Feasibility of Monitoring Functional Capacity in patients undergoing treatment for Head and Neck Cancer

by

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Abstract

Introduction: Functional capacity is an indicator of physical fitness and overall health. Low physical fitness has been reported across the cancer spectrum; this can be addressed through exercise interventions. Functional capacity is largely unstudied in head and neck cancer patients.

Objectives: To evaluate the feasibility and safety of monitoring functional capacity in patients undergoing treatment for head and neck cancer. To assess functional capacity through the different stages of head and neck cancer treatment.

Methods: A pilot, sub-study recruiting recently diagnosed head and neck cancer patients scheduled for oncologic neck dissection. A prospective cohort of subjects underwent a series of five standard 6 minute walk tests spread over the course of their treatment. Physical activity was assessed using the self-reported Godin Leisure Time Physical Activity Questionnaire at baseline and follow-up.

Results: Twenty-seven subjects were screened for eligibility, 25 matched the criteria and underwent baseline testing. The planned 5 testing time points were pooled to 3 time points for analysis. 14 subjects were retained until the midpoint and 11 to follow-up. No adverse events were reported. No difference in functional capacity as assessed by the 6MWT was found between baseline and midpoint tests, or baseline and follow-up tests. Only 40% of participants at baseline were meeting American College of Sports Medicine recommendations for physical activity.

Conclusions: Monitoring functional capacity in head and neck cancer patients is safe. Recruitment prior to treatment is feasible; however retaining subjects to follow-up poses a significant challenge. Steps may be taken to decrease attrition through increasing flexibility of appointments and offering incentive. A larger scale trial is needed to identify factors influencing functional capacity during head and neck cancer treatment. Interventions are required to increase physical activity and functional capacity in head and neck cancer patients.

Preface

This thesis is an original work by Rhys Beaudry. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Intraoperative brief electrical stimulation (BES) for prevention of shoulder dysfunction after oncologic neck dissection" No. Pro00046671, January 7, 2015.

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Abbreviations

HNC - Head and Neck Cancer

QoL - Quality of Life

EF - Ejection Fraction

CO - Cardiac Output

SV - Stroke Volume

VO_2 - Volume of Oxygen

SD - Standard Deviation

6MW - Six Minute Walk

6MWT - Six minute walk test

6MWD - Six minute walk distance

HR - Heart rate

RPE - Rating of perceived exertion

$VO_{2\ Max}$ - Volume of oxygen metabolized at maximal exercise

Glossary

Adjuvant Therapy -	Treatment given in addition to the primary treatment
Afterload -	The load the heart contracts against at the end of systole
Chimeric -	In the case of antibodies, refers to the antibody being made out of a combination of genetic material, for example in cetuximab the antibody contains human and mouse protein.
DNA -	Deoxyribonucleic acid: the most basic genetic information encoding molecule; stores hereditary information.
Ejection Fraction -	Fraction of blood pumped from the heart each beat ((end diastolic volume – end systolic volume)/(end diastolic volume)
Lymph -	A term for body water within the lymph system; largely comprised of interstitial fluid which originates from the blood stream and additives from cellular metabolism, repair, and immune defense.
Lymph System -	Network of vessels, ducts and nodes which return lymph into the blood stream
Malignant -	Uncontrolled/unregulated growth
Metabolic Equivalent -	The amount of oxygen required per unit mass per minute at rest. Generally accepted as 3.5 ml/kg-min.
Metastases -	Spread of cancer from one region to another that is not in direct contact with the lesion.
Necrosis -	Cell death through unregulated digestion of cell components
Precancerous lesion -	An area of morphologically atypical tissue that is not yet malignant but may be more prone to becoming malignant.
Prehabilitation -	In the context of HNC will refer to the time period following surgery but prior to adjuvant treatment.
Preload -	End diastolic pressure providing ventricular stretch
Prosthetic -	An artificial replacement body part.

Purine -	Complementary binding molecule of pyrimidines in DNA
Pyrimidine Analog -	A pyrimidine is a class of specifically structured molecules, two purines are regularly incorporated into DNA and RNA each. A purine analog is a compound which shares similar structural properties but do not chemically behave similar to pyrimidine
RNA-	Ribonucleic acid: carrier of genetic information, used actively in building proteins.
Stroke Volume -	The volume of blood ejected from the heart per heartbeat. Stroke volume is equal to end diastolic volume minus end systolic volume.
Survivorship -	Any time period following the initial diagnosis of cancer.
Training -	Regularly practiced and advanced exercise repeated for the purpose of improving a given parameter.

Chapter 1: Introduction

Review of Head and Neck Cancer

Head and neck cancer (HNC) is a group of cancers arising in the oral cavity, pharynx, larynx, salivary glands, paranasal sinuses, or nasal cavity. Most commonly HNC develops as a squamous cell carcinoma; squamous cells line mucosal surfaces.[1] The most important risk factors include alcohol and tobacco use.[2] As expected with the decline in alcohol and tobacco use HNC incidence is dropping; decreasing incidence may also be attributed to screening in dental practice detecting precancerous lesions.[3] Important exceptions to decreasing incidence include salivary gland cancers for which alcohol and tobacco use are not risk factors, as well as oropharyngeal cancer rates which remain relatively stable largely due to spread of human papilloma virus, a growing risk factor.[2, 4]

HNC accounts for approximately 3% of newly diagnosed cancers. Incidence is nearly twice as high in men which reflects lifestyle risk factors including alcohol and tobacco use.[5] Prognosis is dependent on stage of diagnosis as well as cancer type; 5 year survival ranges from 24-91%.[5-7] The three most common mortalities occurring in the first five years following diagnosis are the primary cancer (29%), secondary metastasis (23%) and cardiovascular disease (21%).[7] Survival rates are increasing with earlier detection and treatment as well as advances in treatment strategies.[5]

Treatment for HNC may include surgery, radiation therapy and chemotherapy. Treatment plans are individualized and may include any or all of the three aforementioned modalities.[8]

Surgery

Surgery for head and neck cancer can typically be categorized into the primary surgery and reconstructive surgery. Reconstructive surgery may occur at the same time as the primary surgery. Several types of surgery may be used in HNC; only the most common, traditional surgical method is discussed.[8-10]

The primary surgery concerns removal of the tumour(s) as well as lymph node dissection of the neck (neck dissection). The tumour and surrounding margin is excised with care to prevent contact with cancerous tissue. Neck dissection involves searching for spread of cancer cells and metastasis down the lymphatic system; the neck lymph nodes are the most likely location for HNC to spread to. Neck dissections are performed when there is evidence that cancerous cells have spread to the lymphatics, as well as when tumour size, location and morphology indicates spread is likely, regardless of evidence from less invasive testing. Neck dissection may be unilateral or bilateral. Extent of dissection is determined by where/if cancerous cells are found; the neck is divided into 6 levels, 1 being the most superior, 6 the most inferior. Dissection in levels 2 and 5 may cause damage to the spinal accessory nerve (cranial nerve XI), consequences are reviewed below.[8, 10, 11]

Reconstructive surgery can have cosmetic as well as functional purposes. Functional purposes include, but are not limited to improving ability to breathe, speak or swallow. Tissue may be harvested from a different part of the patients' body and grafted in place of removed tissue. This is known as a flap; grafts may be soft tissue or bone. Prosthetics may also be used.[8, 10, 12]

Radiation

Radiation therapy involves use of focused beam of high energy radiation to damage cancerous cells beyond repair, inducing necrosis. In HNC typically external beam therapy is used; externally generated radiation is passed through the tumour in a concentrated beam, no radioactive material is left in the patient. Radiation beams are aimed from several angles to maximize the dose received by the tumour while minimizing non-malignant tissue exposure. Special efforts are made to preserve sensitive or important tissue such as the brain, salivary glands, or marrow.[2, 8, 10, 12, 13]

Radiation therapy may be used alone or in combination with surgery and/or systemic adjuvant therapy. Neo-adjuvant (prior to surgery) radiation may be used to shrink the tumour before excision. Adjuvant radiation is used to kill residual cancerous cells following surgery. Radiation potentiates cytotoxic effects of chemotherapy. Radiation alone may be used to treat early stage HNCs, more progressed cancers require multiple treatment modalities.[8, 10, 12-14]

Newer radiation therapy strategies include intensity modulated radiation therapy and TomoTherapy Image-Guided Radiation Therapy. Strategies focus on delivering higher doses of radiation specifically to the cancerous tissue while decreasing unwanted radiation exposure of non-cancerous cells.[8, 15]

Systemic Adjuvant Therapy

Several chemotherapy agents may be used in the treatment of HNC. Chemotherapy is used in combination with surgery and/or radiation therapy in late stage cancers; chemotherapy alone is rarely used. The most commonly administered chemotherapeutic agents are platinum based regimens such as cisplatin given in combination with a taxane and fluorouracil. Methotrexate, bleomycin and cetuximab are used less often.[8, 10, 12, 13]

Cisplatin is a platinum based drug that forms crosslinks in DNA. This can cause irreparable breakages in DNA, preventing cell replication.[16] Fluorouracil is a pyrimidine analog antimetabolite which creates a terminal end during RNA synthesis preventing protein synthesis.[17] Taxanes stabilize tubulin dimers preventing the disassembly of microtubules. Disassembly of microtubules is essential for cell division.[18] Methotrexate prevents purine synthesis which stops DNA synthesis when the cell has exhausted its supply of purines.[19] Bleomycin is an antibiotic that induces DNA strand breaks; cancerous cells often have aberrant DNA repair mechanisms making them unable to cope with bleomycin induced damage.[20] Cetuximab is a chimeric monoclonal antibody targeted for epidermal growth factor receptors. The drug binds these receptors to prevent cell replication.[21] Chemotherapy drugs are best suited for damaging rapidly dividing cells; adverse effects are often related to toxicity of healthy rapidly dividing cells or tissue that may receive excessive exposure as discussed below.[8]

Consequences and Complications

Treatment of HNC can have several consequences and complications. Although some consequences are unavoidable, steps are taken to minimise risk of complications. Consequences/complications are discussed briefly and are not limited to what are discussed below.

Surgical procedures have consequences and complications typical of major surgeries as well as more specific implications. Only aspects following surgery are discussed; it should be acknowledged that the surgical procedure itself has several associated risks.

First, consequences and complications attributed to any major surgery are reviewed. Subjects may be confined to their bed for a number of days following surgery; this detrimentally affects the cardiovascular system and increases risk of cardiovascular events.[22, 23] Mobilisation is encouraged as soon as possible to minimize risk.[24] Drains may be inserted at the area of the incision that help remove excess fluid from the wound. Stitches or staples may be used to close the wound as well as for securing flaps. Drains are typically removed after 2-7 days and stitches/staples after 7 days. The wound is kept clean and dressings are regularly changed to reduce risk of infection.[25-27] Care must be taken to not reopen the wound; this includes restricting lifting and certain movements.

Consequences and complications specific to HNC surgery include nerve damage and swallowing and breathing issues. The spinal accessory nerve may be damaged during neck dissection that results in muscle atrophy and shoulder dysfunction.[12, 28] The spinal accessory nerve innervates the trapezius and sternocleidomastoid muscles which are required for proper shoulder and neck function; without the trapezius the scapula may be pulled downward and in an anterolateral direction creating a condition known as shoulder droop. Shoulder droop may lead to impingement, pain and discomfort.[29] Physiotherapy may be used to preserve shoulder health or compensate for muscle deficits while nerve recovery takes place.[30] Maximal nerve recovery typically occurs within 18 months, however, the nerve may never fully recover.[31] Recovery following surgery may be complicated by nutrition deficits. Surgery may make eating and swallowing difficult; without proper nutrition healing may be impaired.[32] To circumvent this issue, patients may have a feeding tube inserted. The feeding tube may pass through the abdomen into the stomach (PEG tube) or through the nose (nasogastric tube). Feeding tubes ensure adequate nutrition.[33, 34] PEG tubes make patients more prone to herniation after removal; patients are advised against heavy lifting.[35] The benefit of feeding tube use is in question; feeding tubes have been associated with higher mortality. However, directionality of the relationship has not been established; typically feeding tubes are used in more severe cases of weight loss which confounds the association. Although feeding tubes ensure adequate nutrition, concern exists that ability to swallow may be lost or worsen the longer a tube is left in.[36, 37] Returning to normal eating patterns may be further complicated by damage to or removal of salivary glands as well as jaw stiffness limiting jaw opening.[8] Swelling from the surgery may require the insertion of a tracheostomy tube to permit breathing. Tracheostomy tubes may be removed once swelling has subsided; while the tube is in patients are unable to speak and their airways may easily dry or become irritated.[38] Laryngectomies share similar consequences to tracheostomies, however consequences are permanent.[12]

Radiation therapy can elicit several adverse effects. Effects are generally related to radiation damage to exposed tissue. This includes damage to the throat, salivary glands, tongue, joints, muscle and skin; resulting in a sore throat and difficulty swallowing, dry mouth, loss of taste, tight joints/muscles and thin, fragile skin. Side effects of radiation can create nutrition problems through nausea and impaired swallowing and jaw movements. Radiation therapy can impair wound healing as well as immune function placing patients at a higher risk of infection.[8, 39] More than 50% of patients undergoing radiation therapy experience fatigue. Fatigue has been reported as the most debilitating treatment side effect.[40] Exercise has proven efficacy in reducing patient reported fatigue.[41] Fatigue however, presents a considerable barrier to participation in exercise. This can lead to deconditioning and exasperation of fatigue.[40, 42]

