisting solely of therapeutic exercise (PRET) to strengthen the shoulder complex would have

been inappropriate if other impairments, such as pain and joint restriction, had not been addressed.

In all three cases presented, improvements were noted in ROM, strength, and particularly in reported pain symptoms. The patients in case report #2 and #3 were initially taking mild analgesic medication for pain. While none of the patients were taking pain medications on follow-up, ongoing functional deficits were still present in all three patients. The less-than-optimal improvement observed in function may have a number of explanations. First of all, functional activities require the coordinated movement of the whole shoulder complex and are rarely performed in fully supported positions. To optimize function, therefore, the PRET program may need to include, or progress to, more functional postures and activities. Secondly, when the nerve is sacrificed, as in the radical neck dissection procedure, the damage is permanent. Though other muscles can be strengthened to help compensate for the loss of trapezius function, no other muscle or combination of muscles can fully substitute for the trapezius. Patients with permanent trapezius muscle paralysis may need to be instructed in compensatory movement patterns and specific functional tasks may need to be adapted.

As observed in the patients in Cases #2 and #3, when secondary impairments have developed, a more involved and prolonged course of treatment may be necessary. Clearly, efforts toward the treatment of shoulder dysfunction due to spinal accessory nerve damage should be implemented as soon as possible after onset of the condition, when treatment is more likely to be effective. However, in the face of a life-threatening disease and other serious morbidities, the prevention of shoulder dysfunction may not be a priority to the patient at the outset of cancer treatment. It would be, therefore, of benefit

to determine if patients are able and willing to commence treatment earlier and to continue rehabilitation strategies during their cancer treatment, when symptoms such as edematous tissues, general malaise, mucositis, weight loss and fatigue are problematic (2, 4).

III-4. CONCLUSION

The long-term shoulder deficits that occur as a result of neck dissection procedures deserve attention. Randomized controlled trials are needed to determine effective therapeutic interventions for post neck dissection shoulder pain and dysfunction. Progressive resistance exercise training represents a promising area for future research that could benefit the head and neck cancer patient. The benefits of PRET in the healthy population include not only improvements in muscle performance but also include positive effects on the cardiovascular system, connective tissue, and bone (31). More importantly, these effects may allow individuals to perform activities of daily living with less difficulty (31). In the cancer population, general physical exercise, used as an adjunct to standard cancer therapy, has been found to have a positive effect on physical, functional, psychological and emotional aspects of quality of life (32). On this principle, a resistance exercise program for the shoulder, alone or in combination with an overall exercise program, may potentially improve both the shoulder and other symptoms related to the cancer experience. An eminently testable hypothesis would be that early physiotherapy intervention that includes an appropriately prescribed and supervised PRET program may prevent and/or ameliorate shoulder pain and dysfunction, reduce the risk of secondary impairments, and ultimately improve quality of life for the head and neck cancer patient.

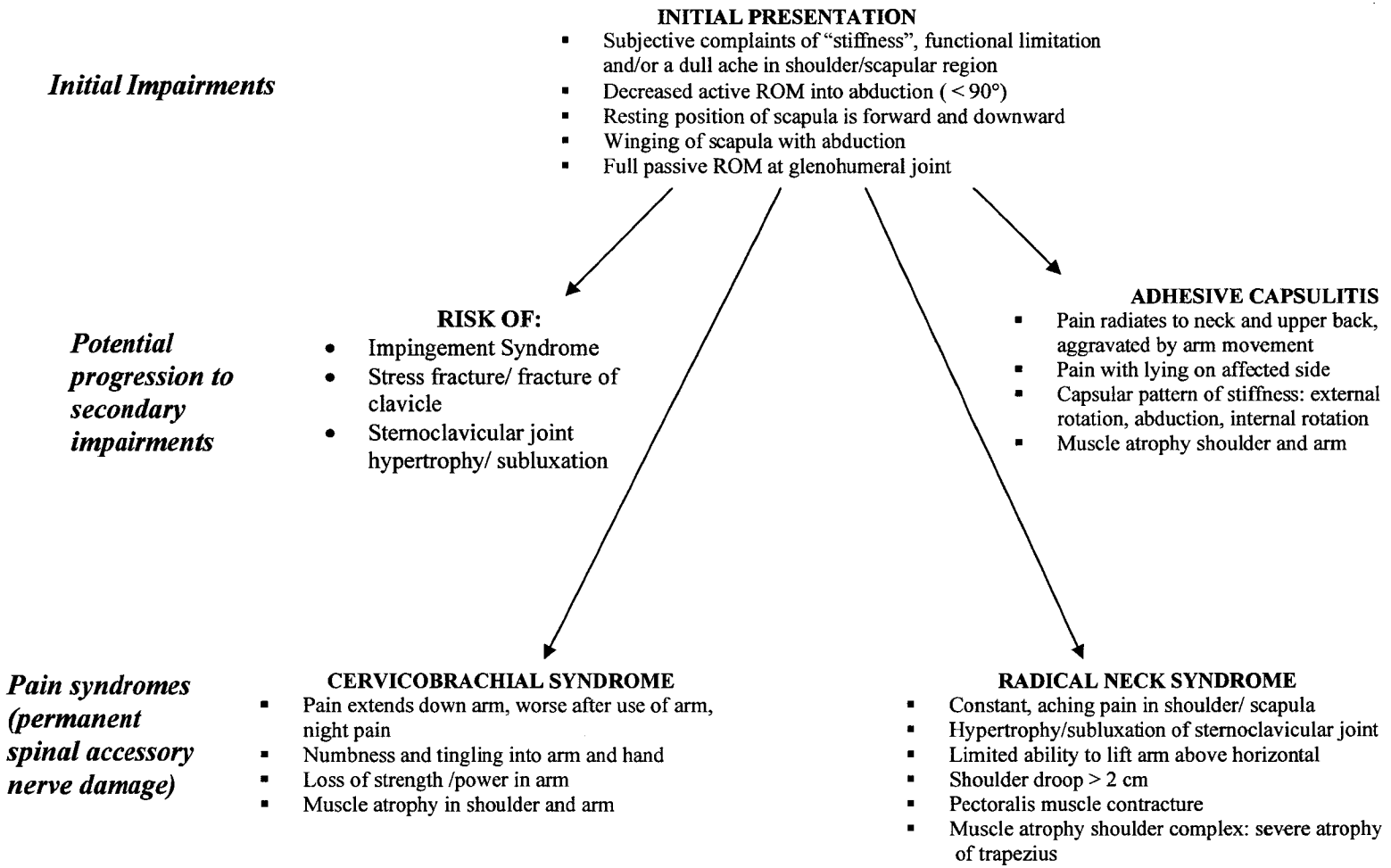

Figure III-1: Signs and symptoms of varied shoulder presentations due to spinal accessory nerve damage

Table III-1: Outcome Measures for Patient presented in Case #1

Case # 1 **Outcome measure**	**Assessment**	**Affected arm at start of resistance training (unaffected arm)**	**Affected arm at 6-month reassessment (unaffected arm)**
Active ROM	Flexion	125° (160°)	127° (164°)
	Abduction	60° (160°)	88° (165°)
	External rotation	70° (80°)	68° (80°)
	Internal rotation	60° (75°)	65° (75°)
	Horizontal abduction	80° (90°)	82° (90°)
	Shoulder elevation	½ ROM (Full ROM)	Full ROM
Pain	Visual analogue scale	3/10	0/10
SPADI	Pain score %	Not assessed	0%: no pain reported
	Disability score %	Not assessed	48%

Table III-2: Guidelines for PRET Program

Program Components	General Guidelines
Muscle Groups to be strengthened	Emphasis on scapular retractors and elevators Shoulder forward flexors Shoulder external rotators Elbow flexors and extensors
Muscle Groups to be avoided*	Scapular protractors and depressors Shoulder internal rotators
Muscles at risk of adaptive shortening (maintain/ restore muscle length)	Pectoralis Major Pectoralis Minor Serratus Anterior
Intensity	Must be able to maintain good posture and scapular stability (no winging, smooth coordinated movement pattern) during performance of exercise. Reduce workload if: ▪ excessive fatigue post exercise ▪ muscle soreness > 48 hours ▪ increased pain during/ post exercise Terminate exercise session if: ▪ increased pain, dizziness, general malaise
Resistance	Progress by: ▪ supported positions to unsupported positions ▪ manual assistance to manual resistance ▪ gravity eliminated to gravity resisted positions ▪ start with the lightest weights and/or resistance band
Type	Concentric exercise within shortened (pain free) ROM, assist as needed for eccentric component. Incorporate isometric "hold" for scapular stabilizers.
Repetitions	Start with 10 repetitions of each exercise. When performing only one set: progress to 25 repetitions.
Sets	Start with one set of each exercise. Progress to two sets. Reduce repetitions when increasing resistance and increase to two sets. i.e. progress from 1 set of 25 repetitions to 2 sets of 12-15 repetitions

* Strengthening of these muscle groups is not advised in the early stages and/or if the scapular is resting downward and laterally. These muscle groups should only be considered for inclusion when sufficient scapular strength and endurance have been achieved.

Table III-3: Outcome Measures for Patient presented in Case #2

Case # 2 Outcome measure	Assessment Findings	Start of resistance training Right arm/ left arm	Right arm/ left arm at 20 week reassessment
Active ROM	Flexion	122° / 135°	154° / 146°
	Abduction	73° / 90°	154°/ 128°
	External rotation	60°/ 60°	70° / 70°
	Internal rotation	60° / 60°	60° / 60°
	Horizontal abduction	80° / 70°	90°/ 85°
Pain	Visual Analogue Scale	9/10 pain in clavicle on right 2/10 on left (occasional)	3/10 pain scapular area on right side 0/10 pain on left

Table III-4: Outcome Measures for Patient presented in Case # 3

Case # 3 Outcome measure	Assessment	Affected arm at start of resistance training (unaffected arm)	Affected arm at 12 week reassessment (unaffected arm)
Active ROM	Flexion	103° (150°)	115° (150°)
	Abduction	60° (160°)	68° (160°)
	External rotation	50° (70°)	70° (70°)
	Horizontal abduction	70° (90°)	90° (90°)
	Shoulder elevation	1/2 ROM gravity-eliminated (Full ROM against gravity)	Full ROM against gravity (Full ROM against gravity)
SPADI	Pain score %	56 %	26 %
	Disability score %	46%	21%

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IV: CHAPTER FOUR

"A pilot randomized study to evaluate progressive resistance exercise to alleviate shoulder dysfunction due to spinal accessory neurapraxia/ neurectomy"

McNeely ML, Parliament M, Courneya KS, Seikaly H, Jha N, Scrimger R, et al. A pilot study of a randomized controlled trial to evaluate the effects of progressive resistance exercise training on shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy in head and neck cancer survivors. *Head & Neck* 2004; 26(6): 518-30.

IV-1. INTRODUCTION

Nodal dissection of the neck is often performed in conjunction with surgical resection of the primary tumour site in head and neck cancers, and is used for the purpose of tumour staging and/or for the treatment of lymph node metastases (1, 2). The debilitating effect of neck dissection procedures on shoulder function is a well-recognized surgical complication and is the result of temporary damage to, or resection of (neurectomy) the spinal accessory nerve (3).

The spinal accessory nerve, or cranial nerve XI, is the principal motor innervation to the trapezius muscle (3-7). The trapezius provides passive support to the shoulder complex and is an important stabilizer of the scapula.(3, 8, 9) Paralysis or weakness of the trapezius alters the alignment of the shoulder and disrupts the normal synchronous motion of the shoulder complex.(3, 8, 10) The "shoulder syndrome" resulting from trapezius dysfunction is characterized by shoulder pain, limitation in shoulder abduction, shoulder droop and scapular winging (11).

In more recent years, this shoulder impairment has been addressed to some extent through the surgical innovation of less radical procedures, which spare the spinal accessory nerve, and now procedures such as the modified neck dissection and selective neck dissection are more frequently performed (12). While the traditional radical neck dissection is associated with a reported incidence of shoulder pain and weakness in 60% to 100% of cases (9, 13), the probability of post-operative trapezius paresis from nerve-sparing procedures is estimated to be between 20% and 60% (3, 9, 14). Though selective neck dissections have been associated with less shoulder pain and dysfunction when

compared to radical and modified radical neck dissection procedures, a variable degree of shoulder dysfunction is reported to occur in 29% to 39% of patients (15-19).

Physical therapy is recommended post-operatively to maintain shoulder range of motion and to strengthen alternative muscles to compensate for the loss of trapezius function (3, 20-22). In the face of a life-threatening head and neck cancer and other serious treatment-related morbidities, however, the prevention of shoulder dysfunction may not be a priority to the patient and/or the health care team at the outset of cancer treatment. As a result, following completion of cancer treatment, when other side effects have improved or resolved, the shoulder weakness and pain have often deteriorated to a chronic state that includes glenohumeral joint restriction and marked deformity of the shoulder complex (3, 14, 23). Over time, shoulder discomfort and neck tightness, as a result of neck dissection techniques, have been found to have the greatest negative effect on quality of life (24).

Shoulder strengthening is a primary component of physical therapy treatment for patients with trapezius dysfunction due to spinal accessory nerve damage. At present, however, no guidelines exist for strength training in the head and neck cancer population (25) or specifically for trapezius dysfunction due to spinal accessory nerve damage. Though anecdotal evidence suggests potential benefit, little effort has been invested in establishing the effectiveness of physical therapy interventions, and to date, no randomized controlled trials have been performed in this patient population (4, 8, 10, 21, 26-28).

We conducted a pilot randomized study to evaluate a progressive resistance exercise training (PRET) program to alleviate shoulder dysfunction due to spinal

accessory neurapraxia/neurectomy in head and neck cancer. We recognized, however, that it might be potentially difficult for patients to engage in rehabilitation strategies during their cancer treatment when problems such as tissue edema, general malaise, mucositis, weight loss and fatigue are problematic (22, 29). Therefore, the primary objective of this study was to assess whether patients were willing and able to participate in a moderate duration PRET program for the shoulder following curative surgery for head and neck cancer. Knowledge of the rate of compliance would be essential to the design of a future intervention study to test the efficacy of early intervention. Secondarily, we sought to determine the effects of the intervention on shoulder function, pain and disability, and overall quality of life. We hypothesized that an appropriately prescribed intensive shoulder strength-training program would reduce shoulder pain and disability, improve function, and enhance overall quality of life. We also hypothesized that the optimal time to initiate this intervention would be as soon as possible post surgery.

IV-2. METHODS

IV-2.1. Setting and Participants

The trial was conducted at the Cross Cancer Institute (CCI) and University of Alberta in Edmonton, Canada. Approval for the study was received from the Health Research Ethics Board of the University of Alberta and the Research Ethics Committee of the Cross Cancer Institute.

All subjects were diagnosed with squamous cell carcinoma of the head and neck, histologically confirmed, which had been managed by definitive surgical resection.

Subjects presenting with squamous cell carcinoma metastatic to the neck from unknown primary site were also eligible if, in the opinion of the both the radiation oncologist and the head and neck surgeon/otolaryngologist, the probable occult mucosal origin was in the head and neck. Eligibility criteria also included the following: 1) surgical treatment included radical neck dissection, modified radical neck dissection and other variants of selective neck dissection, 2) subjects were required to have a medical diagnosis of shoulder dysfunction due to spinal accessory neurapraxia/neurectomy and evidence of trapezius dysfunction (defined as: winging of the scapula with shoulder abduction in the coronal plane and limitation of active shoulder abduction range of motion), 3) Karnofsky Performance Status greater than or equal to 60%, 4) no evidence of residual cancer in the neck as established by clinical examination or CT or MR, 5) no distant metastasis (M0).

Patients were ineligible for the study if they reported co-morbid shoulder pathology and/or presented with a medical illness or psychiatric illness, which, in the opinion of the investigators, would prevent completion of treatment or interfere with follow-up. Eligible subjects were required to sign a consent form, which outlined the right to withdraw, confidentiality, and the risks and benefits potentially involved in study participation.

IV-2.2. Experimental Design and Recruitment

The study was a prospective pilot randomized controlled trial. Potential subjects were identified by the oncologist and/or surgeon at a scheduled cancer follow-up appointment and were screened for eligibility. Ten patients in each of the following strata were accrued: i) "early" – within 8 weeks of neck dissection and able to commence physical therapy with no more than 8 weeks lapsed since surgery; ii) "late" - $\geq$ 8 weeks

after neck dissection. In each stratum, patients were randomized between exercise and standard care intervention by means of a computer-generated code. Randomization was on a 1:1 basis.

IV-2.3. Exercise Training Intervention

Subjects randomized to the exercise arm immediately began the 12-week PRET protocol. Participants exercised three times per week, excluding statutory holidays, for the 12-week intervention period. Therefore, the prescribed exercise sessions ranged from 33 to 35. Any missed exercise sessions were not rescheduled. The PRET program was individualized to suit each subject and a physical therapist and/or physical therapy assistant supervised all exercise-training sessions. The PRET program, including type, intensity (resistance), duration and frequency, was based on guidelines for post-operative cardiac rehabilitation (25).

Subjects were asked to perform a series of six exercises. The specific therapeutic exercises performed were chosen with the goal of enhancing scapular stability and restoring/ maintaining the strength of the upper extremity. These exercises consisted of rhomboids (scapular retraction); levator scapulae (scapular elevation); biceps (elbow flexion); triceps (elbow extension); infraspinatus, posterior deltoid (external rotation); and middle deltoid and supraspinatus and subscapularis (abduction in the plane of the scapula). The resistance training program was progressive in terms of number of sets and repetitions performed as well as the amount of weight lifted, depending on performance status, recovery from surgery, and overall performance status related to concurrent cancer therapy. Early weeks were characterized by fewer exercises (i.e. avoiding certain exercises if range of motion/pain prohibited), fewer sets (i.e. one), fewer repetitions (i.e.

four to six, or to tolerance) and lighter weights (i.e. 1-2 kg). Subjects were progressed to the desired exercise prescription as soon as safely possible. Guidelines for exercise performance included: 1) maintenance of proper posture and scapular stability (no winging of scapula); 2) a rate of perceived exertion on the Borg Scale of no greater than 13 out of 20 (described as "somewhat hard") (30). The resistance weight was increased by one resistance level when all repetitions could be performed, within the set guidelines, in the second set. Subjects also performed five to ten minutes of warm-up (ROM exercises) before, and cool-down exercises (stretching) after, the resistance-training component. Further details on the PRET program are provided in Table 1.

Subjects randomized to the control arm comprised the "standard of care" group, which consisted of active and passive ROM exercises and stretching exercises. As per standard of care, at the six-week follow-up, these subjects were progressed to scapular retraction and elevation strengthening exercises using an elastic resistance band but no progressive resistance exercise training. Subjects on this arm had the option to participate in PRET program after the 12-week delay period. Table 2 presents the main differences in program components of the PRET program and standard care.

IV-2.4. Outcomes

The primary endpoints were 1) recruitment rate, 2) completion rate, and 3) adherence rate. Secondary endpoints were 1) shoulder function, 2) shoulder pain and disability, 3) quality of life. All subjects underwent baseline assessment of past exercise behaviour, quality of life, and specific assessments of shoulder pain, disability, and range of motion.

IV-2.4.1. Feasibility Outcomes

Feasibility was determined by examining the rates of 1) subject recruitment (agreement to participate/ eligible subjects), 2) study completion (number of subjects completing the 12-week intervention period/ number of subjects accrued) and 3) exercise adherence (the number of completed exercise sessions/ scheduled exercise sessions).

IV-2.4.2. Physical Measures (ROM)

Active ROM measurements were taken at baseline, week six and week 12. The measurement of shoulder ROM was performed using a universal goniometer. Goniometric measurements are commonly used in the clinical setting and are highly reliable when repeated by the same assessor (31-33). For the present study, ROM was assessed for the combined motion of the joints comprising the shoulder complex. Active shoulder movements included flexion, abduction and external rotation. Passive shoulder movements included flexion, abduction, external rotation, internal rotation and horizontal abduction. A single assessor (MM), familiar with, and trained in, the measurement procedure was responsible for all ROM measurements for each subject.

IV-2.4.3. Shoulder Pain and Disability Index (SPADI)

The SPADI is a valid and reliable instrument that reflects the pain and disability associated with the clinical syndrome of a painful shoulder (34, 35). The form is self-administered and requires five to ten minutes to complete. Scores for the pain and disability subscales range from zero to 100, with higher scores indicating greater impairment. The total SPADI score is calculated by averaging the pain and disability subscale scores. The SPADI was administered at baseline and week 12.

IV-2.4.4. Quality of Life Outcomes

The Functional Assessment of Cancer Therapy - Head and Neck (FACT H&N) is a cancer-specific QOL instrument which consists of a 27-item core to which an 11-item site-specific Head and Neck (H&N) subscale has been added (Version 2). The measure is completed by the patient and provides a global QOL score and five subscale scores. The subscale scores cover the following domains: Physical (0 to 28), Social (0-28), Emotional (0-24), Functional (0-28), and H&N concerns (0 to 44). The FACT scale has been tested in a large sample of cancer patients and been found to be reliable, valid, responsive, brief and easy to administer (36). The FACT H&N was administered at baseline and week 12.

IV-2.4.5. Baseline Characteristics

During the initial visit, demographic and clinical information was collected on all subjects. Medical Data were abstracted from medical records. Past exercise behaviour was assessed using the Leisure Score Index (LSI) of the Godin Leisure Time Exercise Questionnaire (37, 38). The LSI has established reliability and concurrent validity based on various criteria, including objective activity monitors and fitness indices (37-39). Participants were asked to complete the LSI recalling their average weekly exercise over the prior month. Pain medication use was monitored at baseline, week six and week 12.

IV-2.5. Sample Size Calculation and Statistical Analyses

We hypothesized that a rate of randomization of $\geq$ 20% of eligible patients and a protocol completion rate of >80% (i.e. 80% evaluable) would be desirable to demonstrate feasibility. Based on the premise that if 20 patients were randomized, and at least 16 patients were evaluable, the estimated 95% confidence width for the proportion of

successful completion would be 22% (11-20 subjects). Therefore, our accrual goal was 20 patients in total.

Pilot data were analysed using SPSS version 10.0 software (SPSS Inc., Evanston, Illinois). We compared baseline characteristics using independent samples t-tests for continuous data and Pearson's chi-square for categorical data. Outcome data were analyzed utilizing the independent samples t-tests to compare changes between groups in outcomes from baseline to post-intervention (12 week follow-up). Probabilities of less than 0.05 were accepted as significant.

IV-3. RESULTS

IV-3.1. Flow of Participants through the Trial

Participant recruitment took place between June 15, 2001 and November 30, 2001. Baseline assessments took place as participants were accrued for the pilot study. All treatment and follow-up interventions were completed by June 2002. The subjects for this pilot study consisted of 20 head and neck cancer patients, accounting for a total of 32 neck dissection procedures (12 bilateral procedures). Figure 1 shows the flow of participants through the trial.

IV-3.2. Baseline Characteristics

The groups were balanced on demographic, medical and past exercise variables; however, a small imbalance existed with respect to cancer stage (Table 3). The exercise group was comprised of Stage 3 (n=3) and 4 (n=5) cancers, whereas the control group consisted of Stage 1 (n=3) and 4 (n=6) cancers.

IV-3.3. Pain Medication

Reported medication use at baseline, 6-weeks (monitored for potential changes during radiation therapy for early group) and at 12-week follow-up did not differ between groups (Table 3); however, there were differences in the prescribed medications. While the majority of subjects were prescribed acetaminophen plus codeine, one subject in the late exercise group was following a pain regimen for neck and shoulder pain that included morphine.

IV-3.4. Adverse Events

One subject in the early exercise group complained of nausea following one exercise session. The subject was near completion of radiation therapy at the time of the incident, and reported minimal nutritional intake prior to the exercise session. The incident was reported to the subject's oncologist and was medically managed. This subject had no further difficulties completing the PRET program.

IV-3.5. Feasibility Issues

Twenty-five eligible patients were approached and 20 patients were accrued. Therefore, our recruitment rate was 80%. Three subjects were unable to complete the full 12-week study period. Two subjects were withdrawn due to cancer recurrence (one exercise group, one control group) and one subject was withdrawn due to radiation side effects requiring hospitalization (exercise group). Therefore the completion rate was 85% (17/20). Exercise sessions did not include statutory holidays; therefore the average number of scheduled exercise sessions for a given 12-week intervention period was 33.6. Subjects in the exercise group completed a mean of 31.2 sessions (95% confidence interval: 29.4 to 33.6). Thus, the exercise group completed 93% of scheduled exercise

sessions. Five subjects in the exercise group completed all prescribed exercise sessions (100% adherence). One subject in the "late" exercise group missed 9 scheduled exercise sessions (completed 25 of 34) due to illness (one episode of aspiration pneumonia and one episode of pancreatitis).

Five out of nine control subjects (56%) opted to take part in the PRET program after the 12-week intervention period. These five control subjects were all from the "late" group and four of the five subjects completed the full 12-week protocol (one subject was withdrawn due to cancer recurrence).

IV-3.6. Changes in Physical Measures

Table 4 presents the results for active and passive ROM of the shoulder. There were no differences between the groups for changes in active forward flexion ($p=0.241$) or active abduction movements ($p=0.193$). There was a significant difference between the groups in the change score for external rotation range of motion ($p=0.001$) with the PRET group improving by 13.5% and the control group improving by 3.8%. As presented in Table 4, there were no significant differences between the groups for passive ROM measurements.

IV-3.7. Changes in SPADI

Baseline values for pain, disability and total SPADI score did not differ between the groups (Table 4). The pain score decreased by 17% in the PRET group compared to a slight increase (1.7%) in the control group and this change was statistically significant ($p=0.038$). The disability score decreased by 10.1% in the exercise group compared to 0.1% in the control group; however this finding was not statistically significant ($p=0.111$). The overall SPADI score decreased by 13.5% in the exercise group and

increased by 0.9% in the control group. The overall difference between the groups was significant (p=0.045).