Systemic adjuvant therapy is used less in the treatment of head and neck cancer because of its poor risk/benefit ratio as compared to surgery or radiation. Chemotherapy has high rates of adverse effects which may be severe and potentially life threatening. However, given certain scenarios, benefits of chemotherapy outweigh risks such as in later stage cancers. Undesired effects of chemotherapy may include myelosuppression (marrow damage) which may lead to anemia and impaired immune function. Gastrointestinal toxicity, or sloughing of cells lining the digestive tract can cause excessive bleeding, malabsorption of nutrients, and ulceration including painful sores in the mouth. This in combination with nausea and vomiting may further compromise nutrition through reduced eating. Chemotherapy drugs may cause liver, kidney and nerve damage. Liver and kidney damage may impair patients' ability to excrete drugs and toxins as well as interfere with normal physiological processes. Nerve damage may result in glove and stocking pattern numbness and hearing and balance loss. Cardiotoxicity is a major concern of several agents; both immediate and delayed cardiotoxic effects pose life threatening consequences. Other effects of chemotherapy include impaired ability to think ("chemo brain"), skin damage at the injection site and impaired wound healing. Patients may have their regimen or dose changed or stopped if drugs are not well tolerated.[8, 10, 12, 13, 43]

Review of Aerobic Capacity

Aerobic capacity is a measure of physical fitness which may be quantified in several ways. Beyond physical fitness, aerobic capacity is a good indicator of overall health making it a relevant clinical measure. This is because aerobic capacity relies on integration of several factors including cardiovascular and pulmonary health, height, weight, body composition and muscular strength and endurance.[44-47]

Several studies have demonstrated that higher aerobic capacity is strongly correlated with lower all-cause mortality across diverse patient spectrums. Myers et al (2002) report that aerobic capacity is inversely correlated with risk of cardiovascular events. Furthermore, a 1 metabolic equivalent increase in aerobic capacity is associated with a 12% decrease in all-cause mortality in men.[48] Similar results have been ascertained in healthy women, heart failure patients and cancer survivors.[49-53]

A number of physiological factors are known to affect aerobic capacity. These factors can be broadly categorized into cardiac, muscle and hemodynamic parameters. Briefly; the greatest contributing cardiac parameter is cardiac output. Cardiac output is the product of heart rate and stroke volume, each of which are affected by a myriad of physiological factors. Stroke volume can be increased through training, however, maximal heart rate decreases with age and is largely unaffected by training. Oxidative capacity of the muscle and muscle mass are also important to consider. Training can induce muscle hypertrophy as well as increase the oxidative capacity by increasing the concentration of mitochondria. Hemodynamic parameters include the hematocrit levels, vascularization and vascular health. Training has limited effect on red blood cells' affinity for oxygen and ability to unload oxygen but is important for improving vascular health and increasing hematocrit and vascularization.[54, 55]

Exercise training can be used to increase aerobic capacity; how exactly this occurs has not been fully elucidated. The general principle is that the body adapts to be better suited for the stress it faces. Exercise stresses the body by increasing energy demand; as a result adaptations make the body better suited to meet oxygen demands required to match the energy needs of exercise. This occurs through the physiological factors briefly discussed above.[54, 55]

Statement of the Problem

Advances in HNC care, from earlier diagnosis to improved treatment, continue to increase survival; thus there is greater need for planning care into survivorship. Several aspects of HNC including disease, treatment, and treatment related effects may detrimentally affect fitness.[8] Samuel et al 2013 demonstrated that functional capacity declines over the course of HNC treatment and can be attenuated or reversed with exercise.[56] It has been established that exercise is a useful treatment modality in improving survival from cancer, reducing all-cause mortality and increasing physical functioning and quality of life; improving fitness is thus a relevant clinical and patient concern.[57, 58]

Few studies exist concerning exercise in HNC survivors making the group largely understudied. As a result caregivers have limited directly relevant research to create tailored exercise recommendations for patients. However, given the wealth of research in other cancer groups an efficient, systematic approach may be taken in creating the best exercise guidelines. To begin, studies using other cancer patient populations are now showing pre-treatment interventions have the greatest impact on health and QoL. It is currently unknown whether a time period for a prehabilitation intervention exists in HNC patients.[59-61]

Research Question

We examined whether HNC patients were able to undergo exercise testing through their course of treatment as well as tracked changes in physical fitness as an indicator of overall health. Results may be applied to optimize timing of future exercise interventions in relation to treatment to maximize benefits.

The primary objective of this study was to test the safety and feasibility of functional capacity testing during early HNC survivorship. The ability of HNC patients' to complete exercise through the different stages of cancer treatment is unknown. Results from testing will provide an indication of patients' ability to exercise.

The secondary objective of the study was to determine the extent and rate of functional capacity decline among HNC survivors undergoing cancer treatment. The primary outcome was change in functional capacity over time as measured by the distance walked in 6 minutes. Secondary outcomes included adherence to testing, safety/adverse events as well as subgroup analysis of functional capacity (surgery only versus radiation/chemotherapy plus surgery). These data are indicative of timing and feasibility of a prehabilitation intervention. Cancer treatment completion rates were monitored including delays, reductions or changes in treatment plans. Monitoring treatment aspects gives an indication of potential cost benefit of an intervention.

Hypothesis

Hypotheses related to Feasibility:

1. We hypothesized that subjects would complete 90% of tests.
2. We hypothesized that 6MWTs would not precipitate any adverse events

Hypotheses related to Study Outcomes:

1. We hypothesized that functional capacity would decrease during adjuvant head and neck cancer treatment.
2. We hypothesized that the greatest declines in functional capacity would be seen during the last 2 weeks of adjuvant cancer treatment.
3. We hypothesized that the greatest declines in functional capacity would be seen in subjects undergoing concurrent adjuvant chemoradiation when compared to subjects undergoing surgery-alone or surgery followed by adjuvant radiation therapy.

Limitations

This study has several limitations inherent to its design. The study was designed as a feasibility study so the sample size was relatively small. The small sample size limits what trends can be detected. Other limitations include self-reported physical activity levels and the self-paced 6 minute walk test for quantifying functional capacity.

One limitation of the study which is inherent to many exercise related studies is the inability to blind participants. A Hawthorne effect is possible in which subjects' increase physical activity levels because they are aware that their physical fitness is being monitored. The Godin leisure-time exercise questionnaire was administered to identify changes in exercise habits.

The Godin leisure-time exercise questionnaire is a reliable and sensitive tool used to quantify an individuals' physical activity level.[62, 63] Despite validation across diverse patient spectrums, the question still remains; can/do patients accurately report their physical activity. Pedometers or metabolic arm bands have been regarded as objective measurement tools that are not vulnerable to self-report bias.[64] Pedometers and metabolic arm bands however are subject to Hawthorne effects in which subjects may exercise more because they are aware their physical activity is being monitored. Despite weakness in both methods for accurately quantifying physical activity, using change scores circumvents over or underreporting, assuming the subject reports in a consistent manner. The Godin questionnaire is then the logical measurement tool given its ease of administration, time and cost.

The 6 minute walk test contains subjective aspects in quantifying functional capacity.[65, 66] Directions for the test are generally ambiguous in that subjects are asked to cover as much distance by walking in 6 minutes as possible. No definition is provided for what constitutes walking versus jogging or running, and many patients walk at a pace that is comfortable, not one that is ventilation, fatigue, or symptom limited. Thus, decreases in functional capacity may not be reflected by distances walked in 6 minutes at a comfortable pace. Furthermore, learning effects may inflate repeated 6MWT scores and distances may vary depending on how the subject feels on the day of testing.[67] Despite these problems inherent to the 6MWT, the test is safe, easily administered, quick, and inexpensive, which from a feasibility standpoint permits a greater number of tests.[68] Procedures must remain standardized to preserve the integrity of the test. Recruiting more subjects and measuring functional capacity at multiple time points helps account for variability of effort and interpretation of instructions.

This is a sub-study under the study "brief electrical stimulation for prevention of shoulder dysfunction after oncologic neck dissection". This creates an additional limitation; any effect from brief electrical stimulation may affect functional capacity. It is unlikely that BES will have any direct effect on functional capacity; however, improvement in shoulder function may translate to improved gait efficiency during 6MWTs as well as increased physical activity in daily living.

Ethical Considerations

Consent was obtained from the Health Research Ethics Board of the University of Alberta under the parent study application entitled "Brief electrical stimulation for prevention of shoulder dysfunction after oncologic neck dissection". Subjects were asked to sign a consent form which outlines risks and benefits of the study, confidentiality, and withdrawal. As the 6MWT is self-paced exercise it should pose no health risks greater than activities of daily living. Safety precautions include monitoring heart rate, perceived exertion, hemoglobin oxygen saturation and blood pressure before, during, and following tests to monitor appropriate physiological response to exercise and recovery. Tests were not conducted if resting heart rate was >120 bpm, systolic blood pressure >145 mmHg or diastolic blood pressure was >100 mmHg. Tests were terminated if the subject reports dizziness, excessive fatigue, or pain. Patients were free to rest during the test if required. Medical personnel were present for testing. Patients were free to withdraw from the study at any time; all personal and medical information were kept anonymous. This study may not directly benefit participants, but has very minimal associated risk and patient demand. This study may make participants aware of the importance exercise for their health. Potential benefits from this research will be received by future HNC patients.

Chapter 2: Literature Review

Scope

The three leading causes of death in Canada are cancer, heart disease and cerebrovascular accident, which when combined account for more than 60% of all deaths.[5] Each of these diseases has been the study of extensive research in identifying strategies for treatment, prevention and long term care. Research continues to investigate ways of lessening economic and patient burdens, including ways of identifying at risk individuals so that interventions may be better targeted. Importantly, these diseases often cluster together and share comorbidities.[69]

One treatment that has been beneficial across disease spectrums is exercise, specifically, aerobic exercise.[70] Recommendations are in place that all individuals should exercise, however, adherence to these recommendations is poor.[71] Exercise is of particular importance in the chronically diseased and the best exercise prescription may not be the same for different chronically diseased groups versus the healthy. For this reason research should be conducted to create the best tailored exercise recommendations.[72]

Measuring Aerobic Capacity

Aerobic capacity can be quantified using a number of methods. For this study the 6MWT was used. In this section the 6MW and $VO_{2\ Max}$ tests will be reviewed and discussed.

$VO_{2\ Max}$ Test

$VO_{2\ Max}$ tests are accepted as the gold standard for measuring aerobic capacity. This test objectively quantifies aerobic capacity by measuring the maximal volume of oxygen that can be metabolized.[54] This is achieved at maximal exercise requiring the use of at least 60% of total musculature while breathing air at sea level.[46] Tests typically increase workload until a combination of the following criteria are reached: plateau in oxygen consumption with increasing workload, respiratory exchange ratio greater than 1.15, heart rate within 10 beats/minute of the subject's age predicted maximum and rating of perceived exertion greater than 16/20. If criteria for a maximal test are not satisfied the result is deemed a $VO_{2\ Peak}$, this is the case in symptom limited tests as well as cycle ergometer tests.[46]

The Fick equation can be used to calculate VO_2 and reveals factors influencing aerobic capacity:

$$VO_2 = CO \times (C_a - C_v)$$

When CO is cardiac output in ml/min, C_a is the arterial concentration of oxygen and C_v is the venous concentration of oxygen.[73, 74] CO can be calculated:

$$CO = SV \times HR$$

When HR is heart rate and SV is stroke volume which is equal to the difference between end diastolic volume and end systolic volume.[54, 73] The concentration of oxygen can be calculated using the equation:

$$Oxygen\ Content = 1.36 \times (Hb) \times O_2^{Saturation\ Fraction} + 0.0032 \times P_{Oxygen}$$

When Hb is hemoglobin concentration in g/dl, 1.36 is a constant value of ml of O_2/g of Hb, and P_{Oxygen} is the partial pressure of oxygen in torr. Multiplying P_{Oxygen} by 0.0032 gives the amount of dissolved oxygen not associated with hemoglobin.[54] Thus several factors influencing aerobic capacity are presented, each of which will be briefly reviewed in the context of maximal exercise.

At maximal exercise both heart rate and stroke volume are at their greatest values. Maximal heart rate declines with age and in most cases is unaffected by training.[75] Exercise training can increase stroke volume; increases are an integration of several contributing factors.[76] Chronic exercise loads the heart providing stimuli which cause physiological hypertrophy of cardiac muscle and expansion of heart chambers. Expansion of heart chambers allows the heart to hold a greater volume of blood, and hypertrophy of cardiac muscle preserves ejection fraction. Exercise also helps to improve vascular health and relaxation and provides stimulus for angiogenesis, growth of new vasculature. These factors contribute to decreased peripheral vascular resistance, which relating back to stroke volume, mean lower afterload. More blood can be ejected from the heart due to the decreased pressure/resistance the heart pumps against. [54, 73] Furthermore, improved vascular health also increases venous return, or preload. The heart not only enlarges to increase its absolute capacity, but improved vascular health through increased preload and decreased afterload increase the efficiency of the heart.[54, 73]

The second half of the Fick equation deals with oxygen carrying capacity and extraction which also influence aerobic capacity. Oxygen carrying capacity is almost entirely dependent on concentration of hemoglobin in healthy individuals. Blood is completely saturated with oxygen as it passes through the lungs, even at maximal exercise when transit time through the lungs is greatly decreased.[54, 77] Exercise training can stimulate an absolute increase in hemoglobin. Importantly, aerobic training can stimulate an expansion of blood plasma volume which decreases the hematocrit percentage. This decrease in hemoglobin concentration does not decrease oxygen delivery; it is more than compensated for by cardiac output parameters discussed above. [54, 73] Muscle oxygen extraction is increased by aerobic exercise training. This is accomplished in part through longer blood transit time in active muscle related to greater vascularization, as well as through increased muscular capacity for oxygen use. Training can increase the amount of muscle, as well as increase the concentration of mitochondria per muscle cell.[54, 73]

6 Minute Walk Test

The 6MWT provides an alternative in aerobic capacity testing and actually tests functional capacity.[66, 78] Functional capacity is a measure of endurance; in the case of the 6MW, it is measured by the distance walked in meters. Subjects are asked to walk as far as possible on a set course in 6 minutes. This requires sustained muscular and cardiovascular output which relates to several of the same factors affecting aerobic capacity. Aerobic and functional capacity are well correlated,[79] but more importantly both are good markers of cardiovascular and overall health.[80-82]

The relationship between aerobic capacity and functional capacity as measured by $VO_{2\ Max}$ and 6MW tests respectively is imperfect.[79] If criteria are met for a $VO_{2\ Max}$ the result is an objective measure of aerobic capacity; in contrast the functional capacity measure provided by a 6MWT has several subjective elements. Similar subjective elements are shared in submaximal as well as $VO_{2\ Peak}$ tests. Distance walked in a 6MWT is heavily dependent upon volitional effort which is related to factors discussed under $VO_{2\ Max}$ as well as gait efficiency, turning efficiency and experience. Volitional effort can be defined as how hard a subject works during their test. This can be measured using the Borg Rating of Perceived Exertion (RPE) scale which asks subjects to rate how hard they are working on a scale of 6-20.[83] RPE is correlated well with workload and heart rate.[83]

Guidelines for administering the 6MWT are generally ambiguous. Patients are asked to walk as far as possible in 6 minutes; pace is self-determined by the subject and the subject is permitted to rest or take breaks as needed.[84] Experience plays a critical role in this situation because untrained subjects do not know the limits of their exercise capacity or what pace they can maintain for 6 minutes. As one may expect, in consecutive tests subjects improve their scores as a result of practice rather than improving their fitness.[85] It is unknown how long apart tests must be for the learning effect to be null.[67]

Subjects not accustomed to exercise may perceive exertion as discomfort. This can be reflected in low RPE scores which suggest the subject is underachieving.[86, 87] Training can acclimate subjects to exercise as well as increase their absolute functional capacity.[88] With increased functional capacity the same workload should be perceived as less tasking. A change in distance without a change in RPE scores may then reflect a change in functional capacity. A decrease in RPE scores without change in distance may reflect an increase in functional capacity, while an increase in RPE scores and an increase in distance may reflect better body awareness.

Training can also improve gait and turning efficiency.[89] Gait efficiency can be a limiting factor if the patient is walking at their peak functional capacity; furthermore, a more efficient gait at a given speed may be related to a lower RPE. It is important to consider that without training there is variation across gait efficiency; some individuals expend less effort to walk faster. This is also related to a subject's' comfortable speed of walking; in the scenario that a subject is limited by volitional effort, less efficient gait would be related to shorter distances. Turning speed plays a minor role in scores, but notably faster turners have more time devoted to walking, and faster walkers must turn more than slower walkers. In theory then, the longer the course the more closely the distance score reflects functional capacity. Standardizing the course ensures all participants experience the same sharpness and number of turns given the same walking speed.[90, 91]

Despite producing lower quality data as compared to $VO_{2\ Max}$ testing, 6MWTs are tremendously useful and have several advantages. Firstly, the test is self-paced and does not require maximal cardiac stress; precipitation of adverse events is unlikely, making the test safe. Secondly, no specialized equipment or trained personnel are required. This makes the test inexpensive and easily administered; the test is widely used clinically. Lastly, the test is very brief; the entire testing procedure can be completed in 21 minutes (baseline, test and recovery). As a result population norms have been well established so subjects can be easily compared. Enright and Sherrill created regression equations for the expected 6MW distance (6MWD) in healthy adults:

$$6MWD \text{ for men} = (7.57 \times height) - (5.02 \times age) - (1.76 \times weight) - 309 \text{ m}$$

$$6MWD \text{ for women} = (2.11 \times height) - (2.29 \times weight) - (5.78 \times age) + 667 \text{ m}$$

When height is measured in cm, weight in kg and age in years.[92]

Aerobic Capacity in Head and Neck Cancer

As discussed above, several factors influence aerobic capacity as well as functional capacity. These variables will be discussed below as they relate to 6MW scores and HNC/treatment.

Muscle Mass and Body Composition

One serious consequence of HNC and treatment is marked cachexia. This can be related to inadequate nutrition but is also related to cancer, treatment and fatigue. Given adequate nutrition patients continue to lose lean body mass but gain weight.

The cancer itself may prevent proper nutrition. Tumours can make swallowing difficult and eating unenjoyable.[93] This can result in a caloric deficit, which particularly in lean patients can result in muscle wasting.[94] Treatment can further complicate this matter. Depending on the location of the cancer, patients may have salivary glands, parts of their tongue, jaw or soft palate removed. [95-97] Surgery can also damage nerves controlling the jaw, tongue and facial movements. Radiation damages salivary glands and can cause nausea and tissue and joint stiffness. Chemotherapy can cause painful ulcers in the mouth and severe nausea. All of this culminates to poor physical ability to take in nutrition as well as diminished appetite; to make matters worse healing creates an incredible energy demand, further exasperating the deficit.[95-97]

Overall subjects lose lean body mass and decrease their lean body mass to body mass ratio. Without appreciable changes in the cardiovascular system it should be expected that muscular fatigue may become a limiting factor in functional capacity; this may manifest through a greater RPE at lower workloads. Because of the marked cachexia, resistance exercises may play a critical role in regaining functional capacity in HNC survivors.[98]

Notably, no research currently exists looking at vascularization or cardiovascular changes in HNC. The best method for restoring functional capacity is currently unknown.

Oxygen Absorption

Typically aerobic or functional capacity is limited by cardiovascular parameters, specifically stroke volume. However, several chronic diseases exist in which limitations are imposed by the pulmonary system, HNC being one.[54] Restrictive and obstructive pulmonary disease can cause ventilation limitations, both of which may be present in HNC. The tumour can narrow the airway creating a restriction. Chronic obstructive pulmonary disease (COPD) is common in HNC patients because smoking is a risk factor for both diseases.[99] COPD decreases ventilatory ability and reduces diffusion capacity for oxygen from the lung into the bloodstream.[100] HNC patients may then be limited by dyspnea which can be reflected by their 6MW and RPE scores, or more objectively by decreased hemoglobin saturation following exercise.

Oxygen Delivery

Chemotherapy can cause myelosuppression.[101] As the marrow is damaged less red blood cells are produced resulting in anemia.[102] This decreases the oxygen carrying capacity of blood which decreases delivery. Chemotherapy may also detrimentally affect vascular health. Vessels may have reduced ability to dilate and ability to grow new blood vessels may be diminished.[103] Less blood can be delivered to active muscle.

Lifestyle

Risk factors for HNC include but are not limited to: alcohol and tobacco use, high BMI and physical inactivity.[2] These risk factors are shared across many chronic diseases and HNC is often accompanied by comorbidities.[69] Some common comorbidities include obesity, arthritis, hypertension, metabolic syndrome, diabetes and COPD. All of these comorbidities may present barriers in participating in physical activity.[5] Without regular participation in physical activity functional capacity declines. Further, the lack of physical activity may exacerbate the disease state such as weight gain in obesity overloading joints leading to pain, and increased effort required to move body weight.

Surgery

Some HNC surgeries require a bone flap to replace excised bone in the jaw. The flap is harvested from the fibula. Limited research has been conducted on how this relates to gait or functional capacity. Findings by Kirwil et al (2013) suggest impaired gait which is fully restored 3 months following surgery.[104] Shorter 6MWD's in these patients may not reflect decreases in aerobic fitness.

Spinal accessory nerve function is often compromised following surgery. This results in shoulder droop and dysfunction which may impair gait efficiency.[105] A shorter 6MWD may then reflect impaired gait without change in functional capacity. Notably, shoulder dysfunction may also result in decreased physical activity levels.

Chapter 3: VO_2 Meta Analysis

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Effect of supervised exercise on aerobic capacity in cancer survivors: Adherence and workload predict variance in effect

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Introduction

The burden of cancer continues to increase worldwide due to population growth and aging[1]. More effective cancer screening and novel treatment therapies have resulted in improved detection, earlier treatment and better disease free and overall survival, with the numbers of cancer survivors growing disproportionately to the number of new cancer cases and deaths[2]. Many cancer survivors experience symptoms and side effects related to their cancer or cancer treatment. As many of these effects go undetected and/or untreated, the survivor is placed at increased risk for other health issues such as declining functional status and cardiovascular disease[3,4]. As a result, there is an emerging need for the integration of services and interventions to address the long-term health of survivors[3].

Exercise training is gaining recognition as an important intervention to address acute, late and long-term effects of cancer, and is becoming more widely acceptable as confidence in safety is now established. Importantly, evidence is accumulating to support the benefit of exercise to improve the physical functioning and quality of life of survivors. Currently, the optimal exercise prescription is unknown and the effect of variations in exercise training parameters on cancer-specific outcomes are poorly understood[5]. Therefore, questions remain over how to best tailor exercise prescriptions to optimize the health outcomes of survivors at different times through the cancer continuum[5].

Cardiorespiratory fitness, measured objectively as the highest oxygen consumed during maximal aerobic exercise, provides a means to evaluate associations with disease outcomes. Aerobic capacity is inversely related to the risk of a cardiovascular event and all-cause mortality in healthy individuals and cancer patients[6-10]. Aerobic capacity is best increased by habitual aerobic exercise training that is of a moderate-to-vigorous intensity[11].

Aerobic capacity (VO_{2max}) is the maximum volume of oxygen that the body can consume during maximal exercise, using at least 60% of the musculature, and while breathing air at sea level[12]. This volume is expressed as an absolute rate in litres per minute (L/min) or as a relative rate in millilitres per kilogram of bodyweight per minute (mL/kg per minute). VO_{2peak} is the term used most commonly in clinical populations when a true maximal value is not attained[12]. For example, the test is described as VO_{2peak} rather than VO_{2max} when the test is carried out on a cycle ergometer (bike) rather than a treadmill, or when the highest value reached on the test is limited by the participant’s symptoms.

A meta-analysis by Jones and colleagues included data from six randomized controlled trials (RCTs) and reported a significant benefit from supervised aerobic exercise training, compared with usual care, on VO_{2peak} (2.90 mL/kg per minute; 95%CI: 1.16, 4.64; P = 0.01)[13]. However, statistical and clinical heterogeneity was found among the exercise trials included in their review, leading them to recommend further research to build on and extend the current knowledge in the field. Since this publication, a number of newer studies have been published. Given this amount of new data, we contend that an updated review is warranted.

The primary purpose of this meta-analysis was to examine the efficacy of supervised aerobic exercise training programs on VO_{2peak} in survivors of cancer. Quality of life was analyzed as a secondary outcome measure. As well we aimed to explore heterogeneity in study findings through subgroup analyses and meta-regression where appropriate.

Materials and Methods

The review conforms to the requirements of PRISMA reporting standards. The published protocol for the review can be found at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006215#.U1cOnle9aw).

Inclusion Criteria

Studies were considered eligible for inclusion if they were RCTs comparing supervised aerobic exercise training with 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[14]. Studies with an additional treatment arm or combined intervention (*e.g.*, exercise with diet modification) were included only if the effects of exercise could be isolated. A priori, we excluded reports that were available only in abstract form.

Trials were included if they involved adults (17 years and older) diagnosed with cancer who were actively receiving cancer treatment or off treatment. Included studies were required to measure maximal, peak, or estimated maximal oxygen consumption ($VO_{2max/peak}$) as a study outcome.

Systematic Search

A search was performed of the databases including OVID MEDLINE (1948 to October 2013), PubMed (1975 to October 2013), SCOPUS (1950 to October 2013), Web of Science (1950 to

October 2013), EMBASE (1988 to October 2013), Cochrane Central Registry of Controlled Trials (1991 to October 2013), and LILACS (1982-October 2013). The search strategy was developed and approved by a librarian with extensive database searching knowledge and experience. We searched terms related to cancer (*e.g.*, neoplasms, tumor), exercise (*e.g.*, exercise, exercise therapy/or motion therapy, aerobic training), publication type (*e.g.*, random allocation, clinical trial), and aerobic capacity (*e.g.*, VO_2). The search strategy was modified as necessary for each database. Non-English language publications were eligible for inclusion. To locate unpublished research, we reviewed clinical trial registries and websites housing theses and dissertations. Fourteen experts in the field of cancer and exercise were contacted in order to identify any research that was not published or was pending publication. Table 3.1 includes an example of the MEDLINE search strategy.

Coding and Reliability

The titles and abstracts were screened for eligibility by two independent evaluators (C.K. and R.B.), and coded for exclusion or potential inclusion. Potentially eligible manuscripts were obtained and the same evaluators performed a second round of screening to evaluate full eligibility criteria. Any disagreements were resolved by consensus (C.K., R.B., and M.M.). The two evaluators (C.K. and R.B.) then independently abstracted data on study participants, the intervention and control (usual care) protocols, and study outcomes, and assessed for quality. Studies were evaluated using the quality assessment framework for RCTs developed by the Cochrane Collaboration[[15]] to assess risk of bias in the individual studies. Sensitivity analyses were conducted to examine the effect of including studies with high risk of bias.

For the purpose of evaluating exercise prescription variables, exercise intensity was standardized to a single $\%VO_{2max}$ value[[16-18]]. For studies that used $\%VO_{2max}$ as the intensity prescription the average of the range was used; time spent at different intensities was factored in to create the mean value. High intensity intervals were weighted at 50% of the contributing time. Resistance exercise was not included in intensity ratings. Total exercise workload, or intensity-minutes, was calculated by multiplying the exercise intensity by the prescribed exercise volume (program duration, minutes per session and sessions per week).