IV-3.8. Changes in Quality of Life

There were no significant differences between the groups in change score from baseline to post intervention in overall QOL or for any of the subcomponents of the FACT-H&N scale (Table 4). In general, overall QOL showed a decreasing trend in both groups during the 12-week intervention period but this was not statistically significant.

IV-4. DISCUSSION

Our PRET program differed from traditional physiotherapy interventions for patients with head and neck cancer in that we used the principles of PRET to restore and/ or optimize the strength and endurance of the scapular and upper extremity muscles. In our experience, shoulder pain may be enhanced by inappropriate exercise prescription and/or performance. Therefore exercise sessions were supervised and the intensity progressed by modifying one variable (resistance, repetitions or sets) to progressively challenge the chosen muscle groups. As more research is needed to determine the efficacy of high-intensity strength testing and resistance training in patients with head and neck cancer, we chose to start the exercises with the lowest resistance and to progress within the patient's own tolerance. This method allowed for progression from low intensity to moderate intensity exercise and avoided negative after effects such as secondary muscular soreness and injury (40). Furthermore, the treatment period was extended to 12 weeks to allow adequate time to observe a physical response.

The benefits of PRET in the healthy population include not only improvements in muscle performance but also include positive effects on connective tissue and bone. (40, 41) Research within the cancer population has demonstrated positive effects of exercise interventions on physical, functional, psychological and emotional aspects of quality of life (42). Similar to other populations that experience chronic pain and/or disability, the findings of this pilot study suggest that patients with head and neck cancer can benefit from a structured PRET program (43, 44).

IV-4.1. Feasibility

Our resistance exercise program was a novel mode of exercise for patients with head and neck cancer and therefore our primary objective was to determine the feasibility of a randomized controlled trial. While there are no comparative adherence figures in the literature for rehabilitation interventions within this specific cancer population, the adherence to our PRET program (93%) was higher than adherence rates reported in recent physical exercise trials in breast cancer (71.5%) and prostate cancer (75%) (45, 46). Our study results demonstrate an interest in, and a high rate of adherence with our PRET program among patients with head and neck cancer.

We also sought to determine which of the groups "early" or "late" (if either) would experience better compliance with or benefit from the PRET program. We were particularly interested in determining whether head and neck cancer patients were willing and able to tolerate exercise during radiation therapy. Despite small numbers in our study, subjectively we found that the "early" exercise group (n=4) had more difficulty carrying out the exercise intervention in the latter stages of radiation therapy. These subjects continued to attend despite experiencing side effects from radiation therapy.

During the latter stages of radiation therapy, however, none of the subjects were able to progress in the exercise prescription and two subjects were required to reduce their workload in order to remain within the set exercise guidelines. Once these subjects had recovered from the acute effects of radiation therapy their exercise performance improved and they were able to progress again in the exercise prescription. Therefore, with close supervision and monitoring of weight, hydration and caloric intake, we feel that subjects can safely exercise during radiation therapy. Although improvements in shoulder outcomes may not be possible during the latter stages of radiation therapy, exercise that is performed within the subject's own tolerance may be beneficial in preventing the development of secondary shoulder impairments.

IV-4.2. Range of Motion

A positive effect of our study was observed in active range of motion. Though the improvements in ROM were larger in the exercise group, the only statistically significant finding was for shoulder external rotation ($p=0.001$). There were no significant differences between the groups in change score for passive ROM. Passive ROM improved in both groups and the findings were similar across groups for all measurements. Since both groups had received instruction in shoulder range of motion and stretching exercises, and as patients were closely monitored for development of glenohumeral joint restriction, this finding was anticipated.

IV-4.3. Pain

A clinically significant finding of our study was that our PRET program had a beneficial effect on pain. Though the baseline mean overall pain score was higher in the exercise group, the reported overall pain score decreased by 17% in the exercise group

compared to a slight increase in pain (1.7%) in the control group. This finding, while limited, is consistent with the findings of other authors. Johnson et al. (10) designed a resistance exercise program that focussed on the scapular retractors and elevators and noted improvements in posture, shoulder range of motion and function, and decreased pain. More recently, Salerno et al. (28) in a nonrandomized study examined the effect of a formal physical rehabilitative protocol on patients following functional neck dissection procedures. The comparison group was comprised of patients from out-of-town who were unable to participate in the protocol. The authors reported significant improvements at six-month follow-up in pain, active and passive ROM, and in working and recreational activity in the group receiving formal physical therapy when compared to the control group (28).

Though arguably improvements in pain may have occurred over time regardless of the intervention, more recent evidence indicates that shoulder pain tends to persist rather than improve and is independent of spinal accessory nerve status. Chaplin et al. (23) found that pain in the shoulder and arm, although present in only 14% of patients at diagnosis increased in prevalence post treatment and largely persisted. Patten et al.(14) found that despite eventual recovery of the spinal accessory nerve in 85% of subjects at 18 months following modified neck dissection procedures, 90% remained symptomatic. More recently, van Wilgen et al.(47) in a study examining long term shoulder complaints (> 1 year post-operatively) following differing neck dissection procedures found that only 51% of subjects complaining of shoulder pain had evidence of a dysfunctional spinal accessory nerve. Although, the exact mechanism of long-term shoulder pain is not clearly

understood, it is likely that the symptoms may be the result of secondary impairments such as adhesive capsulitis (14).

IV-4.4. Disability

Another finding of our study was a trend for improvement in reported disability in the PRET group. The reported overall disability in the exercise group improved (10% decrease in disability score) whereas the control group score remained relatively unchanged (0.11% decrease in disability score). Though this finding was not statistically significant, the trend for improvement in the exercise group was consistent with improvements observed in active ROM.

IV-4.5. Quality of Life

Although we anticipated an effect of our intervention on quality of life, unfortunately no such effect was found. The FACT- H&N is a global quality of life instrument and as such may be unable to demonstrate the effect of a treatment directed at only one joint particularly in a cancer population dealing with numerous treatment-related morbidities (34). A more condition specific instrument, such as the recently developed Neck Dissection Impairment Index, may have been more sensitive to the effect of our PRET program on the complications associated with neck dissection procedures (48). Nevertheless, neutral impact or positive changes in overall quality of life would be desirable and hence a global quality of life measure should be used in any future studies.

IV-4.6. Limitations

There are a number of limitations in our pilot study design that should be considered in planning future research. The findings of several studies support the theory that post-operative shoulder pain and dysfunction is less severe with nerve-sparing

procedures (16, 23, 49). Terrell et al.(49) found that neck dissections sparing the spinal accessory nerve were associated with better pain scores on head and neck quality of life (HNQOL), less shoulder and neck pain, and less need for medications. The authors also found that when the spinal accessory nerve is spared, not dissecting level V of the neck was associated with better HNQOL pain scores, less shoulder or neck pain, and fewer physical problems. Despite our small sample size, we found that selective neck dissection was associated with less shoulder pain and dysfunction, and better range of motion in our patients. Though these subjects reported lower pain levels and less disability in activities of daily living, subjects commonly complained of shoulder weakness/ fatigue that limited work and/or recreational activities. It is our feeling that patients undergoing nerve-sparing procedures may ultimately benefit the most from a PRET program as maintaining, or restoring, the strength of the upper extremity may prevent secondary shoulder impairments and allow patients to return to their normal work and recreational activities sooner. Therefore, given the variable presentation of pain and disability following differing neck dissection procedures, we recommend stratification based on the performed neck dissection. We also recommend more stringent control of confounders. For instance, use of pain logs to better determine medication use, evaluation of spinal accessory nerve status and/or monitoring of trapezius muscle function through electromyography. Moreover, a full treatment study, with an adequate sample size, would allow for subgroup analyses and enhance interpretation of the findings.

Another limitation of our study was the fact that we utilized a moderate duration exercise intervention for which we currently lack long-term follow-up. Following

subjects over an extended time period would be needed to determine the effect of the intervention on outcome in both the short and long-term, and would allow for comparison of findings with spinal accessory nerve status.

IV-5. CONCLUSIONS

In summary, our pilot study results indicate that a PRET program focussing on shoulder pain and dysfunction is feasible in the post-operative head and neck cancer patient population. The preliminary findings, while limited, also suggest a potential therapeutic role for a comprehensive PRET program as an adjunct to standard post-operative physical therapy treatment, regardless of spinal accessory nerve status. In light of these positive findings, a larger randomized controlled trial is warranted.

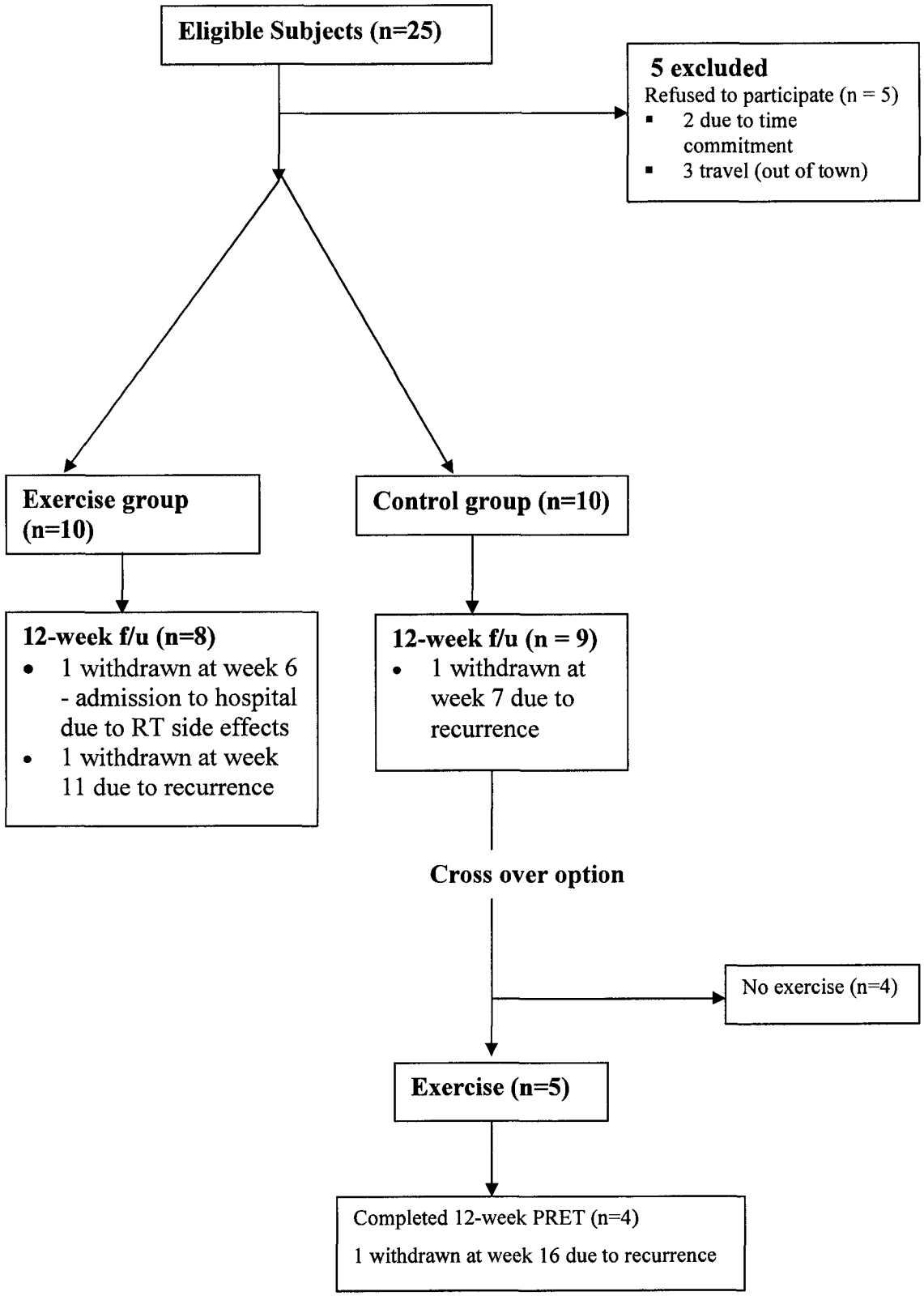

Figure IV-1. Flow of participants through the trial

Table IV-1: Progressive Resistance Exercise Training Program

Program Components	**Program Details**
Purpose	Enhance muscular strength and endurance of upper extremity and scapular muscles
Type	Supervised progressive resistance exercise training
Frequency	3x per week
Muscle Groups: 6 exercises	▪ Rhomboids (scapular retraction) ▪ Levator scapula (scapular elevation) ▪ Biceps (elbow flexion) ▪ Triceps (elbow extension) ▪ Infraspinatus, posterior deltoid (external rotation) ▪ Middle deltoid, supraspinatus and subscapularis (abduction in the plane of the scapula)
Intensity	▪ Start with resistance of 2-3 pound weights progress within guidelines ▪ Must be able to maintain posture and scapular stability (no winging of scapula) ▪ RPE: no greater than 13 on Borg Scale: "somewhat hard"
Repetitions	15-20: progress to maximum of 25 repetitions initially when performing only 1 set
Sets	1 set, progress ⇒ 2 sets @ 2 sets of 20 increase resistance weight
Rest interval	1- 2 minutes between exercise stations and up to 4 minutes between sets
Concentric tempo	2-4 seconds (exhaling)
Eccentric tempo	4 seconds (inhaling)
Total set duration	17.5 minutes/ set for 15 repetitions if maximal rest required. (22 minutes for 20 reps, 25 minutes for 25 reps) Total maximum time for 2 sets = 44 minutes.
Warm-up	Range of motion exercises for glenohumeral joint in supine
Stretching Exercises	▪ Pectoralis major and minor ▪ Serratus anterior
Reduce workload	▪ Excessive fatigue post exercise ▪ Muscle soreness >48 hours ▪ Increased pain post exercise
Terminate exercise	Pain, dizziness, general malaise

Table IV-2: Program Components of PRET Program in comparison to Standard Care

Program Components	PRET	Standard Care
Goals of Physical Therapy	1. Enhance muscular strength and endurance of upper extremity and scapular muscles to: ▪ To compensate for loss of trapezius function ▪ Maintain shoulder alignment and posture	1.Optimize joint range of motion in glenohumeral joint 2. Strengthen alternative muscles to compensate for loss of trapezius 3. Prevent/ alleviate pain
Practical/ Theoretical Differences	1. Primary focus on strengthening scapular muscles (levator scapula and rhomboids) to: ▪ Assist in stabilizing the scapula ▪ Counteract the imbalance of forces on the scapula created by weakened/absent trapezius and unopposed action of scapular protractors (serratus anterior and pectoralis minor) ▪ Prevent stretch weakness of levator scapula and rhomboids 2. Resistance exercise training using the principle of progressive overload to increase strength and endurance of scapular and upper extremity muscles (moderate to slow speed, where possible with full range of motion) 3. Progression of exercises to weight machines where possible (external stabilization provided by weight machine allows for proper muscle action and progression of resistance)	1. Primary focus on maintaining joint integrity and range of motion of glenohumeral joint 2. Strengthening exercises for scapular muscles and upper extremity: elastic resistance band or free weights As needed: 3. Pain relieving modalities i.e. transcutaneous electrical nerve stimulation, massage, relaxation techniques
Components similar in both programs	1. Active and passive ROM exercises 2. Stretching exercises to prevent adaptive muscle shortening of pectoralis major and minor, and serratus anterior 3. Postural education/ supportive positions for upper limb	

Table IV-3: Baseline Characteristics

Variable	Overall (n=17)	Exercise Group (n=8)	Control Group (n=9)	P Value *
Demographics				
Age (years)	61 (7.7)	60 (7.4)	61 (8.4)	0.615
Gender (male)	14 (82%)	7 (88%)	7 (78%)	0.606
Employed full time	6 (35%)	3 (38%)	3 (33%)	0.986
Medical				
Post-surgery				
Early group (weeks)	6.8 (1.3)	6.5 (0.0)	7 (2.0)	0.620
Late Group (weeks)	97 (116.7)	150 (156.8)	54.6 (60.8)	0.247
Treatment Status				
On Radiation Therapy	8 (47)	5 (63)	3 (33)	0.378
Stage				
Stage 1(T1N0)	3 (18)	3 (33)		
Stage 2 (T2N0)	0			
Stage 3 (T1-3,N1 or T3,N0) 3 (18)		3 (37.5)		
Stage 4 (T4N0, any T,N2-3) 11 (65)	5 (63)	6 (67)		0.048
Diagnosis				
Oral Cavity	2 (12)	2 (22)		
Oropharynx	7 (41)	3 (38)	4 (44)	
Larynx/ hypopharynx	5 (29)	3 (38)	2 (22)	
Nasopharynx	1 (6)		1 (11)	
Unknown Primary	1 (6)	1 (13)		
Parotid	1 (6)	1 (13)		0.380
Radiation				
IMRT protocol	2 (12)	1 (13)	1 (11)	
Unilateral Neck	3 (18)	2 (25)	1 (11)	
Bilateral Neck	11 (65)	5 (63)	6 (67)	
No radiation	1 (6)	1 (11)		0.713
Neck Dissection Type	(n=28)	(n=12)	(n=16)	
RND	7 (25)	4 (33)	3 (19)	
MND to level 5	8 (29)	3 (25)	5 (31)	
SND to level 4	3 (11)	1 (8)	2 (22)	
SND to level 3	10 (36)	4 (33)	6 (67)	0.844
Pain Medications				
Baseline routine	4	1	3	
prn	7	4	3	0.580
6-week routine	8	4	4	
prn	4	1	3	0.564
12-week routine	6	2	4	
prn	5	3	2	0.667
Past Exercise				
Moderate (mins/week)	139 (383.4)	329 (574.3)	16 (26.1)	0.122
Strenuous (mins/week)	10 (33.4)	0 (0)	22 (48.4)	0.215
Moderate/ Strenuous (mins/week)	149 (381.6)	329 (574.3)	38 (57.2)	0.151
> 90 Moderate/ Strenuous (n)	6 (35.0)	4 (50)	2 (22.0)	0.247

Data are presented as the mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. * P value for difference between groups. Abbreviations: IMRT= Intensity Modulated Radiation Therapy; RND = Radical Neck Dissection; MND = modified neck dissection; SND = Selective Neck Dissection; routine = narcotic medication of at minimum 2 acetaminophen plus codeine 15 mg per day; prn = pain medication taken as needed

Table IV-4. Effects of PRET program on Shoulder Function, Pain and Disability, and Quality of Life †

Variable	Baseline	P value *	Post intervention	Mean Change	Difference between Groups in Mean Change [95% CI]	P Value ††
SHOULDER FUNCTION						
Forward Flexion						
Exercise Group	124 (24.7)		141 (10.8)	+17.0		
Control Group	126 (21.4)	0.843	136 (19.3)	+10.0	+7.0 (-4.9-18.9)	0.241
Abduction (coronal plane)						
Exercise Group	94 (24.3)		127 (28.4)	+33.0		
Control Group	92 (29.6)	0.897	112 (37.5)	+19.7	+13.3 (-7.1-33.6)	0.193
External Rotation						
Exercise Group	53 (10.6)		67 (8.9)	+13.5		
Control Group	51 (12.3)	0.592	55 (12.9)	+3.8	+9.7 (4.0-15.2)	0.001
Passive Forward Flexion						
Exercise Group	153 (6.9)		164 (7.7)	+10.7		
Control Group	150 (15.9)	0.483	157 (10.9)	+7.1	+3.5 (-7.1-14.1)	0.500
Passive Abduction						
Exercise Group	156 (10.4)		171 (6.0)	+15.1		
Control Group	147 (25.3)	0.275	162 (13.5)	+15.0	+0.1 (-15.6-30.4)	0.991
Passive External Rotation						
Exercise Group	70 (7.4)		79 (8.4)	+9.1		
Control Group	70 (10.6)	0.977	74 (14.6)	+4.6	+4.6 (-5.6-14.7)	0.361
Passive Internal Rotation						
Exercise Group	69 (11)		82 (7.7)	+13.3		
Control Group	65 (8.9)	0.346	72 (12.8)	+6.7	+6.5 (-3.4-16.6)	0.191

Table IV-4 continued: Effects of PRET program on Shoulder Function, Pain and Disability, and Quality of Life

Variable	Baseline	P value *	Post intervention	Mean Change	Difference between Groups in Mean Change [95% CI]	P Value ††
Passive Horizontal Abduction						
Exercise Group	74 (10.2)		87 (7.1)	+13.4 (7.4)		
Control Group	71 (10.2)	0.542	78 (9.8)	+7.3 (11.2)	+6.1 (-1.5-13.7)	0.114
PAIN AND DISABILITY						
SPADI Pain Score (%)						
Exercise Group	40.9 (23.1)		23.9 (20.1)	+17.1 (21.3)		
Control Group	20.7 (22.8)	0.089	22.3 (20.0)	-1.7 (11.8)	+18.8 (1.2-36.3)	0.038
SPADI Disability Score (%)						
Exercise Group	30.9 (27.4)		20.8 (23.7)	+10.1 (15.9)		
Control Group	29.1 (23.1)	0.888	29.0 (25.0)	+0.1 (7.3)	+10.0 (-2.5-22.6)	0.111
SPADI Total Score (%)						
Exercise Group	35.9 (23.7)		22.3 (20.3)	+13.6 (17.6)		
Control Group	24.9 (21.3)	0.328	25.7 (20.1)	-0.9 (8.6)	+14.5 (0.37-28.5)	0.045
QUALITY OF LIFE						
FACT-H&N (0-152)						
Exercise Group	109.5 (12.2)		104.8 (18.5)	-4.6 (9.0)		
Control Group	103.1 (22.4)	0.489	100.9 (23.9)	-2.2 (11.4)	-2.4 (-13.2-8.3)	0.639
FACT- G (0-108)						
Exercise Group	79.25 (9.8)		78.75 (15.3)	-0.5 (7.9)		
Control Group	74.83 (18.1)	0.550	75.51 (16.1)	+0.68 (12.6)	-1.18 (-12.2-9.8)	0.823

Table IV-4 continued: Effects of PRET program on Shoulder Function, Pain and Disability, and Quality of Life

Variable	Baseline	P value *	Post intervention	Mean Change	Difference between Groups in Mean Change [95% CI]	P Value ††
Physical well-being (0-28)						
Exercise Group	20.5 (2.7)		20.6 (3.4)	+0.1 (3.7)		
Control Group	22.44 (4.5)	0.311	21.8 (5.4)	-0.7 (3.8)	+0.8 (-3.1-4.7)	0.673
Functional well-being (0-28)						
Exercise Group	18.12 (4.8)		18.4 (5.5)	+0.3 (2.9)		
Control Group	15.88 (7.5)	0.486	16.6 (7.6)	+0.7 (2.9)	-0.4 (-3.4-2.6)	0.774
Emotional well-being (0-24)						
Exercise Group	18.0 (2.9)		18.1 (3.6)	+0.1 (3.2)		
Control Group	16.44 (6.5)	0.548	16.8 (5.9)	+0.3 (2.7)	-0.2 (-3.2-2.8)	0.886
Social/Family well-being (0-24)						
Exercise Group	22.62 (4.4)		21.6 (7.9)	-1.0 (4.8)		
Control Group	20.05 (4.2)	0.242	20.4 (4.5)	+0.4 (7.8)	-1.4 (-8.1-5.4)	0.678
Head and Neck Subscale (0-44)						
Exercise Group	30.25 (4.2)		26.1 (6.3)	-4.1 (3.4)		
Control Group	28.33 (6.7)	0.500	25.4 (9.1)	-2.9 (4.8)	-1.2 (-5.6-3.1)	0.178

Data are presented as the mean (standard deviation)

† SHOULDER FUNCTION: Exercise Group (n=12 neck dissections); Control Group (n=16 neck dissections); PAIN, DISABILITY AND QOL; Exercise Group (n=8); Control Group (n=9)

* P value for difference between the groups at baseline

†† P value for change between groups from baseline to post intervention

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V: CHAPTER FIVE

A Randomized Controlled Trial of Resistance Exercise Compared to Standard Physical Therapy for Shoulder Pain and Dysfunction in Head and Neck Cancer Survivors

V-1. INTRODUCTION

Shoulder dysfunction is a well-recognized complication following neck dissection procedures and a major concern in the long term quality of life of HNC survivors. Impairment in shoulder function is the result of damage to (neurapraxia/ axonotmesis) or resection (neurectomy) of the spinal accessory nerve and the ensuing denervation of the trapezius muscle (1). Although neck dissection procedures that preserve the spinal accessory nerve are now more commonly performed, a variable degree of shoulder dysfunction occurs in 20% to 60% of patients (2).

Survivors of head and neck cancer who have undergone neck dissection or chemotherapy or have high pain scores have been found to have increased risk for disability from their cancer and/or cancer treatment (3). To date, however, few physical therapy intervention studies have been performed with the intent to reduce pain and disability in head and neck survivors. In 2002, we conducted a pilot study to evaluate the feasibility of progressive resistance exercise training (PRET) for shoulder dysfunction due to spinal accessory neurapraxia/ neurectomy in patients with head and neck cancer (4). The pilot study demonstrated a high rate of follow-up assessment (85%) and excellent adherence to the PRET program (93%) with preliminary evidence of an efficacy benefit for patient-rated shoulder pain and disability.

Here, we report the results of our follow-up efficacy trial comparing the PRET intervention to standard physical therapy (SPT) for shoulder dysfunction in post surgical head and neck cancer survivors. We hypothesized that the PRET program would enhance muscular strength and endurance of the scapular muscles and reduce patient-rated

shoulder pain and disability compared to SPT.