Study Outcomes and Effect Size Calculation

Study results were pooled using random effects models. For continuous outcomes, pooled statistics were calculated using mean differences (MD) when data were on a uniform scale and using standardized MD (SMD) when data were on different scales. All results were calculated with 95%CI. The SMD was interpreted as 0.2, 0.5 and 0.8 representing small, medium and large effects on outcomes respectively[19]. Statistical heterogeneity was assessed using a χ^2 test that considered a *P*-value of less than 0.10 to indicate significant heterogeneity. I^2 values, ranging from 0% (homogeneity) to 100% (heterogeneity) were also calculated to quantify variability in study effect and values of 25%, 50% and 75% were used to describe low, moderate and high heterogeneity respectively[20]. Subgroup analyses and multiple regression moderator analyses were performed to explore and explain heterogeneity among studies. A priori subgroup analyses included examining the pooled effect estimate by level of supervision of exercise (group or individual), the timing of the intervention (on or off treatment), and cancer type. Meta-regression was performed to explore exercise variables of frequency, time, intensity, duration and adherence on effect estimate.

Statistical Analysis

A biomedical statistician (Y.L.) provided oversight on the statistical methods, and performed the meta-regression analyses. All data were entered into Review Manager 5.2 and analyzed with SPSS v15 software utilizing meta-regression scripts created by Lipsey and Wilson and Stata/SE (version 13.0)[21]. Figures were created using Comprehensive Meta-Analysis (version 3: http://www.meta-analysis.com/index.php).

Results

Methodological Characteristics

The search protocol yielded 1269 eligible studies; after removal of duplicates and screening of abstracts, 23 studies remained. Reference tracking and contacting of experts accounted for 4 additional studies. Grey literature and trial register searches yielded no further articles. Full text review of the 27 studies excluded a further 9, leaving 18 studies for qualitative and quantitative synthesis[22-39]. One study was not used for the quantitative analyses due to missing data[32] and one study was divided into two comparison groups as it involved both on and off treatment subgroups[27] (unpublished data provided by author). The remaining 17 studies, generating 18 comparisons, were included in the meta-analyses (Figure 3.1). Kappa statistics for the inclusion of studies was 0.9 ($P < 0.001$). Following discussion there was 100% agreement in scores between evaluators.

Risk of Bias

In general there was high or unclear risk of bias for selection (allocation concealment) and detection bias (lack of blinding of outcome assessors) and low risk of bias for attrition (handling of incomplete data) and reporting bias (outcome reporting) among the included studies (Figure 3.2). Sensitivity analyses were performed after excluding studies with a high or unclear risk of bias for allocation concealment ($n = 10$)[24,31-39] and for use of blinded outcome assessment ($n = 11$)[24,26,27,31-36,38,39]. The results showed minimal differences in the pooled effect estimates for aerobic capacity based on risk of bias. For allocation concealment, the pooled effect estimate increased by 0.6 (SMD: 0.80; 95%CI: 0.51, 1.25) whilst for blinding of outcome assessment the estimate decreased by 0.4 (SMD: 0.7; 95%CI: 0.35, 1.05). After excluding studies with a high or unclear risk of bias for any factor ($n = 13$), the pooled effect estimate decreased by 0.8 (SMD: 0.66, 95%CI: 0.22, 1.11).

Cancer Survivor Characteristics

The 18 included studies involved 1149 participants of which 576 were randomized to receive an aerobic exercise intervention and the remaining 573 received usual care or no exercise. Participants were on average 53 years of age and 76% were female. Survivors of breast cancer were most commonly studied in both breast cancer specific trials and mixed cancer type trials (14 studies)[22-26,28,29,33-39] accounting for 686 participants (60%) of the total participants in the review. Further details on the included studies are provided in Table 3.2.

Exercise Intervention Characteristics

Ten studies consisted exclusively of aerobic exercise training[23-27,29,30,33,34,38], six studies included a resistance exercise component with or without flexibility training[22,28,31,36,37,39], one included physiotherapy exercises and relaxation[35], and one included flexibility training plus a dietary intervention[32]. Exercise interventions consisted primarily of cycling[23-31,34,39] or walking/jogging[23,24,32,35,37-39]. Five studies[22,23,28,35,38] offered exercise programs in a class setting (group exercise format) and the remaining 13 studies[24-27,29-34,36,37,39] were individualized exercise programs, although further detail on the level of supervision was not often provided. Eight studies were carried out during active cancer treatment[22,26,29-31,33,34,38], nine in the post treatment phase[23-25,28,32,35-37,39] and one included participants both on and off treatment[27]. The duration of exercise programs ranged from 4-6 wk to 26 wk with individual exercise sessions ranging from 20-90 min including warm up and cool down. Seventeen studies prescribed aerobic exercise that was of moderate intensity with 4 of these studies[22,27,29,34] including high intensity intervals. One study combined both low and moderate intensity intervention groups into a single intervention group for their analysis due to the small sample size of the study[24]. Further information on the exercise prescription variables is provided in Table 3.3.

The Effect of Supervised Aerobic Exercise on Aerobic Capacity

All eighteen studies reported VO_{2peak}, with 13 studies (14 comparisons) indexing this outcome to body weight (mL/kg per minute)[23-30,35-39], 4 studies measuring absolute (L/min)[22,31,33,34], and 1 study measuring percent change in VO_{2peak} (mL/kg per minute)[32]. The study measuring percent change in VO_{2peak} was excluded from analysis due to insufficient data on measures of variability.

Pooling of all 18 comparisons showed a moderate-to-large effect estimate (SMD: 0.74; 95%CI: 0.52, 0.96; $P < 0.001$) in favour of supervised aerobic exercise training; however, moderate heterogeneity was found among the included studies ($I^2 = 63\%$; $P < 0.001$) (Figure 3.3). Pooling of the 13 studies (14 comparisons) reporting VO_{2peak} (mL/kg per minute) showed a statistically significant mean difference in VO_{2peak} of 3.13 mL/kg per minute (95%CI: 2.21, 4.05; $P < 0.001$) in favour of supervised aerobic exercise training; however, again moderate heterogeneity was found among the included studies ($I^2 = 58\%$; $P < 0.001$).

Subgroup Analysis

Subgroup analyses were performed for level of supervision, treatment timing and cancer type (Table 3.4). A significantly smaller effect estimate ($P = 0.003$) was found for group/ class-led exercise studies[22,23,35,38] (SMD: 0.36; 95%CI: 0.17, 0.56) when compared to studies involving individualized exercise programs[24-31,33,34,36,37,39] (SMD: 0.87; 95%CI: 0.60, 1.15). Non-significant effects ($P = 0.11$) were observed between on and off treatment studies.

Statistically significant differences in pooled effect estimates were observed between cancer types with a significantly larger beneficial effect found among studies including survivors with hematological cancers ($P < 0.001$)[27,31] when compared to other cancer tumour groups (breast cancer, lung cancer and mixed cancer).

Meta-regression

Meta regression was performed analysing the effect estimate with exercise parameters of exercise workload and participant adherence as potential moderators. These two variables, workload and adherence, explained 65.8% ($P = 0.04$) of the between-study variance in effect estimate among the included studies (Figure 3.4).

Quality of Life

Nine studies reported data for health-related quality of life as measured by the Functional Assessment of Cancer Therapy-General (FACT-G) scale[23,25,29,31], the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: EORTC-QLQ-C30[22,28,30,39] and Medical Outcomes Survey: Short Form: SF36[38]. Pooling of all nine studies demonstrated a non-significant effect on quality of life (SMD: 0.3; 95%CI: -0.11, 0.71; P = 0.16), with high heterogeneity found among studies ($I^2 = 80\%$; $P < 0.001$). Further details are provided in Table 3.5.

Discussion

This meta-analysis found that supervised aerobic exercise resulted in a moderate-to-large significant benefit on VO_{2peak} in survivors of cancers. The pooled mean difference showed an improvement in VO_{2peak} of 3.13 mL/kg per minute, which is close to one metabolic equivalent (MET) improvement in fitness and similar to the 2.9 mL/kg per minute increase reported by Jones et al[13]. In the general population, each one MET increase in fitness has been found to translate to a 12% decrease in mortality in men[6] and a 17% decrease in women[40]. In the cancer population, a number of studies have reported an inverse correlation between VO_{2peak} and all-cause mortality, including cardiovascular, lung and breast cancer related deaths[41-43].

We did not find an overall significant effect of supervised aerobic exercise interventions on quality of life. Studies in our review used a variety of quality of life measures and when data were pooled significantly high heterogeneity was found. This finding suggests that the differences between study populations and/or differences inherent in the quality of life questionnaires may be factors. Supporting this premise, the pooled data from four studies using the FACT-General scale showed both statistical homogeneity and significant benefit on quality of life.

Our results showed that survivors of cancer participating in individually-based exercise experienced greater improvement in VO_{2peak} than those participating in group or class-led exercise. A reported advantage to group or class-led exercise is the social interaction and group support that may foster improvements in quality of life among survivors. Similar to our findings, a previous meta-analysis comparing group to individual exercise on quality of life in survivors of breast cancer reported that group exercise showed no benefit over individual exercise[44]. While the findings of our review appear to support individually based exercise programs for the outcome of aerobic capacity, we found that data were generally lacking on the ratio of the exercise participant to exercise specialist to allow for closer examination of impact of the level of supervision.

In contrast to the meta-analysis by Jones *et al*[13] we did not find a significant difference between groups based on the timing of the intervention relative to cancer treatment. Inspection of adherence across studies revealed a bimodal distribution with clusters in the 70-75 and 85-98 percent ranges. This bimodal distribution appeared to reflect on/off treatment status, as better adherence and larger effects were generally seen from exercise intervention studies carried out after completion of cancer treatment. Moreover, the direction of exercise effects compared to usual care may differ in relation to treatment status. For example, Jarden et al[31] demonstrated that exercise during active cancer treatment prevented a decline in VO_{2peak} when compared to usual care, whereas Kim et al[33] found that exercise following cancer treatment increased VO_{2peak} over usual care. More research is required to elucidate the influence of the timing of the exercise intervention through the continuum of cancer treatment and survivorship.

While our overall findings support the benefit of supervised aerobic exercise on VO_{2peak}, the relative benefit varied significantly across studies. As the number of research studies in the area has increased we were able to examine the influence of exercise prescription variables on aerobic capacity. Our analyses showed that VO_{2peak} improved to a larger extent in studies examining survivors of haematological cancers over other cancer groups. However, this finding was based on data from only 2 studies (3 comparisons) and thus, while compelling; further research is needed within this particular cancer subgroup. Of note, significant improvements were found within the subgroups of both breast cancer and mixed cancer groups; however, the effect was smaller.

Better participant adherence and overall exercise workload emerged as important predictors of intervention efficacy. Adherence, in this review, represented attendance to exercise sessions. Data on adherence to intensity and exercise volume were not reported in the majority of trials. Attendance to exercise sessions may reflect the impact of treatment-related side effects, patient motivation, or aspects of the study protocol such as opportunities for making up missed sessions. High adherence to the exercise prescription is critical for ensuring an adequate training stimulus to induce physiological change in cardiorespiratory function. Better reporting of adherence to prescription factors of intensity and duration would allow for more precise examination of the dose response to exercise[5].

Previous meta-analyses examining exercise interventions have reported benefit from more intense aerobic exercise interventions for both quality of life and depressive symptoms[45,46]. In the present meta-analysis, however, overall workload rather than intensity alone was found to predict response to exercise. We found that the majority of studies in the review prescribed moderate intensity exercise training, although some included high intensity interval work. Multiplying the exercise volume by the prescribed intensity provided a workload metric (*i.e.*, intensity-minutes) for discriminating between trials finding large effects from those with small effects. While some studies prescribing lower exercise volumes showed benefit, a target workload (intensity-minutes) of around 600 intensity-minutes (*e.g.*, 10 wk program of 90 min per week of supervised exercise at 70% VO_{2peak}) appears to represent the threshold workload required to obtain a clinically significant large improvement (effect size > 1.0) in VO_{2peak}. A recent meta-analysis by Carayol et al[47] examined the effect of exercise on fatigue and quality of life and found a workload in the range of 90-120 min of moderate intensity exercise was more beneficial in improving fatigue and quality of life than higher volumes of exercise. Our findings suggest that improvements in aerobic capacity can be attained at an exercise workload level that, in theory, should not negatively impact fatigue and quality of life.

Limitations

The major limitations of this meta-analysis were the assumptions revolving around exercise prescription factors. All intensity values represented average values obtained and were standardized to an estimated %VO_{2max} value. Conversions are imperfect as are average values created from studies using intervals and step protocols. Therefore we acknowledge that there is some associated error in our intensity estimates. As well, no data were provided on actual adherence to intensity among participants in the individual studies to allow more precise estimation of intensity. Thus our crude estimates of targeted intensity functioned merely as a means to determine relative ranking for between study comparisons. Assumptions were also made that resistance exercise provided minimal contributions to VO_{2peak}. A further limitation of our meta-analysis was the small number of included studies, which permitted the analysis of only two moderator variables. Thus, further research is needed particularly in survivors of cancers other than breast cancer.

Studies included in this review were generally of good methodological quality with low risk of bias. However, further attention to study quality is needed, as many studies did not adequately report methods for allocation concealment and use of blinded assessment, limiting our ability to evaluate the impact of risk of bias across studies. Of note, the estimated effect size was lower when excluding studies at high risk of bias; thus, our findings may represent an overestimate of the effect of supervised exercise on aerobic capacity.

A final limitation is that the mechanism(s) responsible for the improvement in VO_{2peak} along the oxygen cascade were not studied in any of the studies included in our review; thus, the favourable finding in VO_{2peak} may be due to improved convective and/or diffusive oxygen transport coupled with improved oxygen utilization by the active muscles[48].

Supervised aerobic exercise training was found to have a moderate-to-large beneficial effect on VO_{2peak}. Aerobic capacity increased in a dose response fashion with overall workload, with larger effects found in studies prescribing a higher overall workload of aerobic exercise. Larger benefits were also seen in studies with better participant attendance and among survivors of haematological cancers. There is a need for further randomized controlled trials examining supervised aerobic exercise interventions in understudied but common cancers such as prostate, lung and colorectal cancer.

Comments

Background

Evidence is accumulating to support the benefit of exercise to improve the physical functioning and quality of life of survivors. Currently, the optimal exercise prescription is unknown and the effect of variations in exercise training parameters on cancer-specific outcomes are poorly understood. Therefore, questions remain over how to best tailor exercise prescriptions to optimize the health outcomes of survivors at different times through the cancer continuum.

Research Frontiers

A previous meta-analysis included data from six randomized controlled trials and reported a significant benefit from supervised aerobic exercise training, compared with usual care, on VO_{2peak}(2.90 mL/kg per minute; 95%CI: 1.16, 4.64; $P = 0.01$). However, statistical and clinical heterogeneity was found among the exercise trials included in their review, and therefore further research was indicated to build on and extend the current knowledge in the field.

Innovations and Breakthroughs

Pooling of the 13 studies (14 comparisons) reporting VO_{2peak} (mL/kg per minute) showed a statistically significant mean difference in VO_{2peak} of 3.13 mL/kg per minute (95%CI: 2.21, 4.05; $P< 0.001$) in favour of supervised aerobic exercise training; however, again moderate heterogeneity was found among the included studies ($I^2 = 58\%$; $P < 0.001$). Meta-regression was performed analyzing the effect estimate with exercise parameters of exercise workload and participant adherence as potential moderators. These two variables, workload and adherence, explained 65.8% ($P = 0.04$) of the between-study variance in effect estimate among the included studies.

Applications

Supervised aerobic exercise training is an effective intervention to improve aerobic capacity in survivors of cancer. Aerobic capacity increased in a dose response fashion with overall workload, with larger effects found in studies prescribing a higher overall workload of aerobic exercise. Larger benefits were also seen in studies with better participant attendance and among survivors of haematological cancers.

Terminology

Aerobic capacity (VO_{2max}) is the maximum volume of oxygen that the body can consume during maximal exercise, using at least 60% of the musculature, and while breathing air at sea level. Aerobic capacity is best increased by habitual aerobic exercise training that is of a moderate-to-vigorous intensity.

Peer Review

An excellent systematic review.

Footnotes

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Chapter 4: Methods and Procedures

Subjects

This was a sub-study of the parent Brief Electrical Stimulation (BES) study by O'Connell and colleagues.[106] The BES study is a randomized controlled trial examining the effect of intra-operative brief electrical stimulation for prevention of shoulder dysfunction following oncologic neck dissection. Subjects in both arms of the BES parent study (experimental and control) took part in this study. HNC patients typically undergo surgery 0-2 weeks following their diagnosis. Adjuvant therapy typically starts 4-6 weeks after surgery. Adjuvant therapy consists of radiation, or chemoradiation. Cisplatin is typically used for 3 cycles over the course of radiation therapy; in rare cases patients are switched to carboplatin due to cisplatin toxicity.

Sampling as a sub-study under BES has benefits but also imposes limitations regarding generalizability. Convenience sampling was used from the preselected BES subjects. Recruitment for BES was conducted in clinic by a surgical resident; this ensured all eligible patients were offered the opportunity to participate in the study without burdening health care providers with extra tasks. This enabled more efficient recruitment of a greater number of subjects than a standalone trial. Results from this trial are applicable to all HNC patients undergoing surgical treatment. Interference from the BES procedure was not expected.

Inclusion/Exclusion Criteria

Subjects recruited for the BES study matched the following criteria: 1)18 or older undergoing major bilateral resection and reconstruction surgery for head and neck cancer, 2) speak, read and write English and capable of giving informed consent. Exclusion criteria are: 1) pre-existing shoulder dysfunction, 2) implanted electrical devices, or 3) previous/current neurological diseases, which may adversely affect shoulder dysfunction.

Additional Exclusion Criteria Specific to this Sub-Study:

Patients were excluded if: 1) the subjects' physician or oncologist has advised relevant exercise restrictions, 2) serious pre-existing non-malignant disease which may affect aerobic capacity or ability to walk for 6 minutes (e.g. arthritis, anemia, Parkinson's, ALS).

Sample Size

An estimated 80% of subjects will complete testing to the midpoint of the study (two months, see below) which coincides with a 6-10 week pre-adjuvant/on-treatment intervention from surgery. With the reference proportion set at 0.50, α at 0.05, $\beta = 0.20$ and power calculated to be 0.80, 20 subjects are required for a one proportion test. The BES study aims to recruit 78 subjects total; all subjects will be asked to participate in this feasibility trial. An estimated 40 subjects will be recruited (due to timing of ethics approval), greatly exceeding the number required to detect our estimated results.

Study Design

A prospective cohort was used to determine feasibility and to obtain preliminary data on the effects of cancer therapy on functional capacity in HNC patients. The prospective, single group design was chosen for cost effectiveness; reliable healthy control comparator data is already established. Thus, this study was designed to create data for future application in the narrow HNC population.

Functional capacity was measured with the 6MWT (appendix a). A series of 5 tests were administered as follows, 4 of which coincide with BES testing time points.

1. Baseline (preoperative)
2. Six Weeks (Post operative but prior to initiation of adjuvant treatment)
3. Two months (mid-point of adjuvant cancer treatment)
4. Three months (post adjuvant therapy)
5. Six months (3 months post-adjuvant cancer treatment)

Test 3 (two months, mid-point of adjuvant therapy) was independent of the BES study. Subjects undergoing surgery-alone had their testing time matched. Adherence to testing was monitored as well as reasons for not undergoing testing. The occurrence of any adverse events, both study and non-study related, were recorded. These time points measured functional capacity at different phases of treatment, providing good spread of data for detecting changes. As well coinciding with the BES study time points optimized convenience for the patient.

The Godin physical activity questionnaire (appendix b) was administered at the baseline asking about physical activity prior to diagnosis and prior to surgery and at the 3 month test. This is a simple self-report questionnaire used to assess physical activity level which has been found to be valid, repeatable and sensitive to change. This provided evidence to support a possible Hawthorne effect related to the monitoring of functional capacity, as well as demonstrated the need for an exercise intervention.

Data Collection

Outcomes

The primary outcomes of this study were related to feasibility and safety. These outcomes were measured by exclusion rates, testing completion rates, resting during tests and adverse events.

Secondary outcomes of this study were related to functional capacity and treatment. Functional capacity was measured as distance in meters walked in six minutes using the 6MWT. Treatment outcomes were recorded as treatment completion rates, delays, reductions and changes in treatment strategies and were collected from charts, medical referral forms and interviews. 6MW scores were stratified by treatment type for subgroup analysis when possible.

Confounding Variables

The greatest expected confounding variable was change in physical activity. Physical activity levels were measured using the self-report Godin leisure-time exercise questionnaire. Physical activity levels were assessed prior to diagnosis, prior to surgery and post treatment. Shoulder function may confound 6MWD's; mechanisms may be through changes in gait efficiency, or through change in physical activity attributed to shoulder dysfunction.

Weight changes were monitored as they are related to aerobic capacity. Dexamethasone usage may cause fluid retention as well as cachexia. PEG tube usage can help stabilize weight. Dexamethasone dosage was recorded at each testing time point and PEG tube usage was recorded. Tracking weight changes in relation to functional capacity provided insight into why functional capacity changed.

Demographic Information

Demographic information was obtained from charts, medical referral forms, interviews and the Godin physical activity questionnaire. Cancer specific demographics were collected by type and stage of cancer, surgery, radiation, chemotherapy regimen, surgical neck dissection level and HPV status. Age, gender, height, weight, weight loss prior to diagnosis and weight changes through treatment were also recorded.

Measures

6 Minute Walk Distance

The 6MWT has been found valid and reliable across diverse patient groups. Scores have been well correlated with aerobic capacity as quantified by $VO_{2\ Max}$ testing.[107, 108] The 6MWT was chosen for its safety, ease of administration, brevity and cost effectiveness.

Godin Leisure-Time Exercise Questionnaire

The Godin has been found valid, reliable, repeatable and sensitive in diverse population groups. The questionnaire asks subjects the number of times per week and for how long on average light, moderate and strenuous exercise is performed.[62, 63] For this study the questionnaire was adapted to ask about different time periods. The Godin was chosen for its ease of administration, brevity and cost effectiveness.

Procedures

Procedures for 6MWT's are described in detail in appendix a. Briefly, resting vitals were established and subjects were screened for contraindications to participating in the 6MWT. Subjects were instructed to walk as far as possible in 6 minutes on a flat, 30.57 m (100 ft) course. Pace was self-determined; subjects were given time remaining and standard encouragement every minute on the minute during the test. Heart rate and RPE were recorded every two minutes. Laps were counted and subjects were given a countdown and told to stop at the end of the test, the partial lap was added to the total distance. Patients then rested for a minimum of 5 minutes to ensure proper recovery to exercise; again, vitals were taken. Rests and reasons for stopping during the tests were recorded. Subjects were also asked to complete Godin questionnaires. A sample Godin questionnaire is found in appendix b.

Statistical Analysis

Analysis of feasibility included: exclusion (number excluded divided by total number), completion rates (percentage completing all testing time points) and reasons for nonattendance at testing sessions. Demographic information will be presented using mean with standard deviation and percentage for interval and nominal data respectively. 6MWT data was analysed as percent of baseline distance as well as distance in meters for comparison to population norms. A Friedman nonparametric repeated measures analysis was conducted to test for significant within-group time effects.

Chapter 5: Results

Subjects

Overall 25 subjects with head and neck cancer were recruited. At the time of analysis 20 subjects had completed, dropped out or been removed from the study; 5 subjects were pending future testing. Medical data was abstracted and analysed for the 20 subjects. Of these 20 subjects, 2 subjects were treated with surgery alone, 13 had surgery and adjuvant radiation, and 4 subjects underwent platinum based chemotherapy concurrent with radiation. The standard radiation dose given was 60 GY in 30 fractions.

Subjects were predominantly male with risk factors for developing head and neck cancer. Cancers were predominantly HPV negative squamous cell carcinomas. Subjects had a range of 0-4 comorbidities and smoked for a range of 0-50 pack years. Mean age of subjects was 61.2 (SD 8.7) with a BMI of 26.5 (SD 6). Two subjects had PEG tubes at baseline evaluation.

Subject data can be found in table 5.1. BMI and age distributions can be found in figures 5.1 and 5.2 respectively. PEG tube use was significantly associated with BMI (r^2=0.19, p=0.033), the relationship is visualised in figure 5.3.

Feasibility

Recruitment

All eligible subjects were recruited to the study. Twenty-five of 27 subjects recruited to the BES study were eligible for recruitment to the present study. The two ineligible subjects were excluded because their blood pressure exceeded the allowable limit.

Completion

Test points 2 and 3 were combined to create a single midpoint test, and test points 4 and 5 were combined to create a single follow-up test point. Not enough tests were conducted for analysis using the initially planned 5 testing time points. All 25 subjects recruited to the study underwent baseline testing. 15 of these subjects underwent midpoint testing, and 11 subjects underwent follow-up testing. 7 Subjects dropped out of the study after baseline testing, 1 subject died as a result of complications unrelated to the study. At the time of analysis 5 subjects were undergoing treatment. While only 44% of subjects completed the study, 67% of 6MWT were administered using the revised testing time points. No rests during 6MWTs were recorded. Figure 5.4 displays a subject flow through the study.

Analysis comparing subjects lost to follow-up to those who completed the study revealed no statistical differences (independent samples t-test and Spearman correlation results not displayed). Table 1 displays characteristics of participants lost to follow-up versus participants in follow-up and the group as a whole.

Adverse Events

No adverse events related to testing were reported.

6 Minute Walk

A total of 50 6MWTs were administered. Mean 6MWT results can be found in table 5.2. At baseline, subjects walked approximately 90% as far as predicted. Figure 5.5 shows how normalised 6MW scores changed through treatment. Baseline fitness was related to fitness at follow-up but not related to change. A Friedman non-parametric analysis failed to detect a difference between normalised baseline and midpoint scores ($p=0.285$) as well as normalised baseline and follow-up scores ($p=0.366$).

A Student's T test was used to compare normalised baseline 6MW scores between subjects who dropped out versus completed the study. No significant difference was found between the populations assuming equal variances (Mean Difference=13.6, SE =7.27, $p=0.075$).

Heart Rate and Rating of Perceived Exertion

Peak heart rate and RPE were recorded at each test. Heart rate values were normalised to maximal predicted heart rate using the equation $HR_{Max} = 220 - age$. RPE Values were normalised to the maximal recorded RPE of 16. Friedman non-parametric analyses were conducted to test for differences between 6MW scores when normalised by HR (% predicted 6MW score/% predicted HR_{Max}), RPE (% predicted 6MW score/normalised RPE) and both HR and RPE (% predicted 6MW score/% predicted HR_{Max}/ normalised RPE). A statistical difference was found between 6MW scores when normalised by heart rate between baseline and midpoint tests. No other significant differences were found. Pearson correlations were used to test for relationships between HR and RPE, no correlations were found at baseline or midpoint tests, but a significant correlation was found at follow-up (r=0.603, p=0.05). Pearson tests revealed significant correlations between normalised 6MW scores and normalised heart rate. Results are displayed in tables 5.3 and 5.4. Graphical displays are presented in figures 5.6, 5.7 and 5.8.

Physical Activity

Godin physical activity scores can be found in table 5.5. At baseline less than half of subjects scored greater than 150 on the Godin leisure time physical activity questionnaire. Four subjects reported no physical activity at all. One subject scored 4200 on their pre-diagnosis Godin; this subject filled out the form incorrectly. The result was not excluded from analysis as rate of change was used rather than raw score.

A Pearson correlation showed a significant ($p<0.01$) relationship between pre-diagnosis and pre-surgery physical activity ($r^2=0.59$) but no relation to physical activity at follow-up. Physical activity change from pre-surgery to follow-up showed a weak relationship with normalised 6MWD at follow-up ($r^2=0.4$, $p=0.049$); greater decreases in physical activity were associated with higher 6MW scores. Godin scores can be found in figure 5.9.