V-2. METHODS

V-2.1. Setting and Participants

The trial was conducted at the Cross Cancer Institute and University of Alberta in Edmonton, Canada. Approval for the study was received from the Health Research Ethics Board of the University of Alberta and the Research Ethics Committee of the Alberta Cancer Board. All participants were diagnosed with carcinoma in the head and neck region that had been managed by definitive surgical resection. Eligibility criteria also included: 1) surgical treatment including radical neck dissection, modified radical neck dissection, and other variants of selective neck dissection; 2) shoulder dysfunction as a result of spinal accessory nerve damage; 3) Karnofsky Performance Status greater than or equal to 60% (5, 6); 4) no evidence of residual cancer in the neck and no distant (M0) metastasis; and 5) completion of adjuvant head and neck cancer treatment.

Participants were ineligible if they presented with 1) a history of shoulder or neck pathology unrelated to cancer treatment or 2) comorbid medical illness or psychiatric illness that would prevent completion of treatment or interfere with follow-up. Eligible participants were required to sign a consent form, which outlined the right to withdraw, confidentiality, and the risks and benefits potentially involved in study participation.

V-2.2. Experimental Design and Recruitment

The study was a prospective randomized controlled trial. Potential participants were recruited using two methods. The Alberta Cancer Registry identified head and neck

cancer survivors living within the Edmonton region. Each survivor's primary physician was contacted to approve the survivor for potential participation in the study. A recruitment letter was mailed to the approved survivor who was then required to contact the project coordinator if interested in participating in the study. Potential participants were also identified by their surgeon or oncologist through Otolaryngology Head and Neck follow-up clinics at the University of Alberta Hospital and the Cross Cancer Institute.

V-2.3. Randomization and Blinding

Eligible participants were stratified by tumor location (oral/oropharynx versus hypopharynx/larynx versus thyroid) and type of neck dissection (radical neck dissection versus modified radical neck dissection/ variants of selective neck dissection) and randomly assigned to SPT or PRET. Participants were randomized following baseline testing. An independent researcher generated the allocation sequence using a computer-generated code. A block permutation procedure was used to generate the allocation sequence within each stratum. The allocation sequence and contents of the envelopes were enclosed in sequentially numbered and sealed (opaque) envelopes. The allocation sequence and contents of the envelopes were concealed from all study personnel. Independent assessors blinded to group assignment performed the range of motion and strength and endurance tests.

V-2.4. Standard Physical Therapy Group

Participants randomized to the SPT group were provided with standard physical therapy treatment for the 12-week period. SPT at our center consists of supervised active

and passive range of motion/ stretching exercises, postural exercises, and basic strengthening exercises with light weights and elastic resistance bands. SPT participants were asked to attend a minimum of two physical therapy sessions per week (with the option of a third session) for the 12-week intervention period. Physical therapy sessions took place at the Behavioral Medicine Fitness Centre at the University of Alberta.

V-2.5. Progressive Resistance Exercise Training Group

Participants randomized to the PRET group were asked to attend a minimum of two supervised exercise sessions per week (with the option of a third session) for the 12-week intervention period. Participants in this group received SPT plus the PRET program. The PRET program was tailored to each survivor based on baseline testing results and consisted of two sets of 10-15 repetitions of 5 to 8 exercises, starting at 25-30% of their 1 repetition maximum (1 RM) strength, slowly progressing to 60-70% of their 1 RM by the end of the intervention period. The specific therapeutic exercises focused on the following muscle groups: rhomboids/ middle trapezius; levator scapula/ upper trapezius; biceps; triceps, deltoid and pectoralis major. For participants with recovery of active trapezius muscle function, specific exercises to target the trapezius muscle were introduced between weeks 6 and 8 of the intervention. Guidelines for exercise performance included maintenance of proper posture and scapular stability (e.g. no winging of scapula) and a rating of perceived exertion on the Borg Scale of no greater than 13-15 out of 20 (described as "somewhat hard" to "hard") (7). The response to exercise in terms of post exercise pain and muscle soreness was recorded on the training log at the subsequent exercise session and the prescription was modified as necessary.

The resistance weight was increased by 1 to 2.5 kg once the participant was able to complete two sets of 15 repetitions with proper form. All exercise sessions took place at the Behavioral Medicine Fitness Centre at the University of Alberta.

V-2.6. Assessment of Primary and Secondary Endpoints

Patient-rated and objectively measured outcomes were assessed at baseline and post-intervention. Our primary outcome was change in patient-rated shoulder pain and disability from baseline to post intervention. Shoulder pain and disability were assessed using the Shoulder Pain and Disability Index (SPADI) (8). The SPADI is a valid and reliable instrument that reflects the pain and disability associated with the clinical syndrome of a painful shoulder (9). Scores for the pain and disability subscales range from zero to 100, with higher scores indicating greater impairment. The total SPADI score is calculated by averaging the pain and disability subscale scores.

Muscular strength of the upper extremity was assessed by a one-repetition maximum (1RM) test for the seated row and the chest press. Each upper extremity (right and left) was tested individually (one-arm test) followed by testing of both extremities (two-arm test). In the case where participants presented with impairments in both shoulders as a result of undergoing bilateral neck dissection, the participants were asked to identify their most 'problematic shoulder' for the purpose of analyzing shoulder outcomes. Muscular endurance was assessed by using a sub-maximal seated row test. The weight for this test was set at 50% of the individual's baseline 1-RM weight and the test performed at a cadence of 22 repetitions per minute (set by a metronome). The maximum number of repetitions performed before falling behind the required cadence

was recorded. The same resistance weight (50% of baseline 1 RM) was used for assessing endurance at the post-intervention test. Muscular endurance scores were calculated by multiplying the weight in kilograms by the number of repetitions completed. The measurement of shoulder ROM was performed using a universal goniometer following standardized procedures (10). Active shoulder movements included forward flexion, abduction and external rotation. Passive shoulder movements included forward flexion, abduction, external rotation and horizontal abduction.

Quality of life and fatigue were assessed using the Functional Assessment of Cancer Therapy – Anemia (FACT-An) scale (11, 12). The FACT-An is a valid and reliable cancer-specific quality of life instrument that consists of 27-item core to which a 20-item fatigue and anemia specific subscale is added. The Neck Dissection Impairment Index (NDII) was used to assess treatment specific quality of life. The NDII is a valid and reliable instrument for assessing neck dissection impairment. Individual items from the 10-question NDII are scored from 1 (a lot) to 5 (not at all) with higher scores representing less impairment (13). The total NDII score is scaled to a 100-point cumulative score.

V-2.7. Baseline Characteristics

Demographic and behavioral data were collected by self-report and medical data were abstracted from records. The physical therapist monitored adherence and adverse events.

V-2.8. Sample size

The sample size was calculated based on the mean difference between groups in change score from baseline to post-intervention on the primary outcome. The effect size was determined from the results of the pilot study where the mean difference between exercise and standard care groups in SPADI score was 14.5 with a standard deviation of 20 (effect size of 0.73). The required sample size for the study was approximately 60 participants or 30 participants per group to detect a moderate to large standardized difference (effect size of 0.7) in our primary outcome.

V-2.9. Analysis plan

Baseline characteristics and adverse events of the two groups were compared using independent samples t-tests for continuous data and Pearson's Chi-square tests for categorical data. Primary analysis used independent samples t-tests to compare changes between groups in outcomes from baseline to post-intervention. Intention-to-treat analyses were conducted on all randomized participants using baseline-observation-carried-forward (BOCF). Adjusted analyses controlled for baseline value of the outcome, age, gender, cancer stage, time since surgery, neck dissection type, and pain medication use. Probability levels of less than 0.05 (two-tailed) were accepted as significant.

V-3. RESULTS

Recruitment began October 1, 2005 and ended October 31, 2006 (Figure 1). Fifteen of 45 (33%) eligible participants were recruited through the mail-out letter of invitation. The estimated accrual rate from Otolaryngology/ Head and Neck follow-up

clinics was 37 of 65 potentially eligible participants (57%). Of all patients who contacted the study coordinator, the most common reason for refusal was too busy (n=5). Recruitment of patients was stopped early at 52 participants to allow completion of the trial within the funding period.

The groups were balanced at baseline (Table 1). Full 12-week data was obtained on 46 of 52 (88%) participants, and did not differ by group (p=.995). One participant in the PRET group withdrew due to a soft-tissue injury as a result of exercise participation. One participant (PRET group) was hospitalized for acute cholecystitis and while hospitalized suffered a stroke (unrelated to exercise participation). Two participants in the standard physical therapy group withdrew due to cancer recurrence. Two participants were unable to perform the physical testing component at the end of the intervention period due to health concerns unrelated to study participation (one participant in the PRET group underwent abdominal surgery for colon cancer and one participant in the SPT group was under evaluation for cardiac disease). The SPT group and PRET group attended 87% and 95% of their 24 supervised physical therapy sessions, respectively. Three participants in the SPT group continued with their usual exercises at home during the 12-week intervention period.

V-3.1. Changes in Patient-Rated Outcomes

The overall SPADI score decreased by 14.1 in the PRET group compared to 4.8 in the SPT group [adjusted: -10.0; 95% CI: -15.8 to -4.2; p=.001] (Table 2). The score on the pain subscale decreased by 16.4 in the PRET group and by 2.2 in the SPT group [adjusted: -12.4; 95% CI: -20.8 to -4.1; p=.005]. The disability score decreased by 11.8

in the PRET group and 7.4 in the SPT group and was statistically significant after adjusting for relevant baseline variables [-7.5; 95% CI: -12.8 to -2.3; p =.006]. All other changes in patient-rated outcomes favoured the PRET group but did not reach statistical significance (Table 2 and Table 3).

V-3.2. Changes in Objectively Measured Outcomes

PRET was superior to SPT for all strength endpoints (Table 4). Muscular endurance, as assessed by a standard load test, was significantly improved in the PRET group [+189; 95% CI: 5 to 374; p =.045]. Results for ROM measurements favoured the PRET group with active external rotation ROM [+13; 95% CI: 6 to 20; p< .001] and passive abduction ROM [+8; 95% CI: 1 to 15; p=.034] reaching statistical significance after adjusting for relevant baseline variables (Table 5).

V-3.3. Associations among Objective Measures and Patient-Rated Outcomes

Improvement in muscular strength was significantly associated with reductions in SPADI total score [r = -.35; p = .011] and the pain subscale score [r = -.42; p =.002] but not the disability subscale score [r =-.14; p = .319]. Improvement in muscular endurance was also significantly associated with reductions in SPADI score [r = -.29; p =.037] and pain subscale score [r = -.35; p =.010]. Improvement in abduction range of motion was associated with reductions in disability subscale score [r =-.28; p =.046].

V-3.4. Adverse Events

One participant in the PRET program experienced increased pain as a result of soft-tissue injury to the scapular region. Despite modifications to the exercise program, the participant continued to experience increased pain following exercise sessions and

elected to withdraw from the study.

V-4. DISCUSSION

The major novel finding of the trial was that the PRET program had a beneficial effect on pain score. The standardized effect size of d = .84 represents a large effect on pain (14) and the percentage reduction in pain of 52% in the PRET group and exceeds the 30% to 50% reduction in pain for patient perceived improvement (15, 16). The improvement in pain score was associated with increases in upper extremity strength and endurance. The findings are consistent with the hypothesis that reductions in pain were mediated through improvements in muscular strength and endurance. In our clinical experience, pain is often secondary to the effect of trapezius muscle atrophy that leads to the downward and lateral displacement of the scapula and droop of the shoulder. Increased strength of the scapular muscles may alleviate pain by improving the positioning and thus the mechanics of the shoulder complex.

There was a significant difference in favor of PRET for overall SPADI score. The decrease in overall pain and disability of -10% in favor of the PRET group meets the minimal clinically important difference (MCID) of -10% for the SPADI scale (17). A significant difference in the disability subscale score in favor of the PRET group was also found after adjusting for baseline differences, suggesting greater benefit from PRET in shoulder disability as well as pain.

Positive effects of PRET were observed in both active and passive ROM. Larger effects were consistently found in the PRET group and the data suggest that even ROM

may be improved to a greater degree in PRET compared to SPT.

Although our study did not detect a difference in quality of life, there was a trend in favor of the PRET group that that approached the MCID of 7 points on the FACT-An and exceeded the 4 point MCID on the FACT-G after adjusting for relevant baseline variables. A recent meta-analysis examining exercise interventions for breast cancer survivors reported a significant improvement on the FACT-G scale of 4.6 points (18). This finding in the HNC population suggest a potential efficacy benefit in QoL from PRET that warrants further research with a larger sample of head and neck survivors.

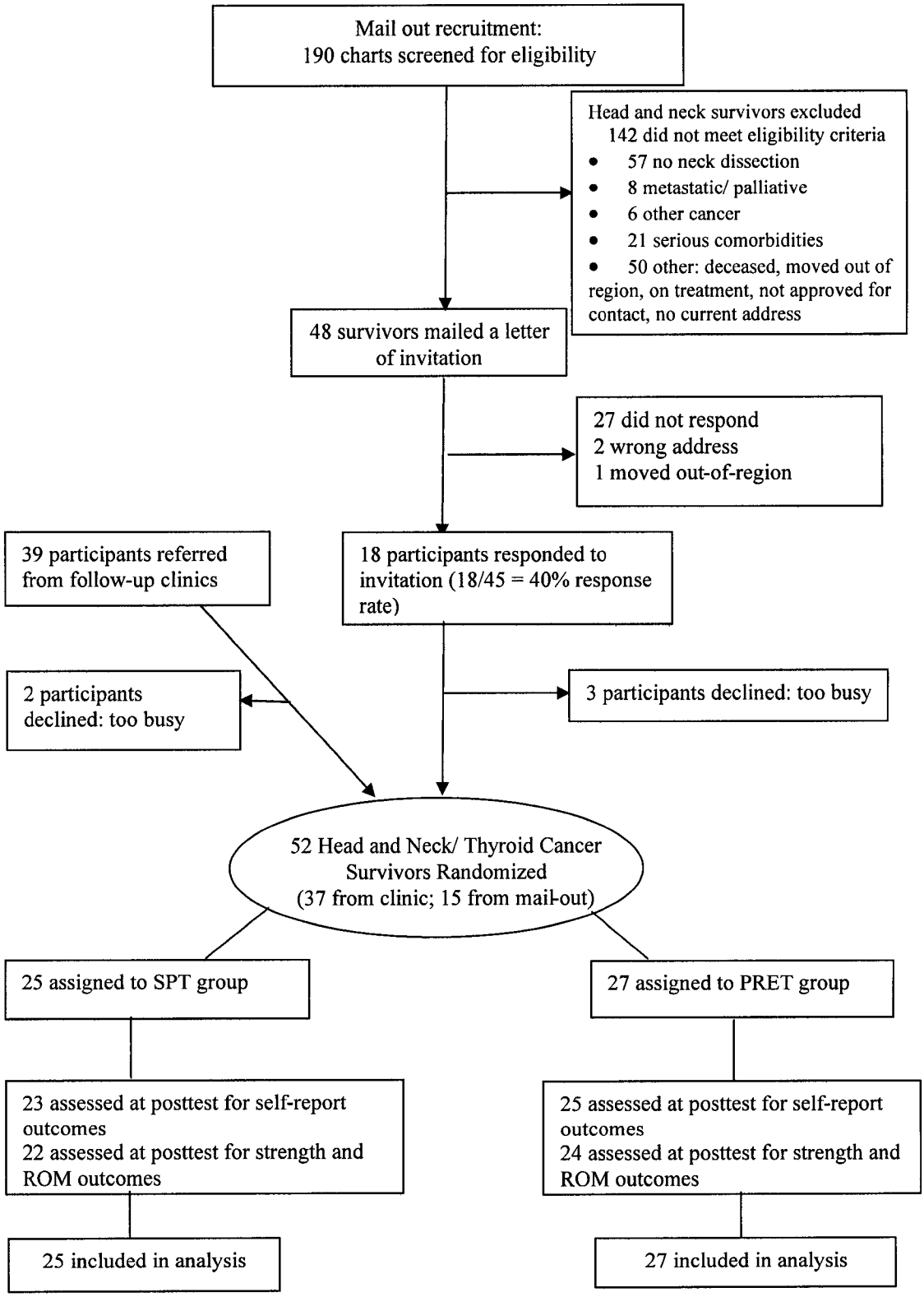
NDII standardized score improved in both groups and favored the exercise group but did not reach statistical significance. The NDII examines the impact of neck dissection on activities beyond those of just daily living and includes items related to work and recreational activities; however, the instrument does not separate shoulder symptoms from neck symptoms. While neck symptoms may have tempered improvements in the NDII, it appears that the shoulder specific PRET program may have some potential benefit beyond SPT for this outcome measure.

The exercise prescription for this study differed from standard upper extremity resistance exercise programs in that the PRET program focused on strengthening the scapular muscles and optimizing the shoulder alignment and posture. Exercise sessions were directly supervised, which has been shown to result in maximal gains in strength compared to unsupervised programs (19). Our resistance training protocol was prescribed with the resistance weight starting at 25-30% of 1RM whereas other studies in the cancer area have prescribed resistance exercise training starting at 60-85% of 1RM

(20, 21). Despite our more conservative approach, the strength gains of 37-48% from the PRET program compare favorably with the reported gains of 30-45% in upper extremity strength from a previous study of 12-week duration with breast cancer survivors (21).

Our trial is one of the first to directly compare a standard physical therapy program to an experimental exercise program in any cancer survivor population. The fact that both groups received an exercise intervention allowed us to control for potential nonspecific intervention factors such as social interaction with the exercise professional, expectation of benefit, and a sense of accomplishment that may confound patient-rated outcomes in improperly controlled exercise trials. Other study strengths include blinded evaluation of outcomes, intention-to-treat analysis, limited loss-to-follow-up, and excellent adherence comparable to other cancer trials (20, 22, 23). Limitations include the 47% recruitment rate and a well-educated, racially homogenous sample that restricts generalizability.

In summary, our trial demonstrates important improvements in patient-rated shoulder pain and disability, upper extremity strength and endurance, and range of motion in post neck dissection head and neck cancer survivors. The addition of PRET to SPT should be considered in the rehabilitation of the head and neck cancer survivor.



FigureV-1. Flow of Participants through the Trial

Table V-1: Baseline Demographic, Medical, and Behavioral Profile of Participants.

Variable	Overall (n =52)	SPT (n =25)	PRET (n =27)	P value
Demographic Profile				
Age, Mean (range), y	52 (32-76)	57(43-76)	53 (32-76)	.092
Female, No. (%)	15 (29%)	8 (32%)	7 (26%)	.762
Married, No. (%)	35 (67%)	18 (72%)	17 (63%)	.625
Completed university, No. (%)	26 (50%)	14 (56%)	12 (44%)	.701
Income >$80,000/year, No. (%)	21 (40%)	12 (48%)	9 (33%)	.401
On disability, No. (%)	20 (38%)	9 (36%)	11 (41%)	.574
Medical Profile				
Diagnosis, No. (%)				.537
Oral/ Oropharynx	32 (62%)	16 (64%)	16 (59%)	
Larynx/ hypopharynx	12 (23%)	6 (24%)	6 (22%)	
Thyroid	2 (4%)	1 (4%)	1 (4%)	
Other*	6(12%)	2 (8%)	4 (15%)	
Disease stage, No. (%)				.254
I	3 (6%)	1 (4%)	2 (7%)	
II	6 (12%)	3 (12%)	3 (11%)	
III	12 (23%)	3 (12%)	9 (33%)	
IV	30 (58%)	18(72%)	12 (44%)	
Bilateral Neck Dissection, No. (%)	40 (77%)	18 (72%)	22 (81%)	.517
Neck Dissection Type, No. (%)				.520
RND	9 (17%)	5 (20%)	4 (15%)	
MND: SCM sacrificed	5 (10%)	1 (4%)	4 (15%)	
MND to Level 5	20 (38%)	11(44%)	9 (33%)	
SND (Level 5 spared)	18 (35%)	8 (32%)	10 (37%)	
Radiation Therapy, No. (%)				.445
Bilateral neck	37 (71%)	15 (60%)	22 (81%)	
IMRT protocol	5 (10%)	4 (16%)	1(4%)	
Unilateral neck	2 (4%)	1 (4%)	1 (4%)	
Chemotherapy protocol, No. (%)				.668
Cisplatin	9 (17%)	4 (16%)	5 (19%)	
Carboplatin	3 (6%)	1 (4%)	2 (7%)	
Carboplatin/ Cisplatin plus 5FU	2 (4%)	1 (4%)	1 (4%)	
Pain medication				
Daily narcotic medication	12 (23%)	7 (28%)	5 (19%)	.315
Behavioral Profile				
Current exerciser, No. (%)	8 (15%)	4 (16%)	4 (15%)	.603
Current smoker, No. (%)	6 (12%)	1 (4%)	5 (19%)	.618
Current regular drinker, No. (%)	3 (6%)	1 (4%)	2 (7%)	.494

Data are presented as the mean (standard deviation) for continuous variables and the number (percentage) for categorical variables. SPT = Standard Physical Therapy PRET= progressive resistance exercise training; SD=standard deviation; No.=number; RND = Radical Neck Dissection; MND = Modified Radical Neck Dissection; SCM = Sternocleidomastiod muscle; SND = Selective Neck Dissection; Current exerciser = > 150 minutes of moderate-strenuous exercise per week.

* Parotid n =2; Sarcoma mandible n =2; Unknown primary n=2

Table V-2: Effects of Progressive Resistance Exercise Training on Patient-Rated Shoulder Outcomes

Variable	Baseline M (SD)	Post-intervention M (SD)	Mean change M [SD]	Unadjusted group differences in mean change: M [95% CI]; p	[1]Adjusted group differences in mean change: M [95% CI]; p
SPADI Total Score					
SPT (n=25)	27.4 (21.9)	22.6 (19.5)	- 4.8 (12.6)		
PRET (n=27)	25.4 (20.7)	11.3 (13.1)	-14.1 (14.4)	-9.3 [-16.8 to -1.7]; p=.017	-10.0 [-15.8 to -4.2]; p =.001
SPADI Pain Subscale					
SPT (n=25)	31.3 (24.7)	29.1 (26.8)	- 2.2 (17.8)		
PRET (n=27)	31.5 (25.7)	15.1 (18.0)	-16.4 (16.0)	-14.2 [-23.6 to -4.8]; p=.004	-12.4 [-20.8 to -4.1]; p =.005
SPADI Disability Subscale					
SPT (n=25)	23.6 (22.6)	16.1 (14.6)	- 7.4 (16.9)		
PRET (n=27)	19.6 (18.8)	7.6 (10.1)	-11.8 (15.3)	-4.2 [-13.3 to 4.7]; p=.337	-7.5 [-12.8 to -2.3]; p =.006
NDII					
SPT (n=25)	52.2 (21.8)	60.2 (21.9)	+8.0 (13.4)		
PRET (n=27)	55.8 (20.9)	68.6 (22.0)	+12.8 (17.5)	+4.8 [-3.9 to 13.5]; p=.278	+4.6 [-4.3 to 13.5]; p =.303

M=mean; SD=standard deviation; CI=confidence interval; SPADI= Shoulder Pain and Disability Index; NDII= Neck Dissection Impairment Index; SPT: Standard Physical Therapy; PRET: Progressive Resistance Exercise Training. [1]Adjusted for baseline value, age, gender, cancer stage, time since surgery, neck dissection type and pain medication use

Table V-3: Effects of Progressive Resistance Exercise Training on Patient-Rated Quality of Life.