A Student's T test was used to compare baseline physical activity levels of subjects who completed the study versus those who did not. No statistical difference was found assuming equal variances (Mean difference=309.8, SE=148, p=0.051).

Weight

Weight was recorded at baseline and follow-up. Subjects lost a mean of 4.7 kg (SD 8.4 kg), or 4.4% of their body mass (SD 9.0%). Weight change was not related to cancer stage, normalised 6MW change, or physical activity change. Weight change was not significantly different between subjects who completed versus dropped out of the trial. Results are presented in table 5.6.

Subgroup Analysis

A larger sample is required for subgroup analysis.

Correlations

Normalised 6MW score was tested for correlations with subject characteristics. Pearson correlations were used for testing 6MW scores against age, physical activity change and weight, a Spearman correlation was used for testing 6MW scores against cancer stage.

Results are found in table 5.7. Associations between PEG tube use and 6MW scores could not be tested due to the small sample size.

Chapter 6: Discussion

Feasibility

Feasibility outcomes suggest monitoring functional capacity via the 6MWT in head and neck cancer patients is safe. No serious or minor adverse events were recorded. Furthermore, high eligibility and recruitment rates suggest exercise interventions in head and neck cancer patients may be feasible. This conclusion must be interpreted with caution as a selection bias was created in recruiting from the BES parent study. A standalone trial may have lower recruitment and eligibility rates. Initially 5 testing time points were planned; data were pooled to 3 testing time points for analysis. Attrition is attributed to complications unrelated to the study and patient inconvenience; for example time commitment, travel or scheduling. One patient was unable to undergo midpoint testing due to a fibular flap open wound and one declined to undergo the follow-up test due to sciatic pain. Patient demographics of those who dropped out of the study were not significantly different from those who completed the study. Visual inspection reveals several emerging trends as shown in table 1. Participants lost to follow-up tended to be older, have later stage cancer, more aggressive treatment (chemotherapy and bilateral surgery), and live outside of the city. Subjects who did not complete the study tended to be less fit as measured by the 6MWT at baseline. Directionality of these trends cannot be assessed.

Missed testing and attrition could be addressed using incentive and increased flexibility. The present study was designed as a prospective cohort which posed no benefits to participants. Participation was a time and money burden added to the difficulties of cancer therapy. Testing was scheduled to coincide with medical appointments with the intention of optimizing convenience for patients. However, tests were often missed due to medical appointments falling behind schedule, or patients declining to be tested after a long day. Paying for parking and coordinating a convenient testing time with the participant may improve retention. High recruitment and ability to undergo baseline testing indicates willingness and ability of patients to exercise. Perhaps the incentive of potential health benefits gained from an exercise intervention would increase retainment.

Subjects recruited to the study covered a balanced spread of head and neck cancer patients. Demographic data and baseline 6MW and physical activity data do not suggest a selection bias regarding physical attributes of the patients. While a balanced sample increases the integrity of results, the diversity prevents subgroup analysis due to the small sample sizes of subgroups. The large standard deviation in 6MW distances attests to the diversity of the patient group. Future interventions must take care in targeting and personalising programs to best address unique patient needs.

Functional Capacity

Functional capacity was assessed using a series of 6MWTs. Analysis was conducted by normalising results against predicted scores from regression equations created by Enright and Sherrill.[85] These regression equations were developed from a healthy population sample. At baseline this head and neck cancer cohort scored approximately 90% of predicted. Baseline scores were normally distributed and showed no indication of high and low fitness groups. Subjects who dropped out tended to have lower initial fitness than those who completed the study. This trend did not reach statistical significance. The study design does not permit for suggesting causative reasons for this emerging trend.

6MW scores did not significantly change from baseline to the mid-point or follow-up tests. Significant declines in aerobic capacity have been reported across the cancer spectrum, including in head and neck cancer. Samuel *et al* (2013) reported a 96 meter median difference decrease from pre-chemoradiation to immediately post.[56] Unfortunately these results are not directly comparable as no mean or normalised scores were provided. However, in an attempt to address the discrepancy in findings potential variables were tested for correlation. Analysis failed to identify factors contributing to variance in response, a larger sample size is needed to explain findings. A correlation between weight loss and increased normalised 6MW score approached significance. This may appear to suggest weight loss improved functional capacity; but this has little prognostic value when considering factors inherent to the 6MWT. Less energy is required to move a lighter versus a heavier subject at a given speed. The 6MW then poorly reflects whether this is maladaptive weight loss from lean tissue, or healthy weight loss from non-lean tissue. This difference could be detected by comparing change in relative versus absolute $VO_{2\ Max}$ results, or by measuring lean body mass and correlating changes with those observed in repeated 6MWTs. Data do not suggest a contribution from differential attrition, no statistical differences were found between participants who dropped out versus those who completed the study.

Stepwise regression did uncover one possible trend. Physical activity level change was negatively correlated with normalised 6MW score at follow-up. Subjects who decreased physical activity over treatment tended to score higher than their peers who did not decrease their physical activity over treatment. Importantly, this effect disappears when comparing physical activity change with normalised 6MW change. While this may suggest physical activity is not related to physical fitness as measured by the 6MWT, it may be more indicative that higher initial fitness is predictive of fitness at follow-up. Indeed, initial fitness is significantly correlated with fitness at follow-up; however, no significant relationship is detected between physical activity at baseline and initial fitness. These relationships, or lack thereof, are then perhaps spurious, and require a larger sample size for detection.

Physical Activity

One result that may be interpreted with reasonable confidence from this data set is the measured physical activity levels. These results indicate the population of head and neck cancer patients at baseline is relatively sedentary as less than half of included subjects were meeting the American College of Sports Medicine minimum weekly physical activity guidelines. Previous studies have reported lower rates of head and neck cancer patients meeting physical activity guidelines.[109, 110]

Change in physical activity over treatment does not appear to follow any trend. Several patients decreased their physical activity while others increased, or stayed the same. It is important to consider that floor effects may impact the relationship between physical activity level and treatment. Change in physical activity did not correlate with changes in functional capacity. Individuals who completed the study did not have markedly different physical activity at baseline versus those who did not complete the study. Importantly, should a difference be detected in a larger sample size, physical activity at baseline may be a marker rather than a determinant of health or other factors that may contribute to a subjects' ability to complete a study. There is a need for increasing physical activity in head and neck cancer survivors through targeted interventions.

The 6MWT

The lack of observed change in functional capacity may be in part attributed to the 6MWT. The general ambiguity of the instructions and need for the test to be standardized results in differential interpretation by subjects. Peak HR and RPE data were collected and used to normalise 6MW scores. Heart rate can be used as an objective measure of exertion; normalised heart rate was found to have a significant, positive correlation with normalised 6MW scores. Adjusting 6MW scores by normalised heart rate then reveals a decline in functional capacity from the baseline to the midpoint of testing, and then recovery from the midpoint to follow-up as displayed in figure 5.6. Comparing this finding to non-heart rate adjusted 6MW scores suggests insensitivity of the 6MWT. This discrepancy may be explained by a combination of differential interpretation of instructions and different volitional effort by subjects across test points. The latter explanation is not supported by our data; heart rate and RPE did not markedly change between testing time points as displayed in table 5.3. Importantly, 2 subjects were on beta-blockers which are known to significantly decrease heart rate.[111] Beta-blocker use was not controlled for in HR adjustments.

Normalisation of 6MW scores with normalised RPE did not improve detection of differences between test points. In contrast to HR, RPE should not be affected by beta-blocker use and therefore naturally controls for the confounder. It is expected that subjects who work harder as quantified by RPE should achieve greater 6MW scores. However, this was not the case. No relationship was found between RPE and 6MW scores, and furthermore no relationship was found between RPE and HR. Previous research has identified a relationship between HR, RPE and work rate.[112] The lack of a relationship found in our data may be explained by misinterpretation of the Borg scale by participants.

Normalising 6MW scores using both RPE and HR did not improve detection. As above, it seems that the integrity of RPE scores prevents their use in normalizing data. Subjective measures such as RPE appear less useful in analysis. A moderate to high RPE and corresponding HR may provide an indication of the integrity of an individuals' 6MW result. If both a moderate-high heart rate and RPE are observed the 6MW result is likely to better reflect the subjects' functional capacity.

To remediate the problem of subjective interpretation, verbal encouragement or personalised instruction could be used. Verbal encouragement has previously been shown to increase performance.[113] Conversely, a recent study has found no effect of verbal encouragement on 6MW results.[114] Personalising instructions to ensure understanding may result in a more standardized result from a patient perspective. However, the concept of individualised instruction compromises the principle of standard procedures for integrity of results. Monitoring 6MW results with heart rate and RPE could provide a reference standard.

A learning effect has previously been reported when sequential 6MWTs have been performed. Jenkins and Cecins (2010) reported 80% of subjects improve their 6MWT in back to back tests.[85] The magnitude of the effect varies but has been reported at 10%.[67] This effect could potentially be mitigated by introducing an objective measure such as heart rate for normalisation as above.

Conclusions

Feasibility outcomes suggest exercise testing in head and neck cancer patients is safe. Self-reported physical activity measures underline the need for exercise interventions. Our data demonstrate feasibility of recruiting and testing head and neck cancer patients prior to treatment. When planning future interventions convenience, proximity and incentive should be considered for improving retainment.

Functional capacity data is inconclusive. A larger sample size is required to identify factors affecting functional capacity, as well as more robust testing strategies. The 6MWT remains a viable option due to its brevity, simplicity, and cost effectiveness; but there is a need to improve the integrity of results.

Tables

3.1 Example of medline search

(1) Exp neoplasms/

(2) (Cancer* or neoplasm* or (tumor* not tumor necrosis factor) or (tumour* not tumour necrosis factor) or malignan* or carcino* or leukaemia* or leukemi* or lymphoma* or myeloma* or adenocarcinoma*).mp.

(3) (1) or (2)

(4) Exercise therapy/or motion therapy, continuous passive/or muscle stretching exercises/or plyometric exercise/

(5) (Aerobic* or exercise or running or treadmill* or training).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

(6) (4) or (5)

(7) (3) and (6)

(8) (VO_2 or Aerobic capacity).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

(9) (7) and (8)

(10) Limit (9) to clinical trial, all

3.2 Description of Included Studies

Ref.	Sample size/ cancer type	Age (SD/range)	Gender (F/M)	Intervention group	Comparison group	Key outcomes	Adverse events
On treatment studies/subgroups							
Adamsen et al[22], 2009 Denmark	*n* = 117 Mixed Cancer Groups	47.2 (± 6.7) yr	F: 78 M: 39	Aerobic Training with High-intensity Intervals + Resistance Exercise + Relaxation + Massage	Usual care: allowed to freely increase physical activity	Estimated VO_{2max}	Seizure (*n* = 1)
Courneya et al[26], 2007 Canada	*n* = 133 Breast Cancer	49 yr (26-78)	F: 133	Aerobic Training	Usual care: continue usual activities	VO_{2peak}QoL: FACT-Anemia	Hypotension (*n* = 1) Dizziness (*n* = 1)

1Courneya et al[27], 2009b Canada	*n* = 54 NHL, HL	[2]53.2 yr (18-80)	[2]F: 50 M: 72	Aerobic Training with High-intensity Intervals	Usual Care: continue usual activities	VO_{2peak}QoL: FACT-B/Ac/An	Back (*n* = 1), hip (*n* = 1) and knee (*n* = 1) pain
Hornsby et al[29], 2013 United States	*n* = 20 Breast Cancer	51 (± 6) yr	F: 10	Aerobic Training with High-intensity Intervals	Control: Continue usual exercise levels	VO_{2peak}FACT-B Adverse Events	Leg pain (*n* = 1)
Hwang et al[30], 2012 Taiwan	*n* = 24 Lung	61 (± 6.3)	F: 12 M: 12	Aerobic Training	Usual Care: general patient education	VO_{2peak}QoL: EORTC	Not reported
Jarden et al[31], 2009 Denmark	*n* = 42 Mixed Cancer Groups	39.1 (12.2)	F: 16 M: 26	Aerobic Training + Resistance Exercise + Flexibility	Usual Care	Estimated VO_{2max}QoL: EORTC, FACT-An	None
Kim et al[33], 2006 United States	*n* = 41 Breast Cancer	51.3 (6.7) yr	F: 41	Aerobic Training	Waitlist Control	VO_{2peak}	Not reported
MacVicar et al[34], 1989 United States	*n* = 34 Breast Cancer	45.4 (10.2) yr	F: 34	Aerobic Training with High-intensity Intervals	Control: Continue normal activities	VO_{2max}L/min	Not reported
Segal et al[38], 2001 Canada	*n* = 66 Breast Cancer	51 (± 8.7) yr	F: 66	Aerobic Training	Control group encouraged to exercise	Estimated VO_{2max}QoL: SF36	Not reported
Off treatment studies/comparisons							
Broderick et al[23], 2013 Ireland	*n* = 43 Mixed Cancer Groups	52.3 (8.3) yr	F: 37 M: 6	Aerobic training	Usual Care	Estimated VO_{2max}QoL: FACT-G, SF36	Not reported
Burnham et al[24], 2000 United States	*n* = 18 Mixed Cancer Groups	54.2 (8.1) yr	F: 15 M: 3	Aerobic training	Control	VO_{2peak}QoL: LASA	Not reported
Courneya et al[25], 2003 Canada	*n* = 50 Breast Cancer	59 (± 6) yr	F: 54	Aerobic training	No exercise	VO_{2peak}QoL: FACT-Breast	Lymphedema (*n* = 3) Gynecological complication (*n* = 1)
1Courneya et al[27], 2009aCanada	*n* = 68 NHL, HL	[2]As per Courneya, 2009[b]	[2]As per Courneya, 2009[b]	[2]As per Courneya, 2009[b]	[2]As per Courneya, 2009[b]	[2]As per Courneya, 2009[b]	[2]As per Courneya, 2009[b]

Herrero et al[28], 2005 Spain	*n* = 16 Breast Cancer	51 (10) yr	F: 16	Aerobic plus Resistance Training	No Exercise	VO_{2peak}QoL: EORTC	Not reported
Kaibori et al[32], 2013 Japan	*n* = 51 Liver Cancer	68 (9.1) yr	F: 15 M: 36	Aerobic Training + Stretching + Diet Intervention	Diet Intervention	VO_{2peak}	Not reported
Mehnert et al[35], 2011 Germany	*n* = 58 Breast Cancer	53 (7.4) yr	F: 58	Aerobic Training + Physiotherapeutic Exercises + Relaxation	Waitlist Control	VO_{2max}QoL: BIQ	Not reported
Naumann et al[36], 2011 Australia	*n* = 21 Breast Cancer	49 (10) yr	F: 21	Aerobic Training + Resistance Exercise + Flexibility	Usual Care	Estimated VO_{2max}QoL: FACT-B	Not reported
Rahnama et al[37], 2010 Iran	*n* = 29 Breast Cancer	58.3 (6.3) yr	F: 29	Aerobic Training + Resistance Exercise	No exercise	Estimated VO_{2max}	Not reported
Thorsen et al[39], 2005 Norway	*n* = 111 Mixed Cancer Groups	39 (8.4) yr	F: 36 M: 75	Aerobic Training + Resistance Exercise	Usual Care	Estimated VO_{2max}QoL: EORTC	Not reported

3.3 Exercise prescription variables

Ref.	Study duration (wk)	Days/ week	Mins/session (mean)	Volume	Standardized intensity (mean)	Workload (intensity minutes)	Adherence (attendance)
Adamsen et al[22]	6	3	15	270	0.83	224	71%
Broderick et al[23]	8	2	30	480	0.57	274	78%
Burnham et al[24]	10	3	23	690	0.41	281	70%
Courneya et al[25]	15	3	25	1125	0.73	816	98%
Courneya et al[26]	12	3	30	1080	0.7	756	70%
Courneya et al[27] (1)	12	3	30	1080	0.79	858	84%
Courneya et al[27] (2)	12	3	30	1080	0.79	858	71%
Herrero et al[28]	8	3	25	600	0.59	351	91%

Hornsby et al[29]	12	3	23	828	0.79	657	82%
Hwang et al[30]	8	3	20	480	0.6	288	71%
Jarden et al[31]	5	5	22.5	563	0.72	405	80%
Kim et al[33]	8	3	30	720	0.65	468	78%
MacVicar et al[34]	10	3	NR	-	0.73	-	NR
Mehnert et al[35]	10	2	30	600	0.6	360	NR
Naumann et al[36]	8	3	53	1272	0.5	636	84%
Rahnama et al[37]	15	2	35	1050	0.28	289	NR
Segal et al[38]	26	3	NR	-	0.55	-	72%
Thorsen et al[39]	14	2	30	840	0.62	518	NR

NR: Not Reported

3.4 Subgroup Analyses

Subgroup category	Subgroup	No. studies	Mean Difference in mL/kg per minute (95%CI)	*P* value between subgroups	No. studies	Standardized mean difference (95%CI)	*P* value between subgroups
Level of exercise supervision	Group Exercise Class	3	1.77 (0.04, 3.51)	*P* = 0.07	4	0.36 (0.17, 0.56)	*P* = 0.003
	Individual Exercise	11	3.53 (2.64, 4.43)		14	0.87 (0.60, 1.15)	
Treatment status	On Treatment	5	2.59 (0.7, 4.48)	*P* = 0.26	9	0.56 (0.32, 0.81)	*P* = 0.11
	Off Treatment	9	3.74 (3.06, 4.42)		9	0.92 (0.56, 1.29)	
Cancer tumour group	Breast	8	2.41 (1.5, 3.31)		10	0.64 (0.34, 0.88)	
	Hematologic	3	5.08 (4.01, 6.16)		3	1.55 (1.09, 2.02)	
	Lung	1	2.10 (-1.36, 5.56)	*P* = 0.002	1	0.48 (-0.34, 1.30)	*P* = 0.0002
	Mixed Cancers	3	3.17 (1.34, 5.0)		4	0.41 (0.21, 0.61)	

3.5 Quality of Life Outcome

Quality of life measure	No. of studies	Mean difference (95%CI)	*P* value between groups	Standardized mean difference (95%CI)	*P* value between groups
All combined	9	Not applicable	-	0.3 (-0.12, 0.70)	$P = 0.16$
EORTC Global	4	1.45 (0.58, 2.32)	$P = 0.001$	0.13 (-0.06, 0.33)	$P = 0.17$
FACT-G	4	3.25 (-0.41, 6.92)	$P = 0.08$	0.47 (0.14, 0.79)	$P = 0.005$
MOS SF36	1	2.2 (1.34, 3.06)	$P < 0.001$	1.22 (0.69, 1.74)	$P < 0.001$

EORTC Global: European Organisation for Research and Treatment of Cancer Global Quality of Life Questionnaire; FACT-G: Functional Assessment of Cancer Therapy-General scale; MOS SF36: Medical Outcomes Survey Short Form.

5.1 Subject Demographics

Variable	Details	Total Group (n=20)	Participants in Follow-Up (n=12)	Participants Withdrawn or Dropped out (n=8)
Age	Median (Range)	60 (43-80)	60(43-70)	67 (59-80)
	Mean (SD)	61.2 (8.74)	58.8 (8.2)	65 (8.6)
Gender	Female (%)	3 (15)	3 (25)	0
Residence	Rural (%)	8 (40)	3 (25)	5 (62.5)
Smoking History	Current (%)	5 (25)	0	5 (62.5)
Alcohol Use	Social (%)	9 (45)	5 (41.7)	4 (50)
	Heavy (%)	3 (15)	1 (8.3)	2 (25)
Cancer Type	SCC (%)	16 (80)	10 (83.3)	6 (75)
	Other (%)	4 (20)	2 (16.7)	2 (25)
Cancer Location	Oral (%)	4 (20)	1 (8.3)	3 (37.5)
	Oropharyngeal (%)	9 (45)	5 (41.7)	4 (50)
	Larynx (%)	4 (20)	3 (25)	1 (12.5)
	Other (%)	2 (10)	2 (16.7)	0
Radiation	Yes (%)	13 (65)	7 (58.3)	6 (75)
Chemotherapy	Yes (%)	5 (25)	1 (8.3)	4 (50)
Comorbidities	1-2 (%)	9 (45)	5 (41.7)	4 (50)
	3+ (%)	5 (25)	3 (25)	2 (25)
HPV+	Yes (%)	4 (20)	2 (16.7)	2 (25)
Surgery	Bilateral %	73.3	62.5	83.3
PEG Tube	Used (%)	2 (10)	1 (8.3)	1 (12.5)
BMI	Mean (SD)	26.5 (6)	27.2 (7.2)	25.7 (4.3)
Weight Change	Mean (SD) %	4.7 (8.4)	3.26 (8.7)	6.98 (10)*
Relative 6MW Baseline	Mean (SD) % Predicted	90 (20)	97.3 (19.3)	81.2 (17.9)
Physical Activity	Pre-treatment >150 Minutes (%)	8 (40)	4 (33.3)	4 (50)

*Deceased subject not included

5.2 Mean 6MWT Results

Measure	Predicted	Baseline (n=25)	Midpoint (n=14)	Follow-Up n=(11)
Absolute (m)	590.6 (84.7)	521.4 (104.6)	499.2 (120.3)	557.2 (123.3)
Relative (%)	100	89.4 (18.8)	83.7 (22.5)	99.5 (19.2)

6MW results: mean and SD of absolute distance walked measured in meters and relative in percent of predicted.

5.3 HR and RPE Results

	Baseline (n=24)	Midpoint (n=13)	Follow-Up (n=11)	BL-MP	BL-FU
%HRM	74.3 (12.5)	73.9 (13.8)	70 (13)	P=0.166	P=0.132
%RPE	12.4 (2.1)	11.5 (1.9)	12.1 (2)	P=0.527	P=0.414
HR-A	121.1 (22)	115 (24.9)	145.5 (35.7)	P= 0.002	P=0.132
RPE-A	119.9 (35.3)	119.4 (35.3)	135.6 (36.5)	P=0.405	P=0.366
HR/RPE-A	163.1 (48.4)	163.7 (45.7)	202.7 (79.6)	P=0.166	P=0.366

%HRM = Percent of predicted maximal heart rate, %RPE = percent of maximal observed RPE (16), HR-A = heart rate adjusted 6MW scores, RPE-A = RPE adjusted 6MW scores, HR/RPE-A = HR and RPE adjusted 6MW scores, BL-MP = baseline to midpoint comparison, BL-FU = baseline to follow-up comparison. Values are mean with standard deviation.

5.4 Heart Rate, RPE and Normalised 6MW Correlations

	Baseline (24)	Midpoint (13)	Follow-up (11)
HR/RPE	0.045(p=0.729)	0.235 (p=0.440)	0.603 (p=0.05)
HR/6MW	0.595 (p=0.002)	0.677(p=0.011)	0.413 (p=0.207)
RPE/6MW	-0.141 (p=0.512)	0.315 (p=0.294)	-0.129 (p=0.704)

Pearson's correlations, R value with p.

5.5 Godin Scores

Pre-Diagnosis (24)	Pre-Surgery (23)	Follow-Up (13)
453(916)	285 (501)	292 (350)

Godin Score: mean and SD

5.6 Weight Change Correlations

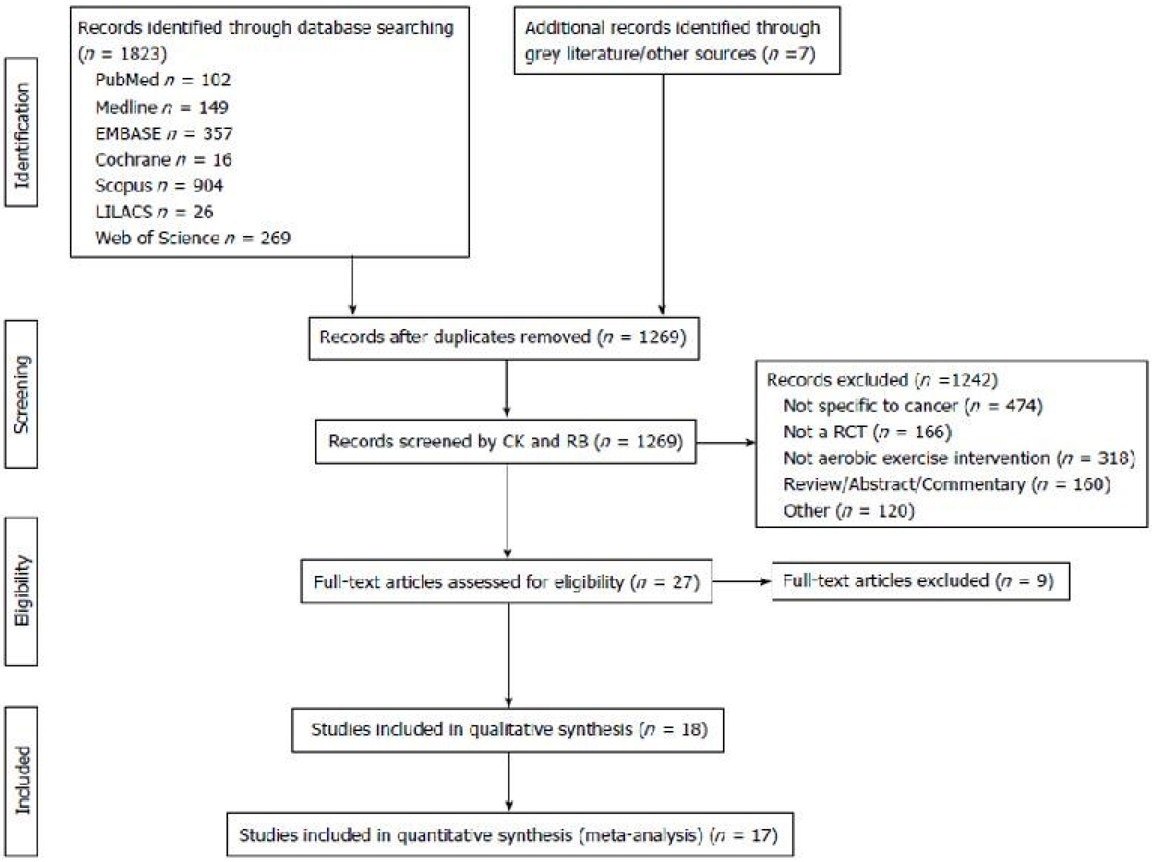
	Normalised 6MW Score Change (n=11)	Physical Activity Change (n=12)	Cancer Stage (n=13)
Weight Change (kg)	R=0.442 (p=0.174)	R=0.175 (p=0.587)	R=0.183 (p=0.549)

5.7 6MW Correlations

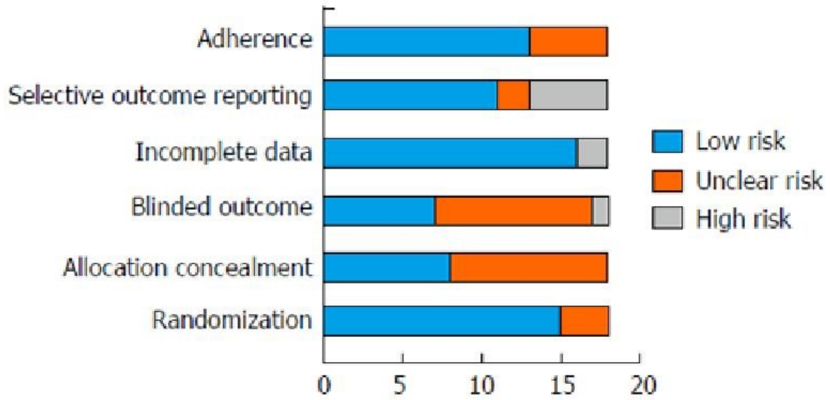
	Age (11)	Physical Activity Change (11)	BMI (11)	Stage (8)
Normalised 6MWD	R=0.108 P=0.753	R=-0.634 P=0.049*	R=0.379 P=0.251	R=-0.165 P=0.696
Normalised 6MWD Change	R=0.545 P=0.083	R=-0.236 P=0.512	R=-0.87 P=0.799	R=-0.014 P=0.974