Variable	Baseline M (SD)	Post-intervention M (SD)	Mean change M [SD]	Unadjusted group differences in mean change: M [95% CI]; p	[1]Adjusted group differences in mean change: M [95% CI]; p
FACT-An (0-188)					
SPT (n=25)	130.6 (30.9)	134.4 (34.0)	+3.9 (10.0)		
PRET (n=27)	133.9 (23.8)	142.4 (27.0)	+8.5 (19.3)	+4.6 [-4.0 to 13.3]; p=.287	+6.4 [-3.1 to 15.9]; p=.180
FACT-G (0-108)					
SPT (n=25)	76.4 (18.4)	78.1 (19.3)	+1.7 (6.9)		
PRET (n=27)	79.4 (13.7)	83.9 (15.6)	+4.4 (10.6)	+2.7 [-2.3 to 7.7]; p=.287	+4.4 [-0.9 to 9.7]; p=.099
Fatigue Subscale (0-52)					
SPT (n=25)	32.7 (11.0)	34.3 (11.1)	+1.6 (5.6)		
PRET (n=27)	33.5 (9.7)	36.7 (9.0)	+3.1 (9.0)	+1.5 [-2.7 to 5.7]; p=.478	+1.7 [-2.6 to 6.1]; p=.426

M=mean; SD=standard deviation; CI=confidence interval; FACT-An=functional assessment of cancer therapy-anemia. FACT-G= functional assessment of cancer therapy- general; SPT=standard physical therapy; PRET=progressive resistance exercise training.[1]Adjusted for baseline value, age, sex, cancer stage, time since surgery, neck dissection type, pain medication use

Table V-4: Effects of Progressive Resistance Exercise Training on Muscular Strength and Endurance

Variable	Baseline M (SD)	Post-intervention M (SD)	Mean change M [SD]	Unadjusted group differences in mean change: M [95% CI]; p	[1]Adjusted group differences in mean change: M [95% CI]; p
1RM Two-arm Seated Row, kg					
SPT (n=25)	35.2 (20.6)	41.3 (23.1)	+ 5.5 (7.9)		
PRET (n=27)	43.9 (17.9)	60.2 (21.1)	+16.3 (11.1)	+10.9 [5.5 to 16.3]; p<.001	+10.8 [5.4 to 16.2]; p<.001
1RM Two-arm Chest press, kg					
SPT (n=25)	30.0 (16.8)	37.0 (21.1)	+ 7.1 (10.0)		
PRET (n=27)	35.4 (14.7)	51.4 (20.6)	+16.0 (12.5)	+8.9 [2.6 to 15.2]; p=.007	+7.0 [0.4 to 13.7]; p =.039
1RM Affected Shoulder Seated Row, kg					
SPT (n=25)	17.1 (10.4)	20.6 (11.1)	+3.6 (4.7)		
PRET (n=27)	19.7 (8.8)	27.6 (10.3)	+7.9 (5.2)	+4.3 [1.5 to 7.1]; p=.003	+4.1 [1.3 to 7.0]; p=.006
1RM Affected Shoulder Chest press, kg					
SPT (n=25)	15.1 (8.9)	17.5 (9.8)	+2.3 (4.6)		
PRET (n=27)	16.2 (7.9)	24.0 (10.7)	+7.8 (6.2)	+5.5 [2.4 to 8.5]; p=.001	+4.7 [1.5 to 7.9]; p=.005
Standard Load Endurance Test					
SPT (n=25)	469 (313)	712 (415)	+243 (325)		
PRET (n=27)	567 (267)	1032 (432)	+466 (324)	+223 [42 to 403]; p=.017	+189 [5 to 374]; p=.045

M=mean; SD=standard deviation; CI=confidence interval; 1 RM = 1 repetition maximum strength; SPT: Standard Physical Therapy; PRET: Progressive Resistance Exercise Training. [1]Adjusted for baseline value, age, gender, cancer stage, time since surgery; neck dissection type, pain medication use

Table V-5: Effects of Progressive Resistance Exercise Training on Active and Passive Range of Motion

Variable	Baseline M (SD)	Post-intervention M (SD)	Mean change M [SD]	Unadjusted group differences in mean change: M [95% CI]; p	[1]Adjusted group differences in mean change: M [95% CI]; p
Active Range of Motion					
Forward Flexion					
SPT (n=25)	139 (18)	145 (18)	+ 7 (16)		
PRET (n=27)	138 (24)	153 (23)	+15 (15)	+9 [-1 to 18]; p=.072	+6 [-2 to 14]; p=.147
Abduction					
SPT (n=25)	126 (37)	139 (31)	+14 (35)		
PRET (n=27)	121 (42)	147 (36)	+26 (35)	+13 [-7 to 32]; p=.198	+7 [-9 to 22]; p=.378
External Rotation					
SPT (n=25)	79 (16)	82 (16)	+ 2 (14)		
PRET (n=27)	82 (19)	97 (16)	+15 (14)	+13 [5 to 21]; p<.002	+13 [6 to 20]; p<.001
Passive Range of Motion					
Forward Flexion					
SPT (n=25)	159 (12)	164 (12)	+ 5 (11)		
PRET (n=27)	157 (17)	170 (13)	+13 (14)	+8 [1 to 15]; p=.026	+5 [-1 to 11]; p=.112
Abduction (degrees)					
SPT (n=25)	166 (19)	167 (17)	+ 1 (13)		
PRET (n=27)	160 (28)	173 (20)	+13 (19)	+12 [3 to 22]; p=.010	+8 [1 to 15]; p=.034
External Rotation					
SPT (n=25)	80 (14)	86 (9)	+6 (14)		
PRET (n=27)	88 (13)	94 (11)	+6 (10)	+0 [-7 to 7]; p=.982	+3 [-2 to 8]; p=.218
Horizontal Abduction					
SPT (n=25)	81 (13)	87 (10)	+6 (11)		
PRET (n=27)	87 (11)	93 (10)	+6 (9)	+0 [-5 to 6]; p=.870	+2 [-2 to 7]; p=.347

Range of Motion measurements in degrees: M=mean; SD=standard deviation; CI=confidence interval; FACT-G= functional assessment of cancer therapy-general; FACT-An=functional assessment of cancer therapy-anemia. SPT=standard physical therapy; PRET=progressive resistance exercise training. [1]Adjusted for baseline value, age, gender, cancer stage, time since surgery, neck dissection type, pain medication use

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VI: CHAPTER SIX

"Cancer Rehabilitation: Recommendations for Integrating Exercise Programming in the Clinical Practice Setting"

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VI-1. INTRODUCTION

Recent attention has been directed toward the role of exercise in the rehabilitation of cancer survivors. Appropriately prescribed exercise training programs are associated with low complication rates and numerous beneficial effects for other chronic diseases including cardiovascular diseases, diabetes, and chronic obstructive pulmonary disease (1-3). Therefore cancer survivors may also benefit from exercise, as a therapeutic intervention, to help manage disease and treatment-related side effects.

The purpose of this paper is to review the potential therapeutic role of exercise training in cancer survivors and examine methods to deliver these services in the clinical setting. Noting the limited direct research on implementation of clinical exercise programs in the cancer setting, we review the literature and propose guidelines for: 1) goals of the prescribed physical activity or exercise program; 2) medical and pre-exercise evaluations; 3) recommendations for exercise programming; 4) safety considerations; 5) barriers to physical activity and exercise training in cancer survivors; 6) self-directed and community based exercise programs; and 7) the role of medical and exercise professionals.

VI-2. POST CANCER SEQUELAE AND COMORBID CONDITIONS

In the process of destroying cancer cells, treatments may cause physiological changes to normal tissues and body functions, leading to an overall decline in performance and functional status (4,5). Severe side effects to body systems and organs may affect exercise testing, prescription, and an individual's response to exercise training. In this

section we focus on post cancer sequelae and comorbid conditions that may alter these components of exercise programming.

VI-2.1. Treatment-related Side Effects

Cancer-related pain is one of the most prevalent symptoms, occurring in up to 50% of patients with cancer (6,7). Pain may be the result of surgery (e.g. post mastectomy syndrome, radical neck syndrome), chemotherapy (e.g. peripheral neuropathy), radiotherapy (e.g. radiation fibrosis, radiation necrosis of bone) or neoplastic disease. Neuropathic pain may result from damage to a nerve or nerve root due to prolonged nerve compression, surgical resection of a nerve, or damage from chemotherapeutic agents and/or radiotherapy. An understanding of when pain is indicative of further tissue injury is necessary to determine the appropriate type and amount of physical activity.

Fatigue is a common side effect of cancer treatment (8). Prevalence rates of fatigue as high as 96% have been reported following chemotherapy and radiation therapy. Fatigue may be described as a lack of energy, muscle weakness, somnolence, dysphoric mood, or impaired cognition. Fatigue can be severe, particularly for patients receiving treatment with interferon and interleukin therapy (8). Factors related to fatigue include pain, sleep problems, infection, poor nutrition, side effects of medications and anemia (9). Deconditioning from inactivity is a secondary problem that may increase fatigue levels in cancer survivors. Anxiety, depression and difficulties coping with cancer or its treatment may further contribute to fatigue (8).

Dyspnea is a distressing and debilitating symptom in some patients with cancer (10). The direct causes of dyspnea are usually related to primary or metastatic lung

cancer (10). Indirect causes of dyspnea include treatment related side effects from radiation therapy (e.g. radiation fibrosis, pneumonitis) or chemotherapy (e.g. pulmonary toxicity, cardiomyopathy) or due to secondary effects of cancer treatment such as anemia, cachexia, pulmonary embolism, and anxiety (10).

The diagnosis of cancer, particularly if incurable, is recognized as a significant psychosocial stressor (11,12). Increased dependency or anticipation of reduced life expectancy may precipitate adjustment disorders or major depression (11). Depression with anxiety is frequently observed in cancer survivors (13), with as many as 25% developing major depression during the course of illness (8). Higher rates of depression are found in individuals with uncontrolled physical symptoms such as pain and fatigue (8, 14). Depression may also be related to medication side effects or to cancer treatments (14). High doses of prednisone, for example, may provoke depressive symptoms (14).

VI-2.2. Body Composition

Changes in weight and body composition occur with cancer and its treatments and may reduce health-related quality of life, increase the risk of other disease conditions, and reduce overall survival. Weight gain related to breast cancer diagnosis and treatment has been reported to occur in 50% to 90% of women (15,16). Treatment-related weight gain results in increased visceral fat mass and a loss in lean muscle mass (15). Androgen deprivation therapy for men with locally advanced or metastatic prostate cancer may also result in increased adipose tissue and a loss of lean body tissue (16,17). Increased body fat and obesity are closely linked to disease states such as heart disease, hypertension, osteoarthritis and diabetes (18).

In contrast, weight loss affects approximately 50% of all cancer survivors (19). Mucositis from chemotherapy or RT administration may prevent oral intake of food and water, and may lead to dehydration, malnutrition and weight loss (20).Xe rostomia may affect swallowing and dental health leading to compromised oral intake (21,22). Digestive tract cancers may lead to a decreased ability to digest, absorb and metabolize nutrients (6) and result in malnutrition. Cancer cachexia, or severe weight loss due to cancer and/or its treatments, is a syndrome that is characterized by weakness, fatigue, anorexia, loss of adipose tissue and skeletal muscle, abnormal metabolism, and impaired immune function (19). Cachexia is known to negatively affect skeletal muscle metabolism, leading to muscle wasting and weakness (19).

VI-2.3. Neuromusculoskeletal Sequelae

Steroid induced myopathy commonly occurs in patients taking high doses of fluorinated corticosteroids and is characterized by weakness in the proximal muscles of the limbs and neck flexors (9). Adrenocorticosteroids are frequently prescribed in patients with brain and spinal cord edema for relief of neuropathic pain and for control of chemotherapy-induced nausea (23). Muscular weakness may develop within weeks, leading to physical inactivity, and possibly further decline in function (9,23). Steroids may result in body composition changes of centripetal obesity, the development of a buffalo hump, and osteopenia (23,24). High dose steroids may also negatively affect respiratory muscle function and can be problematic for persons with pulmonary disease (23).

Cancer and its treatments can affect the integrity of bone and joint. Cancer that involves the cortex of the bone will stretch the periosteum, causing discomfort, and can

lead to decreased weight bearing and subsequent bone softening. Hematological malignancies, such as multiple myeloma, may present with severe bone destruction (24). The effects of radiation therapy (RT) on bone include functional limitations, osteonecrosis, osteoporosis, increased susceptibility to fractures, and poor healing (25). Chemotherapy alone, or in combination with RT, can also lead to osteopenia. For example, aromatase inhibitors, commonly used for the treatment of breast cancer, may cause arthralgias, and increased bone turnover leading to osteoporosis and fractures. Methotrexate and prednisone have also been found to have detrimental effects on bone (24).

Peripheral neuropathy is often a side effect of neurotoxic chemotherapeutic agents such as vincristine, thalidomide, cisplatin and paclitaxel (26). Peripheral neuropathy is defined as inflammation, injury or degeneration of the peripheral nerve fibres (27). Early symptoms include tingling, numbness, and burning in the fingers and toes. Later symptoms may progress to pain, loss of deep tendon reflexes, reduced muscle tone, and loss of two-point discrimination, vibratory, temperature, touch and position sense. Damage may also present as autonomic neuropathy (e.g. orthostatic hypotension) and cranial nerve toxicity (e.g. double vision from damage to cranial nerves controlling extraocular muscles) (26-28).

VI-2.4. Cardiovascular Sequelae

Several chemotherapeutic agents have been associated with cardiac complications, especially the anthracyclines (4). Acute anthracycline-associated cardiotoxicities include supraventricular tachycardia, ventricular ectopy, myopericarditis, significant ECG changes, cardiomyopathy and death. Subacute cardiomyopathy occurs

up to 8 months following chemotherapy administration and late cardiomyopathy generally presents 5 or more years after treatment. Late anthracycline cardiomyopathy often leads to congestive heart failure (CHF) (4). The generally accepted safe cumulative dose of doxorubicin, for example, is up to 500 mg/m^2. Some patients have tolerated higher doses without developing cardiac dysfunction; however, others have developed fatal CHF with doses as low as 40 mg/m^2 (4) Cardiac complications may also occur with other chemotherapeutic agents, hormone therapy and immunotherapy (4) and may present as relatively benign arrhythmias to potentially fatal conditions such as myocardial infarction and cardiomyopathy. When multiple neoplastic agents are prescribed the associated toxicities may have an additive effect (4).

VI-2.5. Comorbid Conditions

As a disease with a high prevalence among older persons, cancer often coexists with other diseases states such as hypertension, cardiac disease, diabetes, arthritis, chronic obstructive pulmonary disease and depression (29). Obesity is a serious and growing public health problem (30). Obesity contributes to the increased incidence of a number of cancers including colon, post menopausal breast and endometrial cancers, and therefore many cancer patients may be overweight or obese at diagnosis (31). Moreover, overweight and obesity are estimated to contribute to 15-20% of cancer deaths (31). There is growing concern regarding comorbid conditions associated with obesity such as cardiovascular disease, arthritis and type II diabetes (31).

These comorbid conditions may predate the cancer diagnosis (e.g. COPD) or present for the first time after cancer treatment (e.g. depression). Existence of one or

more comorbid conditions complicate the rehabilitation process and may negatively impact physical activity levels and exercise participation.

VI-3. REVIEW EXERCISE AND CANCER LITERATURE

A number of systematic reviews and meta-analyses (32-36) have addressed exercise as an intervention for patients and survivors with cancer. Given the plethora of recent reviews on this topic, we have elected to summarize these reviews rather than provide details of the original studies.

Stevinson et al (35) completed a systematic review and meta-analysis of 33 controlled trials (25 randomized) that examined the effects of exercise for all cancer survivor groups. Nineteen of the trials examined the effect of aerobic exercise interventions (mainly walking and biking), three trials examined resistance exercise, while another 10 combined aerobic and resistance exercise. Only 17 trials tested an exercise intervention that lasted 10 weeks or longer. The results from this review showed moderate improvements in physical function in cancer survivors both during and after treatments (35).

Knols et al. (32) completed a systematic review of randomized and controlled trials examining physical exercise in cancer survivors both during and after treatment (32). Thirty-four trials (27 randomized) were included in the review. Twenty-two trials examined exercise during cancer treatment and 12 trials examined exercise after cancer treatment. The intensity of most programs was reported to range from 50% to 90% of estimated maximal oxygen uptake (VO_{2max}), two times per week to twice daily, and a duration ranging from 2 weeks to one year. The authors reported positive results for

physiologic measures, objective performance indicators, self-reported functioning and symptoms, psychological well-being and quality of life (32).

Schmitz et al. (34) completed a systematic review and meta-analysis of 32 controlled exercise trials (27 randomized) in cancer survivors both during and after cancer treatment (34). Twenty of the trials examined exercise during cancer treatment while 12 trials examined exercise after cancer treatment. The majority of the interventions consisted of aerobic exercise of moderate intensity, 3-5 days per week, for 20-30 minutes each day. The length of the interventions was 3 months or less in 25 (79%) of the studies. The results showed that exercise was effective in improving cardiorespiratory fitness during and after cancer treatments, symptoms and physiologic effects during treatment, and vigor post treatment. There was insufficient evidence to make any clear conclusions for other outcomes (34).

Conn et al. (36) performed a meta-analysis of all types of trials examining exercise interventions for patients with cancer (36). This meta-analysis included 33 relevant trials of which 15 were randomized controlled trials. Twenty-one studies tested supervised exercise interventions. Eighteen studies examined aerobic exercise interventions and 11 studies examined resistance exercise interventions. Most studies prescribed moderate intensity exercise at 30% to 70% of maximum oxygen consumption, scheduled three times per week. The authors reported moderate effects from exercise on physical function, body composition and symptoms other than fatigue. Small positive effects were found for mood, quality of life, fatigue, and exercise behavior (36).

McNeely et al. (33) limited their meta-analysis to randomized controlled trials examining exercise interventions for breast cancer patients and survivors (33). This meta-

analysis included 14 relevant studies involving 717 participants. Moderate positive effects from exercise were found for quality of life, cardiorespiratory fitness, and physical functioning. A small positive effect from exercise was found for symptoms of fatigue post treatment. The authors concluded that future research would benefit from increased attention to study quality and examination of long-term effects (33).

Collectively, these findings support the use of exercise to improve both physiological and psychosocial functioning after cancer diagnosis, which is consistent with the American Cancer Society's recommendations for physical activity during and after cancer treatment (37). Although additional validation through large scale randomized controlled trials is necessary, the evidence for cancer survivors to participate in regular exercise, particularly post treatment, is sufficient at the present time to warrant offering exercise programs in this population.

VI-3.1. Exercise behaviors

Research has shown that despite the potential benefits of physical activity, only a small percentage of cancer survivors are physically active. During formal exercise trials, patients with cancer maintain adherence rates that vary from 71.5% to 98.4%; demonstrating the ability of study participants to successfully complete an exercise program. However, the majority of patients participating in these studies have been younger, without significant comorbidities, and in earlier stages of cancer, limiting generalizibility to the general population of cancer survivors. At present, it is unclear whether cancer patients and survivors are able to maintain such adherence rates without the close supervision of a clinical trial.

Several studies have used retrospective (38,39) and prospective (40) methodologies to study the natural effect of cancer on exercise participation. These studies report that the percentage of cancer survivors who exercise regularly is as low as 16 -20% (39,41,42) with a general consensus that the majority of cancer survivors are not exercising at levels that are likely to yield health benefits (41,42).

Several empirical studies have examined changes in exercise behavior during the cancer experience. In an early study, Courneya and colleagues retrospectively examined the exercise patterns of 130 colorectal cancer survivors pre-diagnosis, during treatment and post-treatment (43). Four main patterns of exercise behavior over the three time points were found: 30% of participants were maintainers (those who were active at all three time points), 16% were temporary relapsers (those who were active prediagnosis, inactive during treatment, and active again post treatment), 14% were permanent relapsers (those who were active prediagnosis, inactive during treatment, and inactive post treatment), and 30% were nonexercisers (those who were inactive at all three time points). Cancer treatment had a significant negative effect on exercise participation that was not completely recovered post-treatment. Similarly, in a sample of non-Hodgkins lymphoma survivors, only 34.3%, 6.6%, and 23.9% of survivors were meeting public health guidelines for physical activity pre-treatment, during treatment, and post treatment respectively (44). Corroborating evidence for this pattern of exercise behavior has been shown in breast cancer (38,45), and multiple myeloma (46). Overall, this research highlights the need for interventions to address physical activity and exercise in cancer survivors.

VI-4. IMPLEMENTATION OF EXERCISE PROGRAMS

VI-4.1. Goals of the prescribed physical activity or exercise program

Physical activity is defined as human movement that results in a substantial increase in energy expenditure over resting levels (47). Exercise is defined as a form of physical activity that is performed on a repeated basis over an extended period of time with the intention of improving fitness, performance, or health (47). Physical inactivity can have a detrimental effect on cardiovascular, pulmonary, and musculoskeletal systems, therefore maintenance of, or gradual return to, recommended levels of physical activity (at minimum) should be a primary aim of cancer rehabilitation. An exercise training prescription usually includes activity mode (e.g., walking, swimming, free weights), volume (i.e., frequency, intensity, and duration), progression (i.e., gradually increase training volume over time), periodization (i.e., vary training volume over time to maximize benefits and avoid overtraining), and context (i.e., physical and social environment) (48).

Exercise goals will vary depending on the patient's functional status, treatment trajectory and overall prognosis. The *Physical Exercise Across the Cancer Experience* (PEACE) framework considers six possible exercise intervention periods across the cancer continuum. For example, exercise may be prescribed as buffering before treatment, coping during treatment, rehabilitation following treatment or palliation at the end stages of the disease. The framework also considers survivorship, where the goals of exercise training may shift to a focus on health promotion and disease prevention. More specifically, exercise may be prescribed to improve physical functioning prior to treatment, to prevent or attenuate functional decline during treatment, to address

treatment-specific impairments, or to optimize health in the recovery period following cancer treatment (48)(Figure 1).

VI-4.2. Screening for Exercise Testing and Participation

Physical activity and exercise are normal human functions that can be undertaken with a high level of safety for most individuals when completed appropriately. Exercise is not, however, without its risks. The potential adverse effects of exercise participation are likely to include musculoskeletal injury and major cardiovascular events (30). The goal of medical screening is, thus, to identify when exercise might be inappropriate, unsafe or require medical supervision. A comprehensive evaluation of the cancer survivor is necessary and should include a medical history, physical examination and laboratory tests (e.g. complete blood count, lipid profile and pulmonary function) (30). Prior to performing exercise testing, information must be collected on important diagnostic and treatment variables such as the individual's type and stage of disease, type of cancer treatment and identify any acute or chronic impairments related cancer and/or cancer treatment (48). The evaluation must also include an assessment of risk factors for, and/or symptoms of, cardiovascular, pulmonary and metabolic diseases and identify other existing comorbid conditions such as osteoarthritis or osteoporosis. A simple screening tool such as the Revised PAR-Q or a medical history questionnaire such as the PARmed-X may be useful to identify individuals with comorbid disease for whom exercise and/or exercise testing may be unsafe or require medical supervision (These screening tools are available through Canadian Society for Exercise Physiology's web site http://www.csep.ca). The Preparticipation Screening Tool developed by the American Heart Association and the American College of Sports Medicine is a one-page form that

assesses cardiovascular history, symptoms and risk factors (49). This tool aims to identify high-risk individuals requiring a more comprehensive medical evaluation. Suggested steps for medical and pre-exercise evaluations are outlined in Table 1.

VI-4.3. Exercise Testing

Exercise testing should be performed following cancer diagnosis, ideally prior to initiation of cancer treatment. This testing should be repeated at regular intervals in the recovery period following cancer treatment. Exercise testing results may be used to a) quantify the functional status of the individual; b) identify underlying comorbid conditions that may preclude exercise (e.g. hypertension); c) develop an appropriate exercise prescription to assist the patient in coping with and /or recovering from cancer and its treatments. The decision concerning the appropriate mode of exercise to use for testing will depend on the limitations and impairments imposed by the cancer/ treatment, the presence of comorbidities, and the general health of the cancer survivor. We recommend medical supervision of exercise testing for the cancer survivor, consistent with guidelines for other clinical populations (30).

VI-4.3.1. Testing of Cardiorespiratory Fitness

Cardiorespiratory fitness is the ability to perform moderate-to-high intensity exercise for prolonged periods of time (30). Maximal oxygen uptake (VO_{2max}) is accepted as the gold standard measure of cardiorespiratory fitness and can be tested using an electronically braked cycle ergometer or treadmill. Testing of maximal oxygen uptake provides a precise estimate of the functional state of the respiratory, cardiovascular and musculoskeletal systems.

When direct measurement of VO_{2max} is not practical, a submaximal exercise test can be used to estimate VO_{2max} (30). There are a number of submaximal tests including field tests (e.g. 6-minute walk and 12-minute walk tests), and single-stage and multi-stage cycle, treadmill or step tests. Submaximal exercise tests are less accurate in assessing cardiorespiratory fitness and are dependent on several assumptions of normalcy or predictability (30) that may not be valid for patients who have undergone cancer treatment. The exercise test, whether maximal or submaximal, must assess functional capacity and cardiovascular response to at least the level of the proposed exercise regimen so that any symptoms that might be experienced are identified under the supervised environment (48).

VI-4.3.2. Testing of Muscular Strength and Endurance

Muscular strength is the maximal force that can be generated by a specific muscle or muscle group (30). The gold standard of strength testing is the 1-repetition maximum (1-RM) test. A 1-RM is the heaviest weight that can be lifted only one time using good technique and proper posture (30). When safety is a concern, alternates to the 1-RM test such as the 6-RM and 10-RM test may be considered. Isometric strength can be measured using hand-held dynamometry or cable tensiometry (50). Isokinetic strength testing (e.g., using a Cybex® isokinetic dynamometer) may be useful to assess underlying neuromuscular physiology (50). A number of tests can be completed to assess muscular endurance (30). Examples of maximum repeated contractions tests include the classic abdominal curl-up/crunch or upper extremity push-up tests (30). For assessing muscular endurance in the cancer setting, however, we recommend a standard load test or static contraction test. The standard load test determines the maximum number of

repetitions that can be completed at a fixed submaximal load (e.g. 50% of 1RM) for a given muscle group or exercise. The static contraction test measures the length of time (to fatigue) that a contraction may be held with a submaximal load for a chosen muscle group or resistance exercise (30).

VI-4.3.3. Testing of Flexibility and Joint Range of Motion

General flexibility and joint range of motion can be measured using tests such as the sit-and-reach and shoulder elevation tests (30). For the cancer survivor, postural alterations, loss of flexibility in soft tissues and/or joint stiffness may develop as a result of surgery and/or radiation therapy to a given body region. In these cases, flexibility and joint range of motion are best measured using a universal goniometer.

VI-5. RECOMMENDATIONS FOR EXERCISE PROGRAMMING

Prescribing exercise for cancer survivors is complex because cancer is not a homogeneous disease and the response to a given exercise regimen may not be linear or predictable (51). Therefore, the exercise program should be prescribed individually for each survivor, using all available clinical data and paying special attention to results of the exercise test and physiological training responses as important determinants. The general exercise program should be designed to increase or minimally maintain the cancer survivor's overall fitness and, when needed, address specific disease and/or treatment-related problems.

Many guiding principles of exercise prescription, however, hold true in the cancer rehabilitation setting. These principles include overload, adaptation, specificity and reversibility (30,50). The principle of overload states that a physiological system

develops only when loads are applied that are greater than those normally encountered. In other words, a threshold level must be exceeded for adaptation to occur. Overload occurs through the interaction and manipulation of the prescription variables of intensity, duration and frequency (30,50). If too much stress or overload is encountered, however, then declines or deterioration in the physiological system will result. This "overtraining" is excessive intensity, duration or frequency of exercise training that results in an increase in fatigue or injury and cancer patients may be at greater risk of this negative outcome.

The second principle of exercise prescription is adaptation (50). Adaptation in a physiological system occurs during the recovery period from the exercise training session. Relative rest, which allows time for this adaptation to occur, is an important prescription factor of the exercise program, particularly for the cancer survivor.

The third principle, specificity, relates to the specific training effects derived from a given exercise regimen (50). In other words, you will improve the physiological system that is trained in the exercise regimen. This principle is referred to as the SAID principle (Specific Adaptation to Imposed Demands) (50).

The final principle, reversibility, states that a physiological system will revert to its previous level if training loads are not regularly applied. In other words, regular exercise is needed to maintain a given training effect (50).

In our experience, determining the optimal overload (intensity) is often a challenge in the cancer setting. Therefore, we propose an additional principle, 'modification', specifically for the cancer setting and primarily for the period during adjuvant therapy. Cancer treatments may have a profound effect on physiological systems, therefore the status of, and response to exercise, of a cancer survivor may

fluctuate on a daily basis. Exercise prescriptions that are rigid and mathematical, or based on a regimen for the general "healthy" population may be inappropriate for patients with symptoms such as fatigue and for those undergoing adjuvant therapies. Ongoing modifications may be necessary to a given exercise prescription (and should be anticipated) to ensure that exercise participation is safe and effective (Table 2).

VI-5.1. Exercise Guidelines for the Post Treatment Phase

Numerous exercise guidelines have been published for the cancer population; however, none of these guidelines are considered evidence-based (52). As a result, the most beneficial exercise regimen in terms of type, frequency, duration or intensity for the cancer survivor is currently not known (52). Moreover, the optimal exercise prescription would likely vary depending on the cancer type and stage, cancer treatment and demographic profile of the individual. Despite the lack of consensus on the volume and type of exercise that is optimal for cancer patients, it is likely that an exercise program aimed at maintaining or improving the health-related fitness components in cancer survivors would need to minimally meet the recommendations for maintaining or improving these variables in apparently healthy individuals.

We recommend that formal physical exercise be carried out as a supervised outpatient based programme in the rehabilitation phase immediately post treatment. An initial exercise program should be of a minimum of 8 to 12 weeks duration to ensure that measurable improvements can be achieved. The program should be progressed cautiously over a period of several weeks. Appropriate supervision and monitoring during this early stage will help to optimize the success of the program by ensuring proper exercise performance and allowing modifications to the prescription. The exercise

prescription should be designed to maintain and/or improve an individual's current level of fitness as determined by the exercise test. This may require a prescription involving all or a combination of the key components of health-related fitness: cardiorespiratory fitness (aerobic training), muscular strength and endurance (resistance training), and flexibility training.

The exercise program should be structured to include a warm-up (5-10 minutes), the exercise phase (20-60 minutes), and a cool-down phase (5-10 minutes) (53). The exercise prescription should consider the lifestyle needs and preferences of the individual and include activities that are enjoyable and if desired, incorporate social interaction (48). The exercise session should finish with a gradual cool-down period that includes exercises of diminishing intensities to allow appropriate circulatory adjustments and return of the heart rate and blood pressure to near resting values (30).

VI-5.1.1. Cardiorespiratory fitness (aerobic exercise training)

Aerobic training involves activities such as walking, swimming and cycling that use large muscle groups, are maintained for a prolonged period of time, and are rhythmic in nature. Although walking may be the preferred mode of exercise, cycle ergometry or water exercises may provide alternatives to avoid excessive stress on bone and for individuals with comorbid arthritic conditions (54). The goal, in the initial phases of the exercise program, is to first reach target frequency (e.g. 3 to 5 days per week), then duration (at least 20 minutes; which can be broken into shorter bouts of 5 to 10 minutes) and finally progress to the desired intensity (e.g. 40-60% of heart rate reserve). Progressively increasing the total amount of activity, rather than the intensity, may be the best option to avoid excessive fatigue and/or muscular soreness, and when adherence to

exercise is a potential issue. This gradual progression of exercise will allow for adequate cardiovascular and musculoskeletal adaptation and help avoid injury. It is important to recognize that while exercise of lower intensity is effective in improving muscular endurance and attenuating the decline in physiological function, moderate intensity exercise is necessary to improve cardiovascular function and cardiovascular disease risk factors (50).

For some cancer survivors, functional status may be so impaired that excessive load or stress may occur with basic activities of daily living. In these individuals it is imperative to address symptoms such as fatigue and ameliorate motor function to gain capacity to perform exercise at an intensity level that will increase cardiorespiratory functioning. These cancer survivors may be better served by an exercise prescription that initially focuses on functional activities and/or muscular strengthening exercises.

VI-5.1.2. Muscular Strength and Endurance

Muscular strength and endurance training are particularly important to attenuate both sarcopenia and disease related declines in muscle mass (50). Muscular endurance is the ability of a muscle to complete a repeated number of contractions over time (30). Deficits in this health-related fitness component can greatly impair an individual's functional capacity and ability to carry out activities of daily living. Muscular endurance is improved by performing repeated contractions against a mild resistance. Muscular strength is best enhanced by progressive resistance exercise training performed with high intensity (resistance) but fewer repetitions (30). As the strength of a muscle increases, the cardiovascular response of the muscle improves so that muscular endurance and power also increase (30).

It is recommended that cancer survivors perform at minimum one set of 8 to 12 repetitions of 8-10 exercises that include all of the major muscle groups. Resistance training should be performed two to three times per week with a minimum of 48 hours between training sessions to allow for recovery. Muscular strength can be substantially improved if the training stimulus is progressively increased over time. For the more deconditioned, fatigued or frail cancer survivor, a muscular endurance focus of 12 to 15 repetitions of each exercise may be more appropriate (30). An initial overload of increasing the number of repetitions rather than resistance is recommended to minimize loads on joints and to allow for adaptation of muscle and connective tissue. We recommend initially keeping the resistance low, gradually increasing to 20-25 repetitions, and performing only one set (55). The recovery period or rest time between exercises, sets and sessions is a component of the program that may need to be lengthened, particularly in the first few weeks of an exercise program, to allow for adequate recovery and to avoid fatigue (30). Gradually reducing the recovery or rest time between sets, may be used initially as a progression variable. We have also found that it may be necessary in some cancer survivors to limit the number of exercises performed in the first few weeks and to progress more slowly to the desired exercise prescription (2 sets of 10-15 repetitions of 8-10 exercises). A resistance exercise training program can be as sophisticated as using weights or resistance machines for designated muscle groups or as easy as doing repetitions of specific functional tasks (e.g. repeated sit to stand from a chair).

VI-5.1.3. Flexibility

Stretching and range of motion exercises are prescribed to reduce muscle tension (neuroinhibitory effects), increase range of motion a joint, lengthen muscle and improve muscle capability for circulation and air exchange, provide a stimulus for bone and joint tissue integrity and to decrease muscle soreness (30). A flexibility training program should include a regular set of exercises intended to progressively increase range of motion in a joint or to lengthen shortened muscles. Ideally, the choice of exercises should be individualized to meet the functional needs of the individual (e.g. donning socks) and/ or to address cancer treatment specific deficits (e.g. restriction in shoulder range of motion following breast surgery). Exercises should always consist of slow, static stretches held for 10-30 seconds. At least four repetitions of each stretch should be performed; however, the goal should be to progress to a total stretch time of approximately two minutes per exercise (e.g. four repetitions of 30 seconds duration). Flexibility exercises can be incorporated into the cool-down phases of aerobic or resistance exercise sessions and should be performed at least 2 days per week. Yoga and Tai Chi movements are alternative exercise methods for the cancer survivor to improve flexibility, as well as balance and agility (30,56,57).

VI-5.2. Safety considerations during exercise training

Proper staff training is essential to ensure exercise testing and training is both safe and effective. Requirements for supervision and monitoring will vary as a function of the type of patient, staff, facility, and resources (49). Any facility serving clinical cancer populations should have appropriately trained staff, the necessary medical equipment, an emergency action plan, and staff trained in first aid and cardiopulmonary resuscitation

(CPR). Cancer survivors should be thoroughly screened for comorbidities (55). A useful guide for evaluation of exercise risk is outlined by the American Heart Association 'risk classification for exercise training' (49). This system defines classes and outlines the appropriate level of supervision and monitoring required for each class.

Safety must be a priority when designing and implementing exercise programs for cancer survivors. Contraindications and precautions to exercise training must be taken into account when planning an exercise program for cancer survivors (Table 3) (55, 58). Cancer survivors suffering from ongoing side effects may require additional monitoring during exercise sessions. For example, survivors with radiation-induced lung scarring or interstitial lung disease may require use of a pulse oximeter during exercise to monitor for exertional desaturation. Clinical evaluation of the cancer survivor prior to each training session is necessary to rule out underlying instability and/ or identify deterioration in clinical status. Monitoring of blood pressure, heart rate and other vital signs should be performed prior to, several times during, and following the exercise sessions. Table 4 outlines safety considerations for exercise programming in the post treatment phase.

From a safety perspective walking programs and cycle ergometry have been popular choices for exercise programming in both cancer survivors and elderly populations. Cycle ergometry reduces weight bearing activity and does not place demands on balance. Walking is highly functional, translates well into activities of daily living, and is a highly preferred activity for cancer survivors. Contact sports and high impact activities are contraindicated in cancer survivors with metastasis to the bone as they greatly increase the risk of fracture (55). Overall, individual medical considerations

must be taken into account to ensure a safe and enjoyable exercise training program is established.

VI-5.3. The role of medical and exercise professionals

The complexity of determining appropriate physical activity and exercise in the cancer setting is best served by a team approach. At minimum, the team should include an oncologist, oncology nurse and exercise physiologist. For optimal care, allied health professionals such as physical and occupational therapists, nutritionists, respiratory therapists, social workers and psychologists are valuable members of the multidisciplinary team. The team must designate a medical liaison responsible for developing emergency medical plans, medical emergency drills, and reviewing medical incident reports. Exercise testing should be supervised by a physician and performed by well-trained personnel with adequate knowledge of exercise physiology (59). When appropriate, supervision of exercise testing may be assigned to an appropriately trained physician assistant, nurse practitioner or exercise physiologist, provided a physician is readily available if needed. Exercise sessions should be supervised by a clinical exercise physiologist assisted by trained and certified exercise specialists.

VI-5.4. Barriers to physical activity and exercise training in cancer survivors

Cancer survivors have been found to have unique beliefs about incentives and barriers to exercise when compared with non-clinical populations. Cancer survivors tend to view exercise in terms of helping them to cope with cancer (38). The most important incentives to exercise, as identified by cancer survivors, were distraction (get their mind off cancer and treatment), maintenance of a normal lifestyle, aid in recovery from surgery and treatment, and gain control over their life, feel better and improve well-being, and

cope with stress of cancer and treatment (45,60). Cancer survivors contend with numerous barriers to exercise during treatment. The most commonly sited barriers are lack of time (61,62), fatigue (45,61) pain (45,61), embarrassment (45), lack of support (61), and lack of information and guidance from practitioners (45). Following cancer treatment, survivors contend with barriers similar to individuals in the general population (e.g. lack of time and motivation, inclement weather). Counseling may be required to identify strategies to overcome potential barriers to exercise. The most relevant sources of social influence to exercise in cancer survivors tend to be the spouse, other family members, friends, and sometimes, the physician (61, 63).

In studies examining the preferences of cancer survivors, the majority of cancer survivors reported a desire for exercise counseling after cancer diagnosis (42, 44). About half of the survivors preferred exercise counseling before or during treatment whereas the other half preferred exercise counseling immediately or soon after treatment (42, 44). The majority of participants also reported the preferred mode of exercise as recreational activities such as walking (42, 44).

Long term adherence to exercise is an acknowledged problem in the general population and other disease populations, and may be no different for cancer survivors. A supervised environment ensures that the prescribed exercise regimen is carried out, allows for modifications to the exercise program, and provides advantages in terms of nonspecific effects (e.g. reduction in anxiety). Exercise benefits may not be immediate or even apparent in the first 4 to 6 weeks of an exercise training program. Therefore positive reinforcement from exercise professionals may provide motivation to continue in the early weeks, particularly when symptoms such as fatigue are problematic.

VI-5.5. Self-directed and community based exercise programs

For cancer survivors to maintain the beneficial effects from a supervised exercise program, they must be educated on the need and importance of continuing exercise and physical activity at home or in the community, and be given the knowledge on how to achieve this objective. In addition to maintaining their level of physical functioning, cancer survivors have the potential to continue to improve their fitness if enhanced activity levels are adhered to after completing the initial supervised program. Successful transition to the self-directed and community based programs will likely require the support and regular follow-up from the cancer rehabilitation professionals.

VI-6. CONCLUSIONS

This paper has addressed the potential role of exercise as a clinical intervention for cancer survivors. More important questions remain to be answered on the implementation, feasibility and cost effectiveness of exercise programming. While cardiac rehabilitation provides a model to guide clinical practice, the challenge facing exercise professionals and clinicians in the cancer setting is to provide exercise programs that are safe and effective.

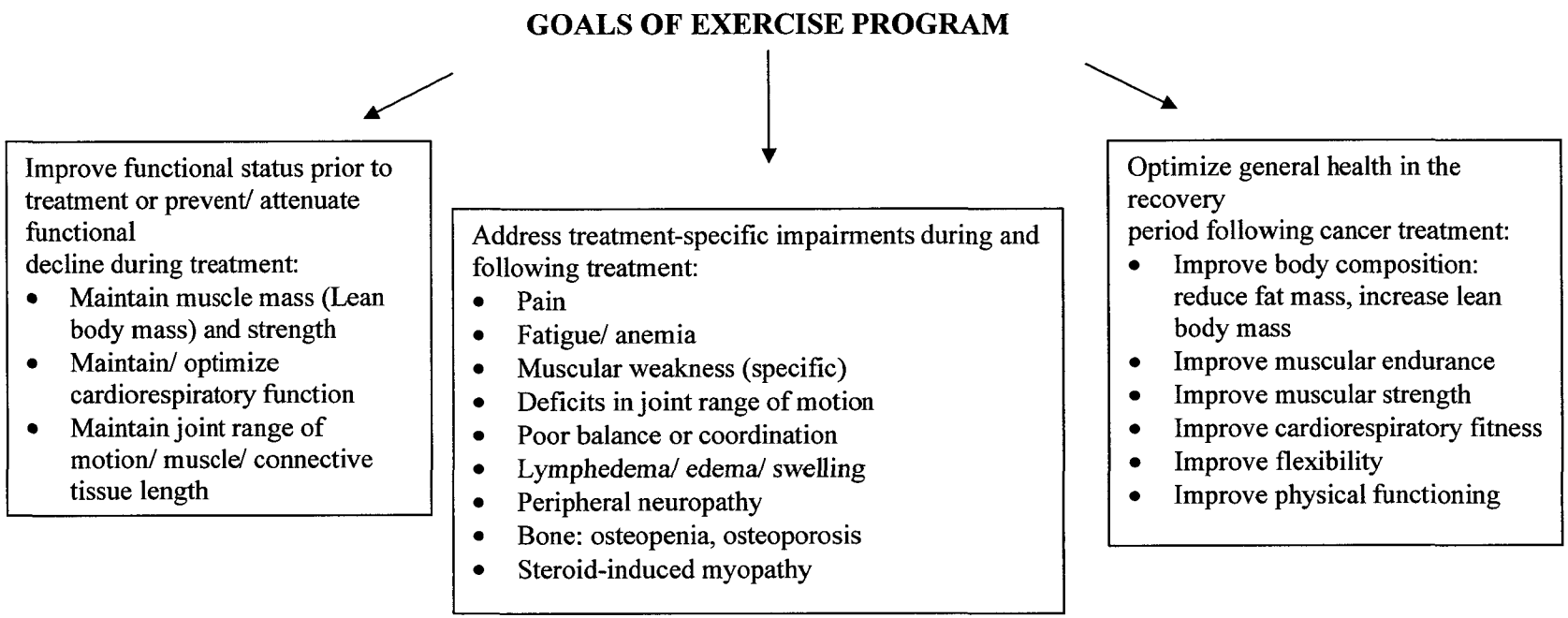

Table VI-1: Medical and Pre-Exercise Evaluations

Step 1: Comprehensive medical evaluation: medical history, physical exam and physician clearance

Step 2: Testing to determine exercise tolerance

- The test(s) should provide appropriate and useful information to aid in exercise prescription
- The test(s) should assess functional capacity and cardiovascular response to at least the level of the proposed exercise regimen
- The test(s) should consider all aspects of physical fitness and functioning (e.g. cardiorespiratory fitness, muscular strength and endurance and flexibility)

Step 3: Follow-up and re-evaluation at regular intervals

Table VI-2: Recommendations for Exercise Programming in Post Treatment Phase

- Individualize the program based on information gathered from exercise testing
- Consider needs, goals and exercise preferences of the survivor
- Identify any potential barriers to exercise including long-term treatment and disease-related side effects that may compromise ability to exercise
- Consider the principles of exercise prescription: overload, adaptation, specificity and reversibility
- Set prescription variables for components of exercise program (e.g. frequency, intensity, type and time of exercise)
- Re-evaluate and modify program to address changes in medical status and physical fitness and functioning

Table VI-3: Contraindications and Precautions to Exercise Testing and Training

	Contraindications to exercise testing and training	**Precautions requiring modification and/or physician approval**
Factors related to cancer treatment	• No exercise on days of intravenous chemotherapy or within 24 hours of treatment • No exercise prior to blood draw • Severe tissue reaction to radiation therapy	• Caution if on treatments that affect lungs and/or heart: recommend medically supervised exercise testing and training • Mouth sores/ulcerations: avoid mouthpieces for maximal testing. Use face masks.
Hematologic (Laboratory values)	• Platelets < 50,000 • White blood cells < 3,000 • Hemoglobin < 10g/dl	• Platelets > 50,000 to 150,000: avoid tests that increase risk of bleeding • White blood cells >3,000 to 4,000: ensure proper sterilization of equipment • Hemoglobin > 10g/dl to 11.5/ 13.5 g/dL: caution with maximal tests
Musculoskeletal	• Bone, back or neck pain of recent origin • Unusual muscular weakness • Severe cachexia • Unusual / extreme fatigue • Poor functional status: avoid exercise testing if Karnofsky Performance Status score ≤ 60%	• Any pain or cramping: investigate • Osteopenia: avoid high impact exercise if risk of fracture • Steroid-induced myopathy • Cachexia: multidisciplinary approach to exercise • Mild to moderate fatigue: closely monitor response to exercise
Systemic	• Acute infections • Febrile illness: fever > 100° F (38° Celsius) • General malaise	• Recent systemic illness or infection: avoid exercise until asymptomatic for > 48 hours
Gastrointestinal	• Severe nausea • Vomiting or diarrhea within previous 24 to 36 hours • Dehydration • Poor nutrition: inadequate fluid and/or food intake	• Compromised fluid and/or food intake: recommend multidisciplinary approach/ consultation with nutritionist
Cardiovascular	• Chest pain • Resting pulse > 100 b/min or < 50 b/min • Resting blood pressure > 145 mm Hg systolic and > 95 mm Hg diastolic • Resting blood pressure < 85 mm Hg systolic • Irregular pulse • Swelling of ankles	• Caution if at risk of cardiac disease: recommend medically supervised exercise testing and training • If on blood pressure medication that controls heart rate, target HR may not be attainable; do not overexert • Lymphedema: wear compression garment on limb when exercising
Pulmonary	• Severe dyspnea • Cough, wheezing • Chest pain increased by deep breath	• Mild to moderate dyspnea: avoid maximal tests
Neurological	• Significant decline in cognitive status • Dizzyness/ lightheaded • Disorientation	• Mild cognitive changes: ensure that patient is able to understand and follow instructions • Poor balance/ peripheral sensory neuropathy: use well supported positions for exercise

Table VI-4: Safety Considerations for Supervised Cancer Rehabilitation Program

- Have appropriately trained and qualified exercise professionals
- Ensure that an Emergency Action Plan is in place
- Choose a mode of exercise that is appropriate for the individual
- Monitor vital signs before, during and following exercise training sessions (e.g. blood pressure, heart rate, oxygen saturation)
- Stop exercise or activity if any unusual symptoms occur (e.g. dizziness, chest pain, nausea)
- Monitor response to exercise both during and immediately following the session (e.g. perceived exertion, symptoms)
- Monitor late response (up to 48 hours after session) to exercise session (e.g. secondary muscular soreness, excessive fatigue, exacerbation of pain)

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VII: CHAPTER SEVEN

DISCUSSION

VII-1. DISCUSSION

As survival from cancer has improved, the focus of cancer care has expanded to include issues related to quality of life and overall health. Research has emerged to examine the benefits of exercise as an intervention to address the negative acute, late and long term effects of cancer treatment on quality of life. The literature has demonstrated that exercise is safe, feasible, and an effective intervention to improve physical functioning and QOL for many cancer survivors both during and following cancer treatment. The purpose of this dissertation was to provide an in-depth examination of exercise rehabilitation in two cancer survivor groups— breast cancer and head and neck cancer. These two cancer tumor groups were chosen for study as survivors of these cancers represent a large proportion of the oncology clinical caseload in physical therapy departments. As such, the examination of the research evidence and development of guidelines for exercise may serve to inform clinical practice.

Breast and HNC are similar in that survivors often have unique physical and functional deficits in the upper extremity requiring physical therapy treatment. Beyond this similarity, the demographic characteristics, the disease prognosis and other treatment-related morbidities, vary greatly between these two survivor groups. The majority of the exercise research, to date, has been limited to breast cancer survivors, with very few studies focusing on survivors of other cancers. Exercise rehabilitation research in the breast cancer area has been largely driven by the high relative survival rate and the need for interventions to address overall health and wellbeing. Furthermore, improvements in surgical and radiotherapy techniques have resulted in reduced incidence and severity of localized morbidities (e.g. lymphedema, shoulder pain and dysfunction)

which has further facilitated this shift in focus. The high proportion of clinical exercise trials in breast cancer has allowed for closer examination of the evidence within the breast cancer population.

In contrast, HNC is not as prevalent as breast cancer, and while advances in the treatment of HNC are promising, the overall survival rate has remained relatively unchanged over the past decades (1). The clinical burden of HNC in terms of mortality and morbidity remains high, yet this survivor group has received much less attention from research in cancer rehabilitation (2). Exercise interventions for HNC are in their infancy, with few studies addressing treatment-related impairments let alone overall health and wellbeing. At this point in time, research evidence is needed to support the safety and efficacy of exercise in the HNC population. Although it would be inappropriate to generalize findings from studies with breast cancer to head and neck cancer survivors, the development and progress of exercise interventions in the breast cancer field serves as a model for research with head and neck survivors.

VII-2. BREAST CANCER

VII-2.1: Breast Cancer: Hypothesis 1

Restricting the SRMA to the clinically homogenous breast cancer population would allow for preliminary estimates on quantitative effects of the physical exercise interventions on objective physical measures, self-reported symptoms, and quality of life outcomes.

As hypothesized, restricting the systematic review of exercise interventions to breast cancer survivors allowed for preliminary estimates on the effect of exercise on objective physical measures, self-reported symptoms, and quality of life outcomes. Although a wide variety of exercise regimens were prescribed, aerobic exercise was the

most common exercise regimen in the trials combined for the meta-analysis. Aerobic exercise is prescribed with the intent to improve cardiorespiratory fitness. Maximal oxygen uptake (VO_{2max}) is accepted as the gold standard measure of cardiorespiratory fitness. As such, the measurement of VO_{2max} provides the most accurate information on the physiological effects of the exercise regimen on the cardiorespiratory system. A significant improvement in cardiorespiratory fitness as measured by $VO_{2max/peak}$ was found from exercise and the magnitude of the improvement was large (effect size; d = 1.14).

In theory, by improving cardiorespiratory fitness, the ability to perform activities of daily living should improve and this should be reflected in self-reported physical functioning and quality of life. In support of this rationale, significant improvements were found in both physical functioning and quality of life. As shown in the meta-analysis, the magnitude of improvement in self-reported physical functioning was large (d = 0.84). A positive effect of exercise was also found on quality of life (FACT-G and FACT-B), and, though not as large, it was still of a moderate effect (effect size: d = .48). The improvement of > 4 points on the FACT-G scale represents a clinically meaningful improvement in quality of life. A variety of exercise regimens appear to be effective in improving quality of life. In general, exercise regimens consisted of moderate intensity aerobic exercise three to five times per week with a duration ranging from 15 to 35 minutes per session. Although the studies included in the meta-analysis produced positive results in physical functioning and quality of life, more research is needed to provide clear guidelines on the optimal type and threshold level of exercise required to obtain benefit.

Fatigue is a common complaint among breast cancer survivors during cancer treatment (3) that often persists years after treatment (4). The pooled data from six studies included in the meta-analysis showed that exercise significantly improved symptoms of fatigue (effect size d= 0.46); however, this finding was largely the result of positive results from studies carried out post treatment. The pooled results of studies carried out during adjuvant cancer treatment showed a nonsignificant effect of exercise on symptoms of fatigue. Several reasons may explain the lack of significance improvement during adjuvant cancer treatment. The majority of studies in the meta-analysis did not include fatigue as a primary outcome; therefore, exercise interventions were not prescribed with the primary intent to reduce or attenuate symptoms of fatigue. Fatigue in breast cancer survivors is complex and its onset during treatment is likely related to a number of factors such as decreased availability of metabolic substrates, hormonal changes, anemia and depression (5). Furthermore, the response to exercise, whether positive or negative, may vary depending on the individual's pretreatment health status, the severity of fatigue, and the body's ability to recover and repair itself during cancer treatment (6, 7). Further research is needed examining the biological mechanisms associated with cancer treatment-related fatigue. This information will allow for closer examination of the effect of differing exercise regimens (e.g. type and/or intensity) on symptoms of fatigue during cancer treatment.

The pooled results of the studies in the meta-analysis did not show statistically or clinically significant changes in body weight or body mass index as a result of the exercise intervention. While early evidence suggests that exercise may prove beneficial in improving measures of lean body mass and reducing fat mass, only two studies provided

data on body composition measures which precluded pooling of data. The findings of the meta-analysis are consistent with exercise trials in overweight populations, where exercise alone has not been found to significantly alter body weight but has been found to maintain or improve lean mass (8). The issues of weight gain and obesity in breast cancer survivors deserve attention. Weight gain following breast cancer diagnosis has been reported to occur in 50 to 90% of women due in part to the effects of systemic cancer treatments (9). The reported weight gain is also associated with a tendency for increased deposition of fat in the visceral region. Body weight and weight gain after a diagnosis may adversely affect survival in subpopulations of breast cancer survivors (10). The evidence from observational studies is now sufficient to support clinical trials of lifestyle interventions including exercise to reduce or maintain body weight with implications for benefit in overall survival (10).

An important consideration in the interpretation of the SRMA relates to the generalizability of the findings. When reported, it appears that a low percentage of breast cancer survivors agreed to participate in the exercise trials included in the SRMA, and, on average, study participants tended to be of younger age and higher socioeconomic status. Therefore, survivors who choose to participate in exercise trials may not be representative of all breast cancer survivors in the clinical setting.

Few adverse events were reported in the exercise trials included in the meta-analysis indicating that within the population of survivors participating in exercise trials, exercise appears to be relatively safe. This finding may be misleading, as some studies did not formally report adverse events and many studies excluded survivors of older age and/or those presenting with comorbidities. Therefore, questions still remain on the

relative safety and benefit of exercise in the varied population of survivors and particularly in older cancer survivors. Moreover, no trials have examined the effect of exercise outcomes in the long-term or examined clinically relevant endpoints of disease-free and overall survival.

VII-2.2: Breast Cancer: Hypothesis 2

The inclusion of only randomized controlled trials in the SRMA would provide the best evidence to evaluate the efficacy of exercise interventions for breast cancer survivors.

One of the main objectives of the SRMA was to better determine the relative benefit of exercise for breast cancer survivors. Ideally, trials included in a SRMA should be of high methodological quality and, therefore, randomized controlled trials are considered the best source of evidence to determine the efficacy of an intervention (11). The randomized controlled design overcomes many of the threats to internal validity (12) such that differences observed in outcome can be attributed to the intervention under investigation. Given the number of studies performed examining the benefits of exercise for breast cancer survivors, the present SRMA was restricted to RCTs with the objective of examining the best available evidence.

The present SRMA included a comprehensive literature search, a vital component of a high-quality SRMA. To optimize the quality of the SRMA, attempts were made to identify all relevant trials, regardless of publication status or language of publication. Trials with positive results (statistical significance) are more likely to be published than trials with negative results (statistically non-significant), and are more likely to be published rapidly, and in the English language. Six studies included in the SRMA were

unpublished at that time of inclusion; however, of note, no RCTs were found in languages other than English.

The quality of the individual RCTs in the SRMA was also considered of importance in the validity of the findings. As reported in the SRMA, not all of the included RCTs were of high quality or free of potential bias. As an example, inadequate or unclear concealment of allocation has been associated with exaggerated treatment effects, and in the present SRMA, 11 of the 14 studies did not meet the criterion for adequate concealment. Although statistically significant benefits of exercise were found, confidence in the conclusions is tempered by the lack of high quality studies. The findings of the present SRMA demonstrate the need for high quality RCTs with larger samples and adequate follow-up of endpoints (11).

VII-3. HEAD AND NECK CANCER

VII-3.1. Case reports

The case reports paper presented the initial concept and considerations in the development of a PRET program for shoulder dysfunction in HNC survivors. The aim of the program was to strengthen scapular muscles to compensate for the lack of trapezius muscle function. Strengthening is a key component of SPT and therefore the concept was not novel. What was novel was the more aggressive approach to muscular strengthening in a population of cancer survivors. The exercise program was based on the principle of progressive overload where variables (e.g. repetitions, resistance) were systematically progressed to continually challenge the chosen muscle groups. Thus, the main difference between strengthening exercises in SPT and PRET may be viewed as one

of exercise intensity.

An intervention consisting solely of PRET was not considered appropriate to address the deficits beyond muscular strength that result from temporary or permanent trapezius paresis. Therefore, the PRET program was prescribed in conjunction with SPT. Active and passive range of motion and stretching exercises as well as glenohumeral joint mobilizations were administered to improve (or maintain) glenohumeral joint integrity and prevent adaptive muscle shortening of the serratus anterior and pectoral muscles. As surgical techniques sparing the spinal accessory nerve have become more common, the PRET program was expanded to include retraining and restrengthening of the trapezius muscle in survivors with spinal accessory nerve recovery.

VII-3.2. Pilot and Efficacy Studies

Based on the review of the literature and the findings of the breast cancer meta-analysis, a number of quality features were incorporated into the study design of the head and neck pilot and efficacy studies. The randomized controlled trial design was chosen for both studies to avoid the potential overestimates of treatment effects associated with nonrandomized trial designs. Participant withdrawals and drop-outs were reported along with reasons for discontinuing the study. For both studies, adherence to exercise sessions and adverse events were recorded. For the efficacy study the following procedures were utilized to minimize bias and enhance quality of the RCT: 1) An independent researcher was appointed to generate the allocation sequence and ensure concealment of allocation. The independent researcher generated the allocation sequence using a computer-generated code and enclosed the contents of the envelopes in sequentially numbered and sealed (opaque) envelopes as per recommended procedures (13); 2) Since double

blinding is not possible in exercise trials, to minimize measurement bias, independent assessors blinded to group assignment were used for the efficacy study; 3) The planned statistical procedures included intention-to-treat analysis, using the baseline observation carried forward.

VII-3.4. Head and Neck Cancer Hypothesis 1

Head and neck cancer survivors would be willing and able to participate in a 12-week resistance exercise program addressing shoulder dysfunction due to spinal accessory nerve damage.

The primary objective of the pilot study was to determine whether head and neck cancer survivors would be willing and able to take part in an exercise intervention. Determining feasibility was considered important as HNC is a disease associated considerable post treatment morbidity. Mastication, speech, respiration and cosmesis can all be radically altered by the cancer and/or cancer treatment (14-16) and, as such, the high clinical burden of HNC may be a barrier to exercise participation. Furthermore, participation in exercise trials in the general population tends to be lower in males, smokers and in those from socially disadvantaged backgrounds, all of which are typical demographic characteristics of HNC survivors (17). Therefore, knowledge of the rate of compliance was considered necessary to the design of the ensuing efficacy study. As hypothesized, head and neck survivors were willing and able to take part in the 12-week PRET program. Twenty-five eligible survivors were approached to participate in the study and 20 survivors agreed to participate. The recruitment rate, of 80%, was higher than the reported 19% agreement to participate in breast cancer and 31% in prostate cancer trials (18, 19). It is unknown whether this high agreement rate to participate was

due to methods of recruitment or whether the existence of pain and dysfunction were motivating factors to participate. In other cancer groups, survivors who have a prior exercise history have been found to be more likely to be interested in participating, which indicates selection bias is a concern in the present trial.

The completion rate for the study was 85% (17/20). Seventeen participants were able to complete the full 12-week study period and non-completion occurred due to cancer recurrence for two participants and side effects of treatment requiring hospitalization for one participant. Adherence to the exercise intervention was excellent with participants completing 93% of scheduled exercise sessions. In conclusion, the results of the pilot study demonstrated that a PRET program focusing on shoulder pain and disability was not only feasible but well received in the post-operative head and neck cancer population.

VII-3.5. Head and Neck Cancer Feasibility Study: Hypothesis 2

The optimal time to administer the intervention would be as soon as possible after the surgery.

A further aim of the pilot study was to determine whether survivors were able to tolerate exercise during radiation therapy. Despite the high adherence and significant improvements in shoulder pain and disability, participants undergoing radiation therapy had more difficulty carrying out the exercise intervention in the latter stages of radiation therapy. Progression in exercise workload was difficult once participants started to develop acute side effects of radiation therapy. Weight loss and fatigue were especially problematic during the latter stages of radiation therapy. In contrast, both the "late" exercise group and the "cross-over" control groups took part in the exercise program after

cancer treatment and had less difficulty carrying out the exercise prescription. A further benefit of the post treatment phase was that trapezius muscle recovery was observed in some of the participants during the exercise intervention period.

A secondary focus of the pilot study was to provide preliminary estimates of treatment effects on shoulder function, pain and disability, and overall quality of life. A clinically significant finding of the pilot study was that the PRET program resulted in a significant reduction in self-reported pain. Moreover, a significant improvement in the pain and disability of 14.5% was found. This finding served to provide preliminary estimates of treatment effect from which to determine the sample size for the efficacy study.

No significant differences in passive range of motion measurements were found between the groups; however, larger nonsignificant improvements in active range of motion were found for forward flexion and abduction and a significant improvement in external rotation was found. These findings were consistent with trends for improvement in reported disability from the PRET program.

No signficant differences were found between the groups in self-reported quality of life. Quality of life declined in both groups during the intervention period. As many of the participants in the trial were undergoing or just completing adjuvant treatment at the time, this decline may have been due to the onset or presence of acute treatment related morbidities.

A number of factors lead to the conclusion that, contrary to the hypothesis, the optimal time for undertaking the efficacy study would be in the post treatment rehabilitation period. Objective measurements of muscular strength were not performed

in the pilot study due to the early timing of the intervention. Many participants were in early stages of healing from surgery and the relative safety and efficacy of muscular strength testing was questionable. For example, the forearm free flap site which was still healing in a number of participants limited the ability to properly grip the handles of the weight machines and, in the early weeks, the amount of resistance was limited by grip strength rather than shoulder strength. Thus, in these participants, the ability to successfully perform strength testing, at baseline, would have been limited by hand grip strength.

The exercise program in the pilot study followed the model of cardiac rehabilitation by starting with resistance using the "lightest weight on the rack". While this concept avoided negative effects of increased muscular soreness and pain, for survivors with higher levels of strength, determining the optimal resistance necessary to challenge the chosen muscle groups was difficult. For many participants, the resistance level was likely below the threshold for improvement. For these reasons, the post treatment time period was viewed as a more stable time period to deliver the program and, additionally, one which would allow for formal evaluation of objective muscular strength.

VII-3.6. Head and Neck Cancer Efficacy Study: Hypothesis 1

We hypothesized that an appropriately prescribed upper body resistance training program using the principles of progressive overload would improve upper extremity strength and endurance.

Few studies have examined interventions for post surgical shoulder dysfunction in head and neck cancer survivors, and none have used the randomized controlled trial

design to our knowledge. Overall, the findings of the efficacy study support the benefit of progressive resistance exercise training to reduce shoulder pain and disability in head and neck cancer survivors. We feel that the benefit from the PRET program in reducing pain was largely the result of improved muscular strength in the scapular region. As hypothesized, the PRET program resulted in significant improvements in muscular strength with a relatively consistent pattern of improvement found across all measurements. In the study, the results of the baseline 1-RM testing provided a clear standard from which to prescribe the exercise for the individual survivor. Individualizing the resistance exercise to the individual's baseline strength allowed for systematic progression of resistance weight. The starting weight was prescribed at 40% of the individual's 1-RM based on recommendations for post surgical Cardiac Rehabilitation. This percentage proved to be too difficult as a starting point. The majority of participants were unable to perform the prescribed number of repetitions with proper form and reported considerable muscular soreness following exercise sessions. Therefore the protocol was modified to start the resistance at 25-30%. This change resulted in improved exercise performance and less reported post-exercise muscular soreness.

The percent improvement in strength for the seated row (scapular retraction) was 37% in the PRET group compared to 16% in the SPT group. The improvement in strength for vertical bench (chest press/protraction) was 45% in the PRET group and 24% for the SPT group. The improvements in strength are consistent with the findings of several other studies with cancer survivors. Courneya et al (2007) reported increased muscular strength by 25% to 30% following 12-weeks of resistance exercise training in breast cancer survivors undergoing adjuvant chemotherapy (Courneya, 2007 (in press)

#351). Schmitz et al (2005) examined the effect of resistance exercise training in breast cancer survivors following treatment (20). The resistance exercise program was carried out twice per week for six months. The authors reported an improvement of 63% in upper body strength (chest press) in the exercise group compared to a 12% improvement in the control group. The larger improvements in strength obtained in the Schmitz study may be the result of differences in the exercise prescription (e.g. 3 sets of each exercise) and/or reflect the extended length of the intervention.

VII-3.7. Head and Neck Cancer Efficacy Study: Hypothesis 2

Improvements in strength and endurance of the scapular muscles would result in a significant reduction in patient-rated shoulder pain and disability.

The major novel finding of the efficacy trial was that the PRET program had a beneficial effect on pain. This finding was consistent with the results of the pilot study. The standardized effect size of d = .84 represents a large effect on pain (21). Moreover, the percentage reduction in pain of 52% in the PRET group exceeds the 30% reduction in pain for patient perceived improvement (22, 23).

The reduction in pain from PRET has the potential to have a positive impact on indirect costs of cancer care (24). Pain has been identified as a major predictor of work-related disability in HNC survivors (24). Shoulder pain following neck dissection may be disabling for a number of reasons. Pain in the shoulder region post neck dissection is thought to result from trapezius muscle atrophy that leads to the downward and lateral displacement of the scapula and droop of the shoulder. The poor mechanics of the shoulder complex often results in an 'impingement' type pain with elevation of the arm limiting the ability to use the arm overhead. Pain is also commonly reported to occur at

the insertion of the levator scapula muscle and rhomboids on the superomedial border of the scapula and is exacerbated by repetitive activities and heavy lifting. Furthermore, pain may lead to and is often associated with both fatigue and depression, in cancer survivors. The effect of PRET in optimizing the strength of the scapular muscles may serve to alleviate pain by improving the alignment of the scapula and thus the mechanics of the shoulder complex. Although not examined in this study, improvements in muscular strength and reductions in shoulder pain and disability may have a positive impact on the survivor's ability to return to normal work and recreational activities.

Of note, a relatively consistent trend in favor of the PRET group was observed for all outcomes even when statistical significance was not achieved. The positive effects of PRET on disability, quality of life and fatigue are promising as the magnitude of the effects was consistent with minimally important differences on these scales. These findings in the HNC population suggest a potential efficacy benefit in QoL and fatigue from PRET that warrants further research with a larger sample of head and neck survivors.

Studies describing the effectiveness of physical therapy for shoulder dysfunction in head and neck survivors are scarce, and the comparison of our study results with those of other studies is hampered by differences in intervention characteristics (e.g. timing, type, length of the intervention) and the use of different outcome measures. Chida et al (2002) in an uncontrolled trial examined the effect of an occupational therapy program on ten participants following radical neck dissection (25). The program was comprised of active and passive ROM exercises, massage and muscle relaxation techniques. The program was carried out five times per week while participants were hospitalized post

surgery and then continued once or twice a week on an outpatient basis following discharge (for a mean time period of 91 days). Each session was 40 minutes in length. The authors reported significant improvements in shoulder flexion and abduction ROM following the intervention; however, the program was found to be ineffective for resting or motion pain (26).

Salerno et al (2002) in a nonrandomized controlled trial examined the effect of active and passive ROM exercises on 60 participants undergoing laryngectomy in conjunction with a nerve sparing neck dissection procedure (27). The goal of their rehabilitation protocol was to maintain or restore passive ROM with the hypothesis that active ROM would recover over time. The comparison group was comprised of patients from out-of-town who were unable to participate in the protocol. The authors reported significant improvements at six-month follow-up in pain, active and passive ROM, and in working and recreational activity in the group receiving formal physical therapy when compared to the control group receiving no treatment. The authors reported a worsening of glenohumeral movement in control participants that was thought to impair recovery of the trapezius muscle. The authors also reported ongoing muscle weakness in many of the participants, in both groups, at the end of the study.

VII-4. STUDY STRENGTHS

A number of unique features of the efficacy study deserve mention. This study represents the first randomized controlled efficacy trial examining resistance exercise for shoulder dysfunction in head and neck cancer survivors. Another unique feature of the trial was the use of a standard physical therapy comparison treatment group. A criticism

of prior exercise trials has been the lack of an appropriate comparison group leading to questions on whether the reported benefits were the result of the exercise or the effects of other factors such as social support and interaction. Although more favourable effects were found with the addition of PRET to SPT in the present study, the absence of a no-exercise group limits the ability to evaluate the SPT intervention. At present, there is limited evidence to support SPT; however, as physical therapy is part of the standard of care in the Edmonton region, it would have been considered unethical to withhold this treatment.

The present study has a number of characteristics that have been identified to increase the likelihood of adoption in the clinical setting (28). First, the PRET program was tested against and demonstrated a relative advantage, over standard care. Recent research has found that adoption of a new intervention in the clinical setting is more likely to occur when the new treatment is tested and found to be more beneficial than current standard practice (28). The magnitude of improvement from PRET over standard care, particularly in reducing pain, provides relevant information that supports adoption in the clinical setting. Secondly, the intervention resulted in visible and measurable changes in range of motion, muscular strength and posture as well as benefits in self-reported pain and disability. Barriers to adoption include the lack of information on the costs related to the delivery of the intervention and the need for space and appropriate exercise equipment in the clinical setting.

VII-8. LIMITATIONS

The main limitation of the efficacy study was that it was terminated early due to difficulties recruiting survivors within the funding period. The slower than anticipated accrual rate was primarily the result of fewer eligible survivors than originally estimated for the mail-out invitation to participate. Originally, it was estimated that approximately 200 eligible survivors would be identified by the Cancer Registry and that 30 would agree to participate. However, only 45 of 190 survivors were deemed eligible after initial screening. The primary reasons for ineligibility at screening included the presence of active cancer or significant co-morbidities, and in many HNC survivors, no neck dissection procedure had been performed. Of the 45 eligible survivors, 15 agreed to participate.

Another limitation of the study was the 47% recruitment rate which was much lower than the pilot study. In contrast to the pilot study, recruitment for this study was passive. In the pilot study, survivors were approached to participate in the clinical setting. For the efficacy study, survivors were provided with written information, either by mail-out or by the healthcare professional at a regular follow-up clinic visit, and were responsible to contact the investigator if interested in participating. The lack of face-to-face contact with the investigator may have deterred some survivors from participating and resulted in a sample of participants with a more positive attitude and interest in exercise. Other limitations include the demographic profile of a well-educated, racially homogenous sample and a 35% proportion of 'never smokers'.

VII-9. RECOMMENDATIONS FOR CLINICAL PRACTICE

The purpose of Chapter Six in the dissertation was to review the potential therapeutic role of exercise training in cancer survivors and examine methods to deliver these services in the clinical setting. As research has emerged to support exercise as an intervention to improve both physical and psychological functioning, there has been growing interest in exercise as an intervention in the clinical setting. Similar to cardiac rehabilitation, exercise will likely become an integral component in the cancer rehabilitation setting.

Prescribing exercise for a given cancer survivor or cancer tumor group, however, is complex because cancer is not a homogeneous disease. Therefore needs may vary across tumor groups and unique late and long term effects may be dependent on the cancer type and treatment regimen. As demonstrated in the dissertation, the needs of breast cancer survivors are different from those of HNC. Advances in treatment have also influenced the direction and focus of rehabilitation for both tumor groups. For example, improvements in surgical and radiotherapeutic techniques for breast cancer have reduced incidence and morbidity in the upper extremity such that there has been a shift in focus from shoulder dysfunction and lymphedema to physical fitness and overall health. In HNC, neck dissection procedures that spare the spinal accessory nerve are now more commonly performed and this has resulted in a lower incidence of survivors with permanent shoulder dysfunction. Paradoxically, as survivors now have a better prognosis for shoulder recovery, this has increased the need for and resulted in a more amenable condition for exercise.

The evidence in support of exercise, particularly post treatment, is sufficient at the present time to warrant offering clinical exercise programs in the breast cancer survivor population. The challenge facing exercise professionals and clinicians in the cancer setting is to provide exercise programs that are safe and effective. Findings in the controlled and closely monitored research setting may not hold true in the clinical setting, particularly when working with older survivors and/or those with co-morbidities. Numerous contraindications and precautions to exercise training have been recommended in the literature. As more evidence emerges on the relative safety and efficacy of exercise, many of the current contraindications to exercise may shift to precautions and/or may be removed from the list entirely. At present, the recommended guidelines should be taken into account when planning an exercise program for cancer survivors in the clinical setting.

VII-10. FUTURE DIRECTIONS FOR RESEARCH

The evidence suggests that exercise is an effective intervention to improve QoL, cardiorespiratory fitness, physical functioning and symptoms of fatigue in breast cancer survivors. Early evidence suggests that the magnitude of benefit may be larger when exercise is delivered in the post treatment rehabilitation phase. There is a need, however, for larger RCTs encompassing representative samples with appropriate statistical power. Future research with methodologically rigorous studies designed to examine different exercise regimens (e.g. comparing moderate vs. low-intensity) are needed in order to better understand of the role of physical exercise among breast cancer survivors. A number of new studies have been recently published examining exercise for breast cancer

survivors, suggesting that an update of the SRMA is likely warranted. Once the role of exercise in breast cancer survivors is better understood, the next step will be to design a trial to definitively assess the effect of exercise on clinically relevant endpoints of recurrence and mortality.

In contrast, despite the high morbidity and mortality associated with HNC, little is known about effective management for the many late and long term effects that develop as a result of HNC treatment. The development of a rehabilitation program to effectively meet the complex and vast needs of HNC survivors is clearly a challenge. The work presented in this dissertation has focussed solely on exercise for post neck dissection shoulder dysfunction. Notwithstanding the positive results from PRET, questions remain over the effectiveness of the program in the long-term and on outcomes such as work-related disability. Determining the optimal length of the intervention and the feasibility of group exercise are other areas requiring investigation. There is also a need to investigate and develop appropriate interventions to address impairments related to neck pain and constriction, and temporomandibular joint dysfunction. As well, physical exercise interventions that include an aerobic exercise component may serve to address overall health and well-being and may be of particular benefit to the nonsurgical HNC survivor in the recovery following treatment with chemotherapy and/or radiation therapy.

VII-10.1. Summary

The purpose of this dissertation was to provide an in-depth examination of exercise rehabilitation in two cancer survivor groups—breast cancer and head and neck cancer. A further objective of this dissertation was to provide research evidence to guide clinical exercise programming. The primary purpose of the SRMA was to summarize

the available evidence concerning the effects of exercise for breast cancer survivors. Exercise led to statistically significant improvements in quality of life as assessed by the Functional Assessment of Cancer Therapy-General and Functional Assessment of Cancer Therapy-Breast. Exercise also led to significant improvements in physical functioning, peak oxygen consumption and fatigue. These results provide valuable information and justification for offering clinical exercise programs for breast cancer survivors. Research is needed to determine the optimal type and volume of exercise required to obtain benefit. In the breast cancer area, future research would benefit from larger sample sizes, increased attention to study quality and examination of the long-term effects of exercise.

In HNC survivors exercise interventions are both feasible and well received. The results of both the pilot and efficacy studies support the use of PRET as an intervention to reduce shoulder pain and disability. Furthermore, PRET resulted in significant improvements in upper extremity strength and endurance that were found to be associated with reductions in pain. Changes in neck dissection impairment, fatigue, and quality of life favored the PRET group but did not reach statistical significance. The findings provide justification for further research with a larger sample size.

The dissertation has examined the research evidence and addressed the potential role of exercise as a clinical intervention for cancer survivors. More important questions remain to be answered on the implementation, feasibility and cost effectiveness of exercise programming in the clinical setting. The evidence in the breast cancer area is sufficient to support the clinical implementation of exercise in the post treatment rehabilitation phase. Exercise interventions in the HNC area are in their infancy and while results are promising, further research is clearly warranted.

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APPENDICES

APPENDIX II-1. Medline Search

1. exp Breast Neoplasms/
2. (breast cancer$ or breast tumor$ or breast tumour$ or breast neoplasm$).tw.
3. or/1-2
4. exp "Physical Therapy (Specialty)"/ or exp Physical Therapy Techniques/ or Physical therapy.mp.
5. (physiotherap$ or physical therap$ or physical activit$ or rehabilit$).mp,hw.
6. exp exercise movement techniques/ or exercise/ or exp exertion/
7. (exercis$ or exert$).mp,hw.
8. rehabilitation/ or activities of daily living/ or occupational therapy/ or physical therapy techniques/
9. or/4-8
10. 3 and 9
11. exp breast neoplasms/rh
12. or/10-11
13. RANDOMIZED CONTROLLED TRIAL.pt.
14. CONTROLLED CLINICAL TRIAL.pt.
15. RANDOMIZED CONTROLLED TRIALS/
16. RANDOM ALLOCATION/
17. DOUBLE BLIND METHOD/
18. SINGLE-BLIND METHOD/
19. or/13-18
20. ANIMAL/ not HUMAN/
21. 19 not 20
22. CLINICAL TRIAL.pt.
23. exp CLINICAL TRIALS/
24. (clin$ adj25 trial$).ti,ab.
25. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
26. PLACEBOS/
27. placebo$.ti,ab.
28. random$.ti,ab.
29. RESEARCH DESIGN/
30. or/22-29
31. 30 not 20
32. 31 not 21
33. COMPARATIVE STUDY/
34. exp EVALUATION STUDIES/
35. FOLLOW UP STUDIES/
36. PROSPECTIVE STUDIES/
37. (control$ or prospectiv$ or volunteer$).ti,ab.
38. or/33-37
39. 38 not 20
40. 39 not (21 or 32)
41. 21 or 32 or 40
42. 40 and 41
43. cohort$.mp,hw.
44. letter.pt.
45. 43 or 44
46. 42 not 45

APPENDIX V-1: SCREENING CHART FOR SUBJECT ELIGIBILITY

Name: _____ **ACB #:** _____

1. **Squamous cell carcinoma of head and neck** **yes** **no**
   (Unknown primary eligible if occult mucosal origin in the head and neck)

2. **Surgical treatment that includes radical neck dissection/ modified neck dissection**
   Selective neck dissection **yes** **no**

3. **Karnofsky performance status > or = 60%** **yes** **no**

4. **No evidence of residual cancer or distant metastases** **yes** **no**

5. **Able to attend sessions 3x per week for 12 weeks** **yes** **no**

6. **Willing to be randomized to either group** **yes** **no**

Ineligible if:

1. **co-morbid condition: pre-existing shoulder pathology, medical illness or psychiatric illness**
   yes **no**

APPENDIX V-2: INFORMATION LETTER AND PAMPHLET

Study Title: Randomized controlled trial of progressive resistance exercise training in head and neck cancer survivors

Investigators: Margie McNeely, Physical Therapist & Graduate Student, University of Alberta
Dr. Kerry Courneya, Professor, University of Alberta
Dr. Matthew Parliament, Radiation Oncologist, Cross Cancer Institute
Dr. Hadi Seikaly, Head and Neck Surgeon, Capital Health Region

Dear _____,

You are being asked to participate in an exercise study for head and neck cancer survivors. Your doctor has given us permission to contact you to take part in this study.

This study will be examining the effect of a specialized upper body strengthening program on shoulder pain and function, and quality of life in head and neck cancer survivors. This type of exercise has been used in patients who have had head and neck surgery with reported success. However, it has not been properly tested and therefore it is not widely used in the care of head and neck cancer patients who have had surgery. We feel that it may be beneficial and thus an important part of the care provided to head and neck cancer patients.

We have attached an information pamphlet that provides further information about the study. Participation in the study may be of no personal benefit to you. However, based on the results of this study, it is hoped that, in the long-term, patient care can be improved.

If you would like more information about the study, or if you are interested in taking part, please call Margie McNeely whose number is listed below.

Sincerely,

Margie McNeely
Behavioural Medicine Laboratory
University of Alberta
780-492-2829

INFORMATION PAMPHLET

Study: Randomized controlled trial of progressive resistance exercise training in head and neck cancer survivors

What is the purpose of the study?

The purpose of this study is to determine whether it is useful for patients who have had surgery for head and neck cancer to do a specialized strengthening program for the upper body. We will do this by comparing the effects of the specialized strengthening program with usual care to see which is better.

Who is eligible for the study?

You are eligible for the study if you have had surgery for your head and neck cancer that includes removal of lymph nodes in the neck.

To participate you need to be finished your cancer treatments and have no other major health concerns.

You do NOT need to have pain to take part in the study. You are eligible for the study even if your shoulder symptoms are minor (e.g. you have noticed that the muscles in your upper body feel weaker since your surgery).

What will my participation involve?

If you take part in this study, you will have the following tests and procedures done:

- An exercise specialist will measure your shoulder movement and strength. These measurements will be done at the beginning of the study and at the end of 12 weeks. This examination will take about one hour to complete.
- You will also be asked to complete four self-administered questionnaires. The questionnaires will take about 20 to 30 minutes in total to complete.

If you take part in the study, we will ask you to have the following tests and procedures performed:

- You will have the option to have special tests done to see if your spinal accessory nerve (nerve conduction testing) and your trapezius muscle at the back of your shoulder (electromyography or EMG testing) are working normally. If you agree, these tests will be done at the beginning of the study and will take about an hour and a half. These tests will only be repeated at the end of the study if results from the first test show that your nerve and muscle have not yet recovered.

In this study, one group will take part in a supervised strength-training program (exercise). The other group will continue with their usual activities (usual care). You will be followed to see what effect the treatment has on your upper body function and strength, and your quality of life.

Treatment A - Exercise Group:

If you are assigned to the exercise program, you will take part in a supervised shoulder strength-training program. You will be expected to attend exercise sessions 3 times per week for 12 weeks. The program will consist of 6 strength-training exercises and the program will be carried out at the Behavioural Medicine Fitness Centre (University of Alberta Campus). You will need to exercise three days per week (e.g. Monday, Wednesday and Friday) and you will have a set time to exercise (at your convenience) sometime during the day or early evening. Each exercise session will take approximately 45 minutes to complete.

Treatment B – Usual Care:
If you are assigned to the usual care group, you will continue with your normal activities and/or exercises at home. This group is very important because it helps us understand whether the exercise program is beneficial. You will have the option to learn the strength-training program after the 12-week study period.

Who will decide which group I will be in?

Once you have agreed to enter the trial, you will be randomized to either the exercise or usual care group. This means that a computer will randomly assign you to one of the two groups in the study. This is similar to a 'toss of a coin' and is done so that each group has a similar mix of patients of different ages, sex and state of health. You will have an equal chance of being assigned to treatment A (exercise) or B (usual care).

Your decision whether or not to participate in the study will in no way affect the other treatment or services you receive. Your doctor can discuss with you treatment options available for problems in the shoulder.

Who do I contact if I want further information on the study?

If you are interested in taking part in the study or if you would like more information, please contact Margie McNeely by phone (492-2829) or email (mmcneely@ualberta.ca) at the Behavioural Medicine Laboratory, University of Alberta.

APPENDIX V-3: DEMOGRAPHIC INFORMATION

Name: _____Age: _____

Gender: M or F Employment status: _____

Date of diagnosis: _____

Date of surgery: _____

Date completed cancer treatment: _____

Cancer Stage: _____ Location of cancer: _____

Neck dissection type: _____

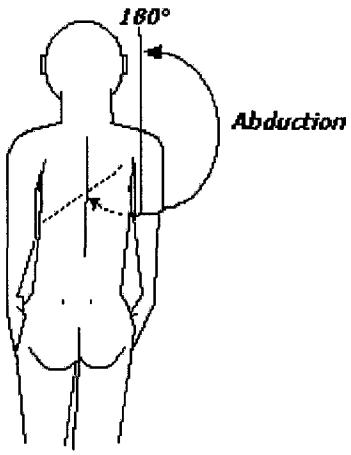
Radiation: yes no Type of radiation: _____ Dosage: _____

Chemotherapy: yes no Type of chemotherapy: _____

Currently pain medication use: type: _____dosage: _____

APPENDIX V-4: RANGE OF MOTION (ROM)

Abduction ROM

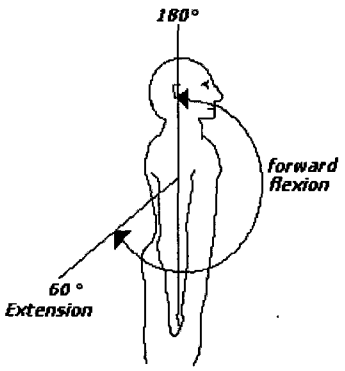


Active ROM into abduction: Active elevation through abduction is normally 170-180 degrees. The measurement is accomplished in the standing position. The axis of the goniometer lies on the acromion in the coronal plane. The based lever arm is aligned with the axis of the trunk. The moving lever arm is aligned with the medial midline of the humerus. Active abduction will be done with the humerus externally rotated (Norkin, 1995).

Passive ROM into abduction: Passive elevation through abduction will be measured in the supine position. The axis of the goniometer lies over the anterior aspect of the acromion process. The based lever arm is aligned with the trunk, parallel to the sternum. The moving lever arm is aligned with the medial midline of the humeous. The movement will be done with the humerus in an externally rotated position (Norkin, 1995)

APPENDIX V-4 CONTINUED:

Forward flexion ROM

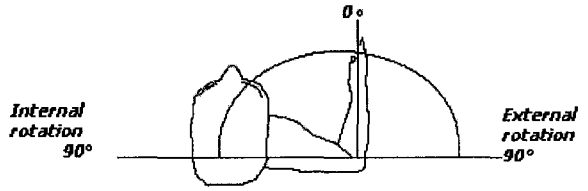


Active Forward Flexion ROM: The normal range of motion into forward flexion is 160 to 180 degrees. The motion will be in the sagittal plane around a medial-lateral axis. The measurement will be accomplished in the sitting position. The arm will be positioned at the subject's side with the elbow extended. The forearm will be resting in a neutral position so that the palm of the hand faces the body. The axis of the goniometer will rest on the acromion in the sagittal plane. The based lever will be aligned with the lateral midline of the trunk. The moving lever will be aligned with the lateral midline of the humerus and extend over the lateral epicondyle (Norkin, 1995).

Passive Forward Flexion ROM: Passive flexion will be measured in the supine position with the knees flexed to flatten the lumbar spine. The arm will be positioned at the subject's side with the elbow extended. The forearm will be in a neutral position with the palm facing the body. The fulcrum of the goniometer will be aligned with the acromion process. The based lever will be aligned with the lateral midline of the trunk. The moving lever will be aligned with the lateral midline of the humerus and extend over the lateral epicondyle (Norkin, 1995).

APPENDIX V-4 CONTINUED:

External and Internal Rotation and Horizontal Abduction ROM



Active External and Internal Rotation ROM: The measurement will be accomplished in the sitting position with the elbow flexed and the arm supported in 90 degrees of abduction. The fulcrum of the goniometer will be aligned with the olecranon in the sagittal plane. The base lever will be placed on the vertical line. The moving lever will be positioned on the lateral aspect of the forearm.

Passive External and Internal Rotation ROM: The measurement will be accomplished in the supine position. The arm will be positioned in 90 degrees of abduction and 90 degrees of elbow flexion. The fulcrum of the goniometer will be aligned with the olecranon. The base lever will be placed on the vertical line. The moving lever will be placed on the lateral side of the forearm.

Passive Horizontal Abduction ROM: The measurement will be accomplished in the supine position with the arm positioned in 90 degrees of shoulder flexion with the elbow extended. The abduction movement will be in the transverse plane. The fulcrum of the goniometer will be aligned with the axis of the shoulder. The base lever will be placed on the vertical line. The moving lever will be placed along the medial aspect of the humerus.

APPENDIX V-5: STRENGTH AND ENDURANCE TESTING

Muscle Group	Arm Right/ Left/ Both*	1 RM Weight	Endurance Test
Retraction	Right	_____	XXXXX
	Left		XXXXX
Protraction	Right	_____	XXXXX
	Left	_____	XXXXX
Retraction	Bilateral	_____	XXXXX
Protraction	Bilateral	_____	XXXXX
Retraction	Bilateral	XXXXX	_____

* The unaffected arm will be tested first, followed by the affected arm

ENDURANCE:

1RM _____ X 0.50 = _____ (Resistance weight)

Total number of repetitions until fatigue _____

APPENDIX V-6: QUESTIONNAIRE

Identification #_____ Date: _____

Strength Training Study
For Head and Neck Cancer Survivors
Baseline Questionnaire

Principal Investigators: Margie McNeely, MSc PT and K.S. Courneya, PhD
Co-Investigators: Dr. Matthew Parliament, MD and Dr. Hadi Seikaly, MD

Instructions

Thank you for agreeing to participate in this study. In this questionnaire, we are going to ask you a series of questions about yourself. The questionnaire will tell us about the affect of your cancer, your surgery and your shoulder, on your well-being and your day-to-day life. As well, we will ask you questions about your energy levels, lifestyle and past activity level. There are no right or wrong answers and all we ask is that you provide responses that are as honest and accurate as possible. The questionnaire should take about 30-45 minutes to complete. All responses are completely confidential and will never be used in any way that could link them to you. It is important to complete all questions if possible so that we can include your responses in our analyses. If you have any questions about completing the questionnaire, please contact Margie McNeely (Investigator) at 492-2829 or Prof. Kerry Courneya (Investigator) at 492-1031.

QUALITY OF LIFE SCALE

Below is a list of statements that other people with cancer have said are important to their quality of life. Please indicate the extent to which you have experienced each of the statements during the past 7 days by circling the appropriate number using the following scale.

0	1	2	3	4
not at all	a little bit	somewhat	quite a bit	very much

During the PAST 7 DAYS:

PHYSICAL WELL - BEING

1. I have a lack of energy	0	1	2	3	4
2. I have nausea	0	1	2	3	4
3. Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4. I have pain	0	1	2	3	4
5. I am bothered by side effects of treatment	0	1	2	3	4
6. I feel sick	0	1	2	3	4
7. I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL - BEING

8. I feel close to my friends	0	1	2	3	4
9. I get emotional support from my family	0	1	2	3	4
10. I get support from my friends	0	1	2	3	4
11. My family has accepted my illness	0	1	2	3	4
12. I am satisfied with family communication about my illness	0	1	2	3	4
13. I feel close to my partner (or the person who is my main support)	0	1	2	3	4

14. I am satisfied with my sex life	0	1	2	3	4

0	1	2	3	4
not at all	a little bit	somewhat	quite a bit	very much

During the PAST 7 DAYS:

EMOTIONAL WELL - BEING

15. I feel sad	0	1	2	3	4
16. I am satisfied with how I am coping with my illness	0	1	2	3	4
17. I am losing hope in the fight against my illness	0	1	2	3	4
18. I feel nervous	0	1	2	3	4
19. I worry about dying	0	1	2	3	4
20. I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL - BEING

21. I am able to work (include work at home)	0	1	2	3	4
22. My work (include work at home) is fulfilling	0	1	2	3	4
23. I am able to enjoy life	0	1	2	3	4
24. I have accepted my illness	0	1	2	3	4
25. I am sleeping well	0	1	2	3	4
26. I am enjoying the things I usually do for fun	0	1	2	3	4
27. I am content with the quality of my life right now	0	1	2	3	4

0	1	2	3	4
not at all	a little bit	somewhat	quite a bit	very much

FATIGUE AND ENERGY

28. I feel fatigued	0	1	2	3	4
29. I feel weak all over	0	1	2	3	4
30. I feel listless ("washed out")	0	1	2	3	4
31. I feel tired	0	1	2	3	4
32. I have trouble starting things because I am tired	0	1	2	3	4
33. I have trouble finishing things because I am tired	0	1	2	3	4
34. I have energy	0	1	2	3	4
35. I have trouble walking	0	1	2	3	4
36. I am able to do my usual activities	0	1	2	3	4
37. I need to sleep during the day	0	1	2	3	4
38. I feel lightheaded (dizzy)	0	1	2	3	4
39. I get headaches	0	1	2	3	4
40. I have been short of breath	0	1	2	3	4
41. I have pain in my chest	0	1	2	3	4
42. I am too tired to eat	0	1	2	3	4
43. I am interested in sex	0	1	2	3	4
44. I am motivated to do my usual activities	0	1	2	3	4
45. I need help doing my usual activities	0	1	2	3	4
46. I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
47. I have to limit my social activity because I am tired	0	1	2	3	4

NECK DISSECTION IMPAIRMENT INDEX (NDII)

As a result of the cancer treatment of your neck, how much have you been bothered by the following over the past 4 weeks?

Please use the following descriptors to answer these questions:

"Not at all" = 1
"A little bit" = 2
"A moderate amount" = 3
"Quite a bit" = 4
"A lot" = 5

1. Are you bothered by neck or shoulder pain or discomfort?	**1**	**2**	**3**	**4**	**5**
2. Are you bothered by neck or shoulder stiffness?	**1**	**2**	**3**	**4**	**5**
3. Are you bothered by difficulty with self-care activities because of your neck or shoulder (combing hair, dressing, bathing)	**1**	**2**	**3**	**4**	**5**
4. Have you been limited in your ability to lift light objects because of your shoulder or neck?	**1**	**2**	**3**	**4**	**5**
5. Have you been limited in your ability to lift heavy objects because of your shoulder or neck?	**1**	**2**	**3**	**4**	**5**
6. Have you been limited in your ability to reach above for objects because of your shoulder or neck (from shelves, tables, or counters)?	**1**	**2**	**3**	**4**	**5**
7. Are you bothered by your overall activity level because of your shoulder or neck?	**1**	**2**	**3**	**4**	**5**
8. Has the treatment of your neck affected your participation in social activities?	**1**	**2**	**3**	**4**	**5**
9. Have you been limited in your ability to do leisure or recreational activities because of your neck or shoulder?	**1**	**2**	**3**	**4**	**5**
10. Have you been limited in your ability to work (including work at home) because of your neck or shoulder?	**1**	**2**	**3**	**4**	**5**

SHOULDER PAIN AND DISABILITY INDEX

The line next to each item represents the amount of pain you have in each situation. The far left of the line represents "No pain" and the far right of the line represents "Worst imaginable pain". Place a mark on the line to indicate how much pain you had during the past week in each of the following situations. Mark NA if you did not experience this situation during the past week.

Pain Scale

A. How severe is your shoulder pain:

			Score
1. At its worst?.....No pain	_____	**Worst Pain**	_____
2. When lying on involved side?.....No pain	_____	**Worst Pain**	_____
3. When reaching for something on a high shelf?.....No pain	_____	**Worst Pain**	_____
4. When touching the back of your neck?.....No pain	_____	**Worst Pain**	_____
5. Pushing with the involved arm?.....No pain	_____	**Worst Pain**	_____

DISABILITY SCALE

The line next to each item represents how much difficulty you had doing that activity. The far left of the line represents "No difficulty" and the far right of the line represents "So difficult required help". Place a mark on the line to indicate how much difficulty you had during the past week in each of the following situations. Mark NA if you did not experience this situation during the past week.

B. How much difficulty did you have:

		Score
1. Washing your hair?.....No difficulty _____	**So difficult required help**	_____
2. Washing your back?.....No difficulty _____	**So difficult required help**	_____
3. Putting on an undershirt or pullover sweater?.....No difficulty _____	**So difficult required help**	_____
4. Putting on a shirt that buttons up the from?.....No difficulty _____	**So difficult required help**	_____
5. Putting on your pants?...No difficulty _____	**So difficult required help**	_____
6. Placing an object on a high shelf?.....No difficulty _____	**So difficult required help**	_____
7. Carrying a heavy object of 10 lbs or more?.....No difficulty _____	**So difficult required help**	_____
8. Removing something from your back pocket?.....No difficulty _____	**So difficult required help**	_____

The following questions concern the general perceptions that you currently have about yourself. Please circle the number that best reflects your current view of yourself using the following scale as a guide for your responses.

1 strongly disagree	2 disagree	3 agree	4 strongly agree

1. On the whole I am satisfied with myself.	1	2	3	4
2. At times I think that I am no good at all.	1	2	3	4
3. I feel that I have a number of good qualities.	1	2	3	4
4. I am able to do things as well as most other people.	1	2	3	4
5. I feel I do not have much to be proud of.	1	2	3	4
6. I certainly feel useless at times.	1	2	3	4
7. I feel that I am a person of worth, at least on an equal plane with others.	1	2	3	4
8. I wish I could have more respect for myself.	1	2	3	4
9. All in all, I am inclined to feel that I am a failure.	1	2	3	4
10. I take a positive attitude toward myself.	1	2	3	4

Below is a list of statements concerning how you might have felt or behaved in the past week. Use the following scale to indicate how often you felt or behaved in these ways in the past week.

0	1	2	3
< 1 day	1-2 days	3-4 days	5-7 days

During the PAST 7 DAYS:

1. I was bothered by things that don't usually bother me.	0	1	2	3
2. I had trouble keeping my mind on what I was doing.	0	1	2	3
3. I felt depressed.	0	1	2	3
4. I felt that everything I did was an effort.	0	1	2	3
5. I felt hopeful about the future.	0	1	2	3
6. I felt fearful.	0	1	2	3
7. My sleep was restless.	0	1	2	3
8. I was happy.	0	1	2	3
9. I felt lonely.	0	1	2	3
10. I could not get "going".	0	1	2	3

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number that best indicates how you

have felt during the past week. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that best describes how you felt.

1	2	3	4
not at all	somewhat	moderately so	very much so

During the PAST 7 DAYS:

1. I felt calm	1	2	3	4
2. I was tense	1	2	3	4
3. I felt at ease	1	2	3	4
4. I worried over possible misfortunes	1	2	3	4
5. I felt frightened	1	2	3	4
6. I felt nervous	1	2	3	4
7. I was jittery	1	2	3	4
8. I was relaxed	1	2	3	4
9. I was worried	1	2	3	4
10. I felt steady	1	2	3	4

The following questions ask you to rate how you feel about a weight-training program over the next 12 weeks. Please pay careful attention to the words and descriptors at the end of each scale and circle the number that best represents how you feel.

I feel that for me to weight train over the next 12 weeks will be:

1	2	3	4	5	6	7
extremely useless	quite useless	slightly useless	neutral	slightly useful	quite useful	extremely useful

I feel that for me to weight train over the next 12 weeks will be:

1	2	3	4	5	6	7
extremely unenjoyable	quite unenjoyable	slightly unenjoyable	neutral	slightly enjoyable	quite enjoyable	extremely enjoyable

If I weight trained over the next 12 weeks most people who are important to me would be:

1	2	3	4	5	6	7
extremely unsupportive	quite unsupportive	slightly unsupportive	neutral	slightly supportive	quite supportive	extremely supportive

Most people who are important to me are themselves doing a weight-training program.

1	2	3	4	5	6	7
strongly disagree	moderately disagree	slightly disagree	neutral	slightly agree	moderately agree	strongly agree

How motivated are you to weight train over the next 12 weeks?

1	2	3	4	5	6	7
extremely unmotivated	quite unmotivated	slightly unmotivated	neutral	slightly motivated	quite motivated	extremely motivated

If you were really motivated...
How easy or difficult would it be for you to weight train over the next 12 weeks?

1	2	3	4	5	6	7
extremely difficult	quite difficult	slightly difficult	neutral	slightly easy	quite easy	extremely easy

How confident would you be that you could weight train over the next 12 weeks?

1	2	3	4	5	6	7
extremely unconfident	quite unconfident	slightly unconfident	neutral	slightly confident	quite confident	extremely confident

For this next question, we would like you to recall your average weekly exercise in the months BEFORE you were diagnosed with cancer. Please focus on the time period before you had significant symptoms or when you were not feeling well from your disease.

When answering these questions please:

- only count exercise sessions that lasted 10 minutes or longer in duration.

- only count exercise that was done during free time (i.e., not occupation or housework).

- note that the main difference between the three categories is the intensity of the exercise.

- please write the average frequency on the first line and the average duration on the second.

Considering a typical week (7 days) how many times on the average did you do the following kinds of exercise in the months BEFORE you were diagnosed with lymphoma cancer?

	Times Per Week	Average Duration
a. STRENUOUS EXERCISE (HEART BEATS RAPIDLY, SWEATING) (e.g., running, aerobics classes, cross country skiing, vigorous swimming, vigorous bicycling).	_____	_____
b. MODERATE EXERCISE (NOT EXHAUSTING, LIGHT PERSPIRATION) (e.g., fast walking, tennis, easy bicycling, easy swimming, popular and folk dancing).	_____	_____
c. MILD EXERCISE (MINIMAL EFFORT, NO PERSPIRATION) (e.g., easy walking, yoga, bowling, lawn bowling, shuffleboard).	_____	_____

For this next question, we would like you to recall your average weekly exercise in the PAST MONTH.

When answering these questions please:

- only count exercise sessions that lasted 10 minutes or longer in duration.

- only count exercise that was done during free time (i.e., not occupation or housework).

- note that the main difference between the three categories is the intensity of the exercise.

- please write the average frequency on the first line and the average duration on the second.

Considering a typical week (7 days) how many times on the average did you do the following kinds of exercise in the PAST MONTH?

	Times Per Week	Average Duration
a. STRENUOUS EXERCISE (HEART BEATS RAPIDLY, SWEATING) (e.g., running, aerobics classes, cross country skiing, vigorous swimming, vigorous bicycling).	_____	_____
b. MODERATE EXERCISE (NOT EXHAUSTING, LIGHT PERSPIRATION) (e.g., fast walking, tennis, easy bicycling, easy swimming, popular and folk dancing).	_____	_____
c. MILD EXERCISE (MINIMAL EFFORT, NO PERSPIRATION) (e.g., easy walking, yoga, bowling, lawn bowling, shuffleboard).	_____	_____

This last part of the questionnaire is needed to help understand the characteristics of the people participating in the study. For this reason it is very important information. All information is held in strict confidence and its presentation to the public will be group data only.

1. Age: _____

2. Sex: male _____ female _____

3. Marital Status: Never Married _____ Married _____ Common Law _____

Separated _____ Widowed _____ Divorced _____

4. Education (Please check highest level attained):

Some High School _____ Completed High School _____

Some University/College _____ Completed University/College _____

Some Graduate School _____ Completed Graduate School _____

5. Annual Family Income: < 20,000 _____ 20-39,999 _____ 40-59,999 _____

60-79,999 _____ 80-99,999 _____ > 100,000 _____

6. Current Employment Status: Disability _____ Retired _____ Part Time _____

Homemaker _____ Full Time _____ Temporarily Unemployed _____

7. What is your ethnic origin or ancestry? _____

The next set of questions ask you about your smoking and diet habits and current health. This information is to help us understand other important health issues. Please provide as honest and accurate responses as possible.

1. Which of the following best describes your current smoking status?

____ Never Smoked ____ Ex-Smoker ____ Occasional Smoker ____ Regular Smoker (smoke every day)

2. Which of the following best describes your current drinking status?

____ Never Drank ____ Ex-Drinker ____ Social Drinker ____ Regular Drinker (drink every day)

3. How would you rate your general health?

_____ *Excellent* _____ *Very Good*_____ *Good* _____ *Fair* _____ *Poor*

4. Has a doctor or nurse ever told you that you had any of the following conditions?

(check all that apply):

High blood pressure	_____*No*	_____*Yes*	*High cholesterol*	_____*No*	_____*Yes*
Heart attack	_____*No*	_____*Yes*	*Stroke*	_____*No*	_____*Yes*
Emphysema	_____*No*	_____*Yes*	*Chronic bronchitis*	____*No*	_____*Yes*
Diabetes	_____*No*	_____*Yes*	*Other cancer*	_____*No*	_____*Yes*
Angina (chest pains)	_____*No*	_____*Yes*	*Arthritis*	_____*No*	_____*Yes*

Any other long-term health condition? _____

5. In the past month, was your ability to exercise limited by a health condition, injury, or disability?

1	*2*	*3*	*4*	*5*
No, Not at All	*A Little*	*Somewhat*	*Quite a lot*	*Completely*

Approximately how long did it take you to answer this questionnaire? _____Minutes

Anything else you would like to tell us? On this final page, please feel free to make any comments concerning your medical condition, the questionnaire itself, the exercise programs, or anything else you think may be helpful to us. All comments are welcome.

Thank you very much for your participation in this research project. Please place the completed questionnaire in the envelope provided and bring it to your next scheduled visit.

APPENDIX V-7: EXERCISE PROGRAM

Progressive Resistance Exercise Training Protocol

- All exercises from all sessions will be recorded in logbooks

Prescription:

- Initial prescription will be based on a percentage of the one repetition maximum
- This information will be collected during the baseline fitness assessment
- Exercise prescriptions will be prepared for the participant's first exercise session

Exercise type:

- Specific exercises have been chosen and details are provided in the following tables: Tables 1, 2 and 3.

Frequency, duration and intensity:

Weeks	Frequency	Repetitions	Sets	Intensity (% of one repetition maximum)
0-1	3	12-25 or to tolerance	1	25-30% of 1 RM
2	3	10-12 or to tolerance	2	40% of 1 RM
3-4	3	12-15 or to tolerance	2	50% of 1 RM
5-6	3	10-15 or to tolerance	2	50% of 1 RM
7-9	3	8-10 or to tolerance	2	60% of 1 RM
10-12	3	10-12 or to tolerance	2	60-70% of 1 RM

- **Note that it is important that resistance exercise training occur on non-consecutive days.**
- **For exercises other than retraction: resistance weight will increase by approximately 5% when 12-15 repetitions can be performed in the second set.**

Appendix V-7 continued: TABLE 1: Progressive Resistance Exercise Training Program

Program Components	Program Details
Purpose	Enhancement of muscular strength and endurance of upper extremity and scapular muscles
Warm-up	Range of motion exercises for glenohumeral joint in supine
Muscle Groups to be strengthened	▪ Rhomboids (scapular retraction) ▪ Levator scapula (scapular elevation) ▪ Biceps (elbow flexion) ▪ Triceps (elbow extension) ▪ Infraspinatus, posterior deltoid (external rotation) ▪ Middle deltoid, supraspinatus and subscapularis (abduction in the plane of the scapula)
Intensity	▪ Start with resistance of 1-2 Kg weights progress within guidelines ▪ Must be able to maintain posture, control of movement and scapular stability (no winging of scapula) ▪ RPE: no greater than 13 on Borg Scale: "somewhat hard"
Repetitions	15-20: progress to maximum of 25 repetitions initially when performing only 1 set
Sets	1 set, progress ⇒ 2 sets @ 2 sets of 20 increase resistance weight
Rest continuous	1- 2 minutes between exercise stations and up to 4 minutes between sets
Concentric tempo	2-4 seconds (exhaling)
Eccentric tempo	4 seconds (inhaling)
Total set duration	Approximately 20-minutes/ set for 15 repetitions each. Total for 2 sets of 20 repetitions each = approximately 45 minutes.
# Exercises	6 exercises
Stretching Exercises (Cool down)	▪ Pectoralis major and minor ▪ Serratus anterior
Reduce workload	▪ Excessive fatigue post exercise ▪ Muscle soreness >48 hours ▪ Increased pain post exercise
Terminate repetitions	Poor posture, accessory movements of body/trunk, movement pattern is uncontrolled
Terminate exercise	Pain, dizziness, general malaise

Appendix V-7 continued: Table 2. Exercise Program Details

Therapeutic Exercises

Exercise	Purpose	Muscle groups	Equipment	Position
1A. Seated row: elbows neutral	Strengthen rhomboids to compensate for weakened or absent middle trapezius	Rhomboids	Atlas: vertical row machine	Sitting
1B. Seated row: elbows at 45-90 degrees abduction	Alternate to 1A above (preferred method of strengthening if adequate ROM is available)	Rhomboids Posterior deltoid	Atlas: vertical row machine	Sitting
2. Shoulder shrug	Strengthen levator scapulae to compensate for weakened or absent upper trapezius	Levator scapulae	Atlas: bicep machine - modified exercise	Standing
3. Elbow flexion	To maintain/ enhance upper arm strength for functional compensation	Biceps	Free weights: 2-5 lbs • progress to Atlas: bicep machine	Supported sitting Sitting
4. Elbow extension	To maintain/ enhance upper arm strength for functional compensation	Triceps	Free weights: 2-5 lbs • progress to Atlas: triceps machine	Supine Sitting
5. Resisted external rotation	To maintain/ enhance strength of rotator cuff muscles	Infraspinatus Deltoid: posterior fibres Teres Minor	Theraband • progress to resistance with Free weights	Sitting Side Lying
6. Abduction with arm laterally rotated	To maintain/ enhance strength of rotator cuff muscles	Deltoid: middle fibres Supraspinatus Infraspinatus Subscapularis Teres Minor Biceps long head	No resistance at start • progress to anti-gravity with elbow flexion of 90 degrees • progress to resistance with Free weights	Supine Sitting Sitting

Appendix V-7 continued: TABLE 3. Program Components of PRET Program in comparison to Standard Care

Program Components	PRET	Standard Care
Goals of Physical Therapy	1. Enhance muscular strength and endurance of upper extremity and scapular muscles to: ▪ To compensate for loss of trapezius function ▪ Maintain shoulder alignment and posture	1.Optimize joint range of motion in glenohumeral joint 2. Strengthen alternative muscles to compensate for loss of trapezius 3. Prevent/ alleviate pain
Practical/ Theoretical Differences	1. Primary focus on strengthening scapular muscles (levator scapula and rhomboids) to: ▪ Assist in stabilizing the scapula ▪ Counteract the imbalance of forces on the scapula created by weakened/absent trapezius and unopposed action of scapular protractors (serratus anterior and pectoralis minor) ▪ Prevent stretch weakness of levator scapula and rhomboids 2. Supervised resistance exercise training program using the principle of progressive overload to increase strength and endurance of scapular and upper extremity muscles (moderate to slow speed, where possible with full range of motion) 3. Progression of exercises to weight machines where possible (external stabilization provided by weight machine allows for optimal muscle action and progression of resistance)	1. Primary focus on maintaining joint integrity and range of motion of glenohumeral joint to: ▪ Prevent adhesive capsulitis 2. Strengthening exercises using elastic resistance band or free weights
Components similar in both programs	1. Active and passive ROM exercises 2. Stretching exercises to prevent adaptive muscle shortening of pectoralis major and minor, and serratus anterior 3. Postural education/ supportive positions for upper limb	

APPENDIX V-8: BORG SCALE

Borg Perceived Exertion Scale

The Borg Perceived Exertion Scale gives you an idea of how hard your exercise feels. If it feels light (less than 12), you should increase the pace of your exercise, walking, biking, swimming, etc. If the exercise feels hard (14 or greater, you need to slow the pace. Exercise should feel somewhat hard (12-13). Borg's Scale:

6	
7	very, very light
8	
9	very light
10	
11	fairly light
12	
13	somewhat hard
14	
15	hard
16	
17	very hard
18	
19	very, very hard
20	

APPENDIX V-9: STATISTICS

Baseline Descriptive Data

Variable	Data	Descriptive Statistic	Inferential Statistic
Demographics			
Age (years)	Continuous	Mean (SD)	independent t-test
Gender (male/ female)	Categorical	Frequency/Percentage	chi-square
Employed status (full time)	Categorical	Frequency/Percentage	chi-square
Medical			
Stage			chi-square
Stage 1(T1N0)	Categorical	Frequency/Percentage	
Stage 2 (T2N0)	Categorical	Frequency/Percentage	
Stage 3 (T1-3N1 or T3, N0)	Categorical	Frequency/Percentage	
Stage 4 (T4N0, any T, N2-3)	Categorical	Frequency/Percentage	
Diagnosis			chi-square
Oral Cavity	Categorical	Frequency/Percentage	
Oropharynx	Categorical	Frequency/Percentage	
Larynx/ hypopharynx	Categorical	Frequency/Percentage	
Nasopharynx	Categorical	Frequency/Percentage	
Unknown Primary	Categorical	Frequency/Percentage	
Parotid	Categorical	Frequency/Percentage	
Radiation			chi-square
IMRT protocol	Categorical	Frequency/Percentage	
Unilateral Neck	Categorical	Frequency/Percentage	
Bilateral Neck	Categorical	Frequency/Percentage	
No radiation	Categorical	Frequency/Percentage	
Neck Dissection Type			chi-square
RND	Categorical	Frequency/Percentage	
MND to level 5	Categorical	Frequency/Percentage	
MND to level 4	Categorical	Frequency/Percentage	
SND to level 3	Categorical	Frequency/Percentage	
Pain Medications (opiod vs nonopiod)			
Baseline routine	Categorical	Frequency/Percentage	
12-week routine	Categorical	Frequency/Percentage	
Past Exercise			
Moderate (mins/week)	Continuous	independent t-test	
Strenuous (mins/week)	Continuous	independent t-test	
Moderate/ Strenuous (mins/week)	Continuous	independent t-test	
> 90 Moderate/ Strenuous (n)	Continuous	independent t-test	

Abbreviations: IMRT= Intensity Modulated Radiation Therapy; RND = Radical Neck Dissection; MND = modified neck dissection; SND = Selective Neck Dissection; routine = narcotic medication of at minimum 2 acetaminophen plus codeine 15 mg per day; prn = pain medication taken as needed

APPENDIX V-9 CONTINUED: DESCRIPTIVE AND INFERENTIAL STATISTICAL PROCEDURES

Outcome Variable	Data	Descriptive Statistic	Inferential Statistic
Active and Passive ROM (degrees)	continuous	mean (SD)	independent sample t-test (CI)
SPADI Pain Score (%)	continuous	mean (SD)	independent sample t-test (CI)
SPADI Disability Score (%)	continuous	mean (SD)	independent sample t-test (CI)
SPADI Total Score (%)	continuous	mean (SD)	independent sample t-test (CI)
NDII (%)	continuous	mean (SD)	independent sample t-test (CI)
HNQOL pain domain	continuous	mean (SD)	independent sample t-test (CI)
1RM chest press	continuous	mean (SD)	independent sample t-test (CI)
1RM retraction	continuous	mean (SD)	independent sample t-test (CI)
Adherence	continuous	mean (SD)	Confidence Interval

APPENDIX V-10: CONSENT FORM

RANDOMIZED CONTROLLED TRIAL OF PROGRESSIVE RESISTANCE EXERCISE TRAINING IN HEAD AND NECK CANCER SURVIVORS

(A study to determine if an intensive strength training program is beneficial in reducing pain and muscle weakness in the shoulder for patients who have undergone head and neck cancer surgery)

CONSENT FORM

This form is part of the process of informed consent. It is designed to explain this research study and what will happen to you if you choose to be in the study.

If you would like to know more about something mentioned in this consent form, or have any questions at anytime regarding this research study, please be sure to ask your doctor, nurse or the Project Coordinator (Margie McNeely). Read this consent form carefully to make sure you understand all the information it provides. You will get a copy of this consent form to keep.

Your doctor has given us permission to ask you to be in this study. You do not have to take part in this study and your care does not depend on whether or not you take part.

Your participation in this study is entirely voluntary. Please take your time to make your decision. It is recommended that you discuss with your friends and/or family about whether to participate in this study.

"WHY IS THIS STUDY BEING DONE?"

You are being asked to take part in this study because you have had surgery for head and neck cancer that includes removal of lymph nodes in the neck. While the aim of treatment is to completely remove the cancer, surgery involving the neck may cause some nerve damage. One important nerve that may be damaged during surgery is the spinal accessory nerve. The spinal accessory nerve provides the "power supply" to the large muscle at the back of your neck and shoulder, called the trapezius muscle. Damage to this nerve (e.g. from bruising or stretching or complete removal of the nerve) will cause the trapezius muscle to stop working. The trapezius supports and moves the shoulder blade to allow you to lift your arm above your head. Following surgery, all you may notice is that it is difficult to lift your arm out to your side. Over several months, however, you may notice that your shoulder starts to feel stiff and/or weak. You may also have pain with movement of the arm. The damage to your nerve function may be temporary or permanent. However, even temporary nerve damage may take a full year or more to recover.

These changes to your shoulder, even in their less severe form, may result in greater fatigue and lower levels of strength, and may make it difficult for you to return to normal work and/or recreational activities.

Physical Therapy is recommended to prevent stiffness and to strengthen the muscles around the shoulder. Progressive resistance exercise training (PRET) is a strength-training method that is used to improve muscle strength. Proper strengthening of the muscles around the shoulder will help to make up for weakness or loss of function in the trapezius muscle. This type of strengthening has been used in patients who have had head and neck surgery with reported success. However, PRET has not been properly tested and therefore it is not widely used in the care of cancer patients with nerve damage following surgery to the neck region. We feel that it may be beneficial and thus an important part of the care provided to head and neck cancer patients.

"WHAT DO WE HOPE TO LEARN?"

The purpose of this study is to determine whether it is useful for patients who have had neck surgery to do a specialized strengthening program for the upper body. We will do this by comparing the effects of the specialized strengthening program with usual care to see which is better.

"WHAT IS INVOLVED IN THIS STUDY?"

You will be "randomized" to receive one of the treatments described below. Randomization means the treatment which you are assigned will be determined by chance. It is like flipping a coin. Randomization is done by a computer. Neither you nor the researcher will choose which treatment you will be assigned. You will have an equal chance of being assigned to treatment A (exercise) or B (standard/ usual care). In this study one group will take part in a supervised strength-training program (exercise). The other group will continue with their usual activities (usual care) or receive standard physical therapy care. You will be followed to see what effect the treatment has on your shoulder.

Treatment A - Exercise Group:
If you are assigned to the exercise program, you will take part in a supervised shoulder strength-training program. You will be expected to attend exercise sessions 2 to 3 times per week for 12 weeks. The program will consist of 6 strength-training exercises and the program will be carried out at the Behavioural Medicine Fitness Centre (University of Alberta Campus).

These sessions will be run two or three days per week (e.g. Monday, Wednesday and Friday) and you will have a set time to exercise each time. Each exercise session will take approximately 45 minutes to complete.

Treatment B – Usual or Standard Care:
If you are assigned to the usual/ standard care group, you will continue with your normal exercises at home OR you will take part in standard physical therapy treatment, at the Behavioural Medicine Fitness Centre (University of Alberta Campus), 2 or 3 days per week for

the 12-week study period. This group is very important because it helps us understand whether the exercise program is harmful or beneficial. You will have the option to learn the strength-training program after the 12-week study period.

"HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?"

About 60 people will take part in this study.

"WHAT WILL MY PARTICIPATION INVOLVE?"

If you take part in this study, you will have the following tests and procedures:

- An exercise specialist will measure your shoulder movement and strength. These measurements will be done at the beginning of the study and at the end of 12 weeks. This examination will take about one hour to complete.

- You will also be asked to complete a self-administered questionnaire. The questionnaire will take about 30 to 40 minutes in total to complete. The questionnaire will tell us about about the affect of your cancer, your surgery and your shoulder, on your day-to-day life. You will be asked to complete this questionnaire at the start and end of the study, as well as 6 and 12 months later.

- You may also be asked whether you are willing to have tests done to see if your trapezius muscle (surface electromyography or EMG testing) and spinal accessory nerve (nerve conduction testing) are working normally. EMG and nerve conduction studies are usually done together to provide more complete information. If these tests are normal then they will be done only at the beginning of the study. If the first series of tests show that the nerve and muscle are not working normally then the tests may need to be repeated again at the end of the study (12 weeks later). This testing will take from 60 to 90 minutes to complete.
    - The Electromyography (EMG) test will measure the electrical impulses of trapezius muscle at rest and during contraction. During the test, small electrodes are placed on the trapezius muscle. The electrical activity picked up by the electrodes is then displayed on an oscilloscope (a monitor that displays electrical activity in the form of waves).
    - The nerve conduction study (NCS) will measure how well the spinal accessory nerve can transmit electrical signals. In the case of nerve injury from surgery, the actual site of nerve damage can often be located.

"HOW LONG WILL I BE INVOLVED IN THE STUDY?"

You may be in this study for as long as 14 weeks.

"WHAT ARE THE SIDE EFFECTS?"

Every treatment can have side effects. It is important that you know the possible side effects of the treatments given in this study. You may experience some pain or discomfort during and/or following both the testing and the treatment. You may also notice some muscle fatigue, soreness and stiffness, in and around the shoulder. There is also the possibility that you may sustain an injury in the shoulder region or arm should you exercise too hard. These complications are rare, and your testing and exercise sessions will be carefully supervised in order to avoid any injury.

The nerve conduction and EMG testing may cause some minor discomfort but again this is normal and only temporary. If any new problems or side effects occur that are not listed or not expected, you will be informed of changes in the way the study will be done, and any new risks to which you may be exposed.

"WHAT ARE MY ALTERNATIVES?"

Your doctor will discuss with you other options available and will explain the risks and benefits of these options. The current option is a referral to a physiotherapy clinic.

"ARE THERE ANY BENEFITS TO PARTICIPATING IN THIS STUDY?"

The potential benefit from the treatment for you is an increase in your shoulder strength and function. The information you provide may help us understand whether this type of exercise is an effective intervention to improve upper body function in head and neck cancer survivors.

Participation in this study may or may not be of personal benefit to you. However, based on the results of this study, it is hoped that, in the long-term, patient care can be improved. We understand that there is a significant time commitment to the study, but this is necessary for the successful completion of the research.

"CAN I WITHDRAW FROM THIS STUDY?"

In discussion with you, your doctor may withdraw you from the study at any time if it is in your best interests. You may also withdraw from the study at any time if you wish to do so.

"ARE THERE COSTS TO ME FOR TAKING PART IN THIS STUDY?"

There will be no financial cost to you in participating in this study. You will not have to pay for any assessments or treatment you receive in this study. We will pay for your parking when you come for any tests or procedures associated with the study, and when you come for your exercise sessions.

"WHAT ARE MY RIGHTS AS A PARTICIPANT?"

It is important to note that nothing said in this consent form alters your legal rights to recover damages. However, if you suffer an injury as a result of participating in this research, compensation will not be provided. However, you retain your legal rights to pursue other avenues of compensation (e.g. legal action).

"WILL MY PERSONAL INFORMATION BE KEPT CONFIDENTIAL?"

Your medical records will be accessed and will only be seen by individuals directly involved with the research project. All information you provide and that we collect will be held in confidence but will be shared with other researchers and doctors. However, you will not be identified in any of these reports. All study results will only be presented as group data, so that no one person is identifiable. We will be retaining the anonymous data file for a period of 5 years after the completion of the research project. The data will be stored in the Behavioural Medicine Laboratory. This laboratory is secure. If a secondary analysis is planned using the data, appropriate ethical approval will be obtained.

Direct access to your identifiable health information collected for this study will be restricted to the researchers who are directly involved in this study except in the following circumstances.

The following organizations may inspect and/or copy your research record for quality assurance and data analysis:

- Health Canada, the Canadian regulatory body.
- Alberta Cancer Board Research Ethics Board, the institutional review board at this center
- Office of the Information Privacy Commissioner

Each person looking at your records at the Cross Cancer Institute will follow the relevant Alberta Cancer Board policies and procedures that control these actions. However, you will not be identified by name in any information released or in information resulting from this study when it is published.

The potential outputs associated with this study include publications in professional and applied journals, presentation of information at local and national conferences, presentations to students and researchers in oncology, medicine and physical therapy, and workshops presented to health practitioners. You will not be identified in any of these publications/presentations.

The researchers who are directly involved in your study may share information about you with other researchers, but you will not be identified in that shared information except by a number. The key that indicates what number you have been assigned will be kept secure by the researchers directly involved with you study and will not be released.

Although absolute confidentiality can never be guaranteed, the Alberta Cancer Board will make every effort to keep your identifiable health information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information in accordance with the Health Information Act and other regulatory requirements.

UNDERSTANDING OF PARTICIPANTS

I can refuse to take part or withdraw from this study at any time without jeopardizing my health care. If I continue to take part in the study, I will be kept informed of any important new developments and information learned after the time I gave my original consent.

I also give consent for the Principal Investigator and the Alberta Cancer Board (the Custodian) to disclose identifiable health information, as per the Health Information Act, to the organizations mentioned on the previous page.

I have read and understood all of the information in this consent form. I have asked questions, and received answers concerning areas I did not understand. I am free to ask for further explanations about this study. I understand that I may contact Margie McNeely at (780) 492-2829 or Dr. Kerry Courneya at (780) 492-1031 to answer any questions I have about this study. My consent has not been forced or influenced in any way. I consent to participate in this research study.

If I feel, at any time, that I have not been informed to my satisfaction about the risks, benefits, or alternatives of this study, or that I have been encouraged to continue in this study after I wanted to withdraw, I can call the Alberta Cancer Board Patient Representative at (780) 432-8585. The patient representative is not associated with the study.

I will get to keep a copy of this consent for information and for future reference.

(PRINT NAMES CLEARLY)

Name of Patient	Signature of Patient	Date & Time
Name of Witness	Signature of Witness	Date & Time
Name of Investigator	Signature of Investigator	Date & Time

Version: June 23, 2006

APPENDIX V-11: ETHICS APPROVAL

Alberta Cancer Board

Provincial Office
1220, Standard Life Building
10405 Jasper Avenue
Edmonton, Alberta
Canada T5J 3N4
Tel: (780) 412-4900

ACB Provincial Office
Edmonton

Tertiary Cancer Centres
Cross Cancer Institute
Tom Baker Cancer Centre

Associate Cancer Centres
Central Alberta Cancer Centre
(Red Deer)
Grande Prairie Cancer Centre
Lethbridge Cancer Centre
Medicine Hat Cancer Centre

Community Cancer Centres
Barrhead
Bonnyville
Camrose
Canmore
Drayton Valley
Drumheller
Ft. McMurray
High River
Hinton
Lloydminster
Peace River

Epidemiology, Prevention & Screening
Calgary

Medical Affairs & Community Oncology
Edmonton

Research
Edmonton

Alberta Cancer Foundation
Accepts donations in support of ACB facilities and programs.
Toll-free: 1-866-412-4222

www.cancerboard.ab.ca

ALBERTA CANCER BOARD

25 May 2005

Dr. Kerry Courneya
Faculty of Physical Education
University of Alberta

Dear Dr. Courneya

RE: **ETH-21778: A Randomized Controlled Trial of Progressive Resistance Exercise Training in Head and Neck Cancer Survivors**

The Research Ethics Board (full board) met on 8 February 2005 to discuss the above protocol. Thank you for Margie McNeely response to my correspondence dated date. I am pleased to grant approval to your participation in the above noted study on behalf of the Research Ethics Board (REB). The following documents have been reviewed and approved as of 25 May 2005:

- Protocol (5 April 2005)
- Patient Consent Form (10 May 2005)

Please note that this approval is based on the following conditions:

- a copy of the informed consent form must be given to each research subject and consent obtained prior to enrollment on the study;
- if there are any other changes to the protocol or consent form during the year, or if any serious adverse events to the treatment are found, a letter describing the changes/reactions must be forwarded to the REB as per the Alberta Cancer Board Policy J3.11b together with an updated consent form;
- an Annual Renewal form must be submitted two months prior to the deadline date of 7 February 2006 (one year from date of the convened REB meeting), containing the information as per our annual renewal form;
- a Final Report must be submitted at the termination of the project.

The deliberations of the REB included all elements described in Section 50 of the Health Information Act, and found the study to be in compliance with all the applicable requirements of the Act. The REB determined that consent will be obtained from study participants for disclosure of the health information to be used in the research.

The Alberta Cancer Board REB, complies with the following guidelines and regulations:

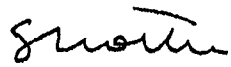
- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans;
- Health Information Act which has been proclaimed on April 25, 2001 in Alberta;

- Health Canada, as defined in C.05 (Part C Division 5) (1024-Clinical Trials) of the Food And Drug Regulations-Amendment and the Therapeutic Products Directorate Guidelines/ICH Harmonized Tripartite Guidelines-Good Clinical Practice: Consolidate Guidelines;
- National Institutes of Health-Code of Federal Regulations (USA); and
- Our institution has been approved by the Office for Human Research Protections in the United States.

Members of the REB who are named as investigators or co-investigators in research studies do not participate in discussion related to, nor vote on, such studies when they are presented to the REB.

Please accept the Board's best wishes for success in your research.

Sincerely,



Scott North, MD
Chair, Research Ethics Board

/jg

PC: Margie McNeely
CPA
Brenda Bird-Cantelon
OIPC

Health Research Ethics Board

218 Heritage Medical Research Centre
University of Alberta, Edmonton, Alberta T6G 2S2
p.780.492.9724 (Biomedical Panel)
p.780.492.0932 (Health Panel)
p.780.492.0429
p.780.492.0859
f.780.492.7800

July 5, 2005

Dr. Kerry Courneya
Faculty of Physical Education and Recreation
Van Vliet Centre P320B

Dear Dr. Courneya:

Re: A randomized controlled trial of progressive resistance exercise training in head and neck cancer survivors

The Alberta Cancer Board (ACB) REB approved the above named protocol on May 25, 2005. That approval has been accepted by the University of Alberta and by its Health Research Ethics Board, and a signed document is enclosed for your records.

The ACB REB will remain your REB-of-record.

Yours sincerely,

Judith Abbott
Senior Coordinator
Health Research Ethics Board (Biomedical Panel)

/ja
enc.