Figures

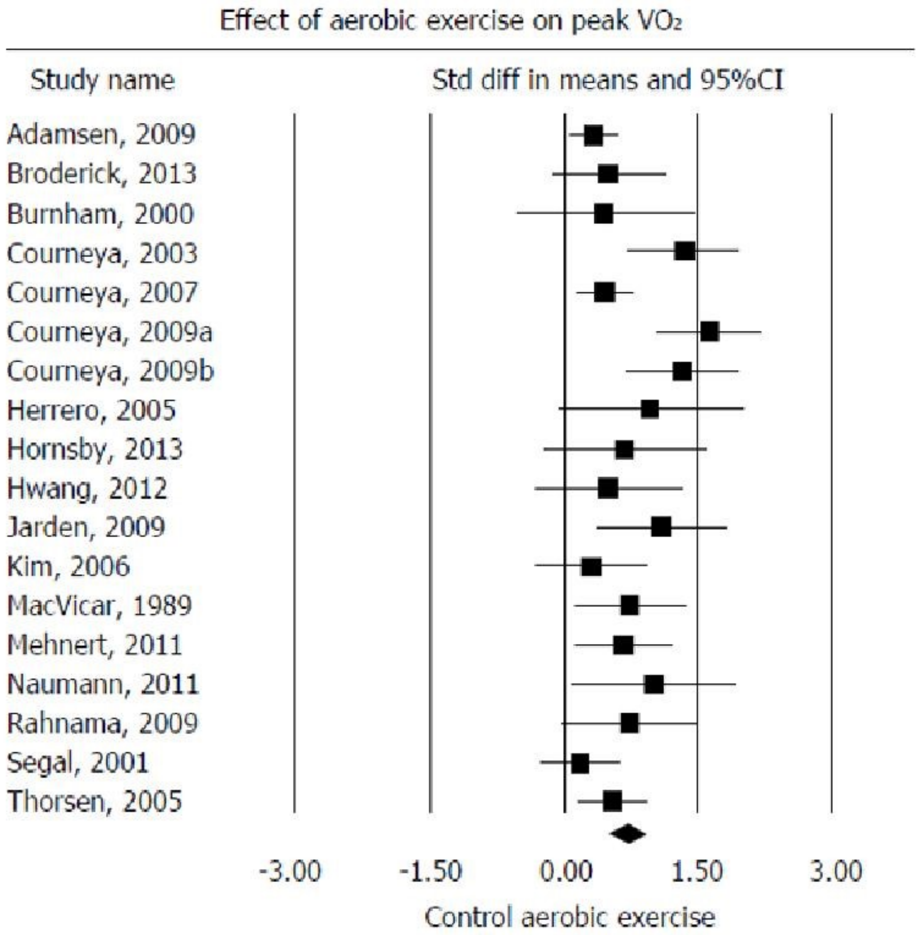
3.1 PRISMA flow diagram of study selection process



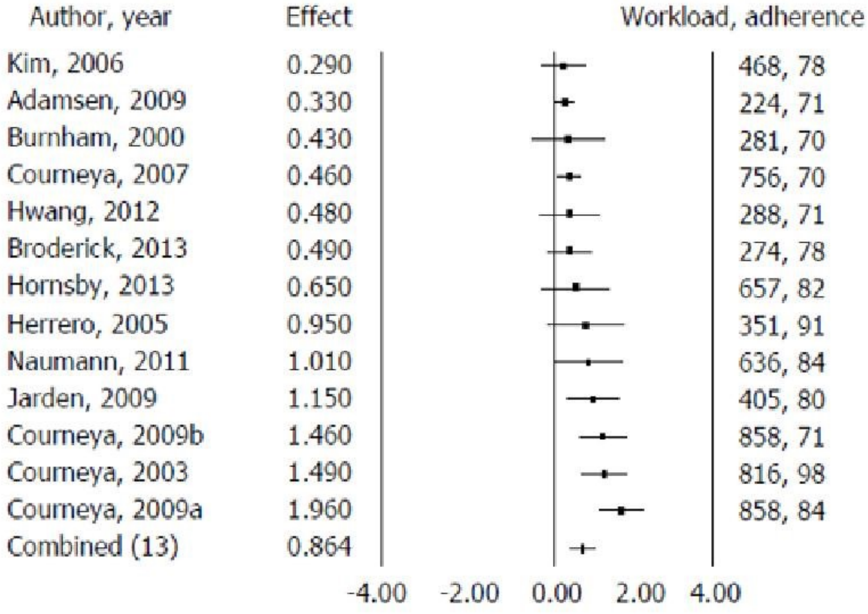
3.2 Risk of Bias Summary



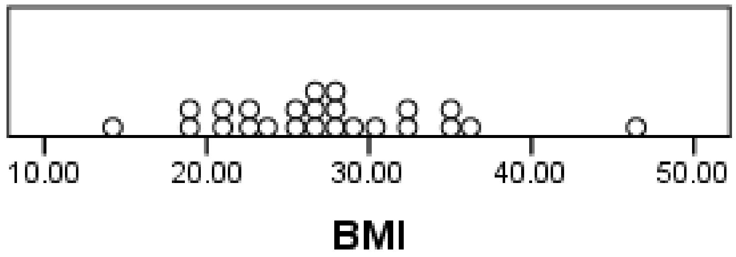
3.3 VO_2 Effect Size



3.4 Meta-Regression Analysis: Workload, Adherence



5.1 BMI Distribution (kg/m²)



5.2 Age Distribution

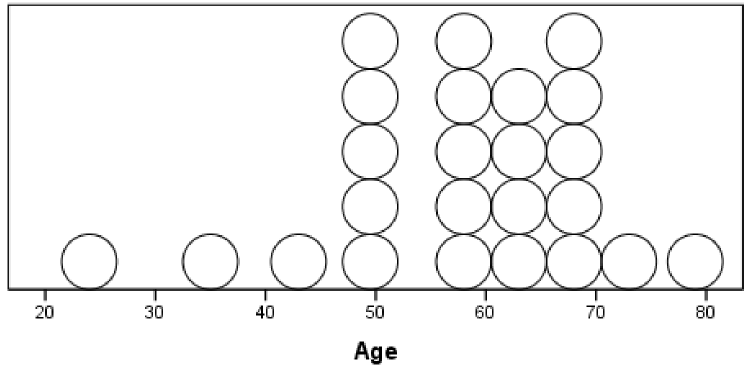


Figure 5.3 PEG Tube Use and BMI

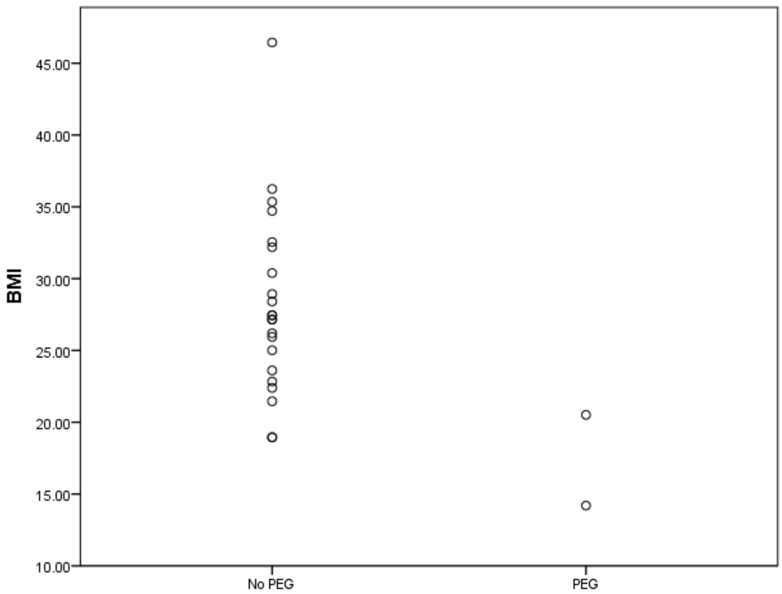


Figure 5.4 Subject Flow Chart

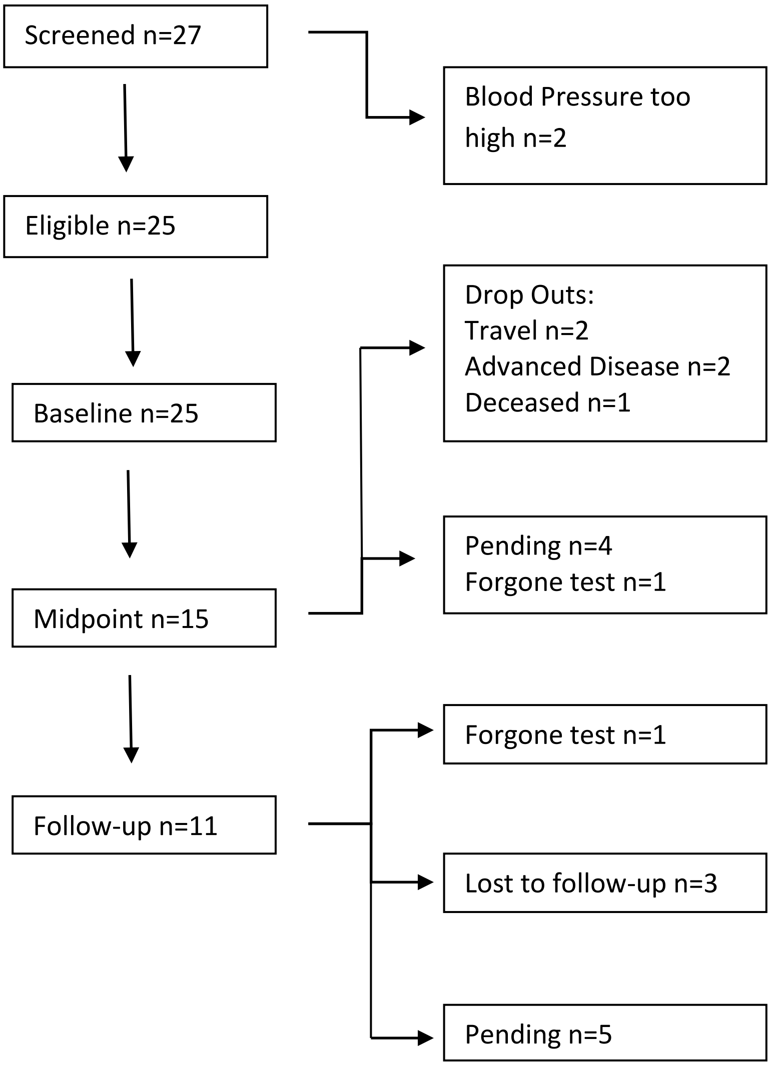


Figure 5.5 Normalised 6MW Scores over Time

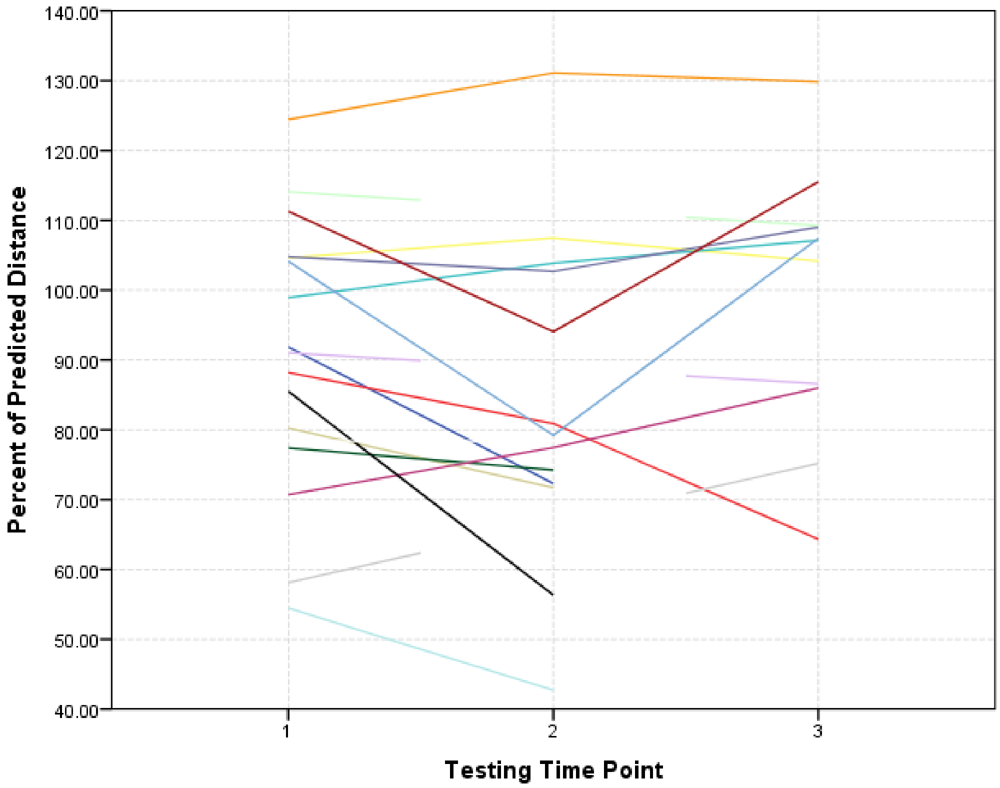


Figure 5.6 Heart Rate Adjusted 6MW Scores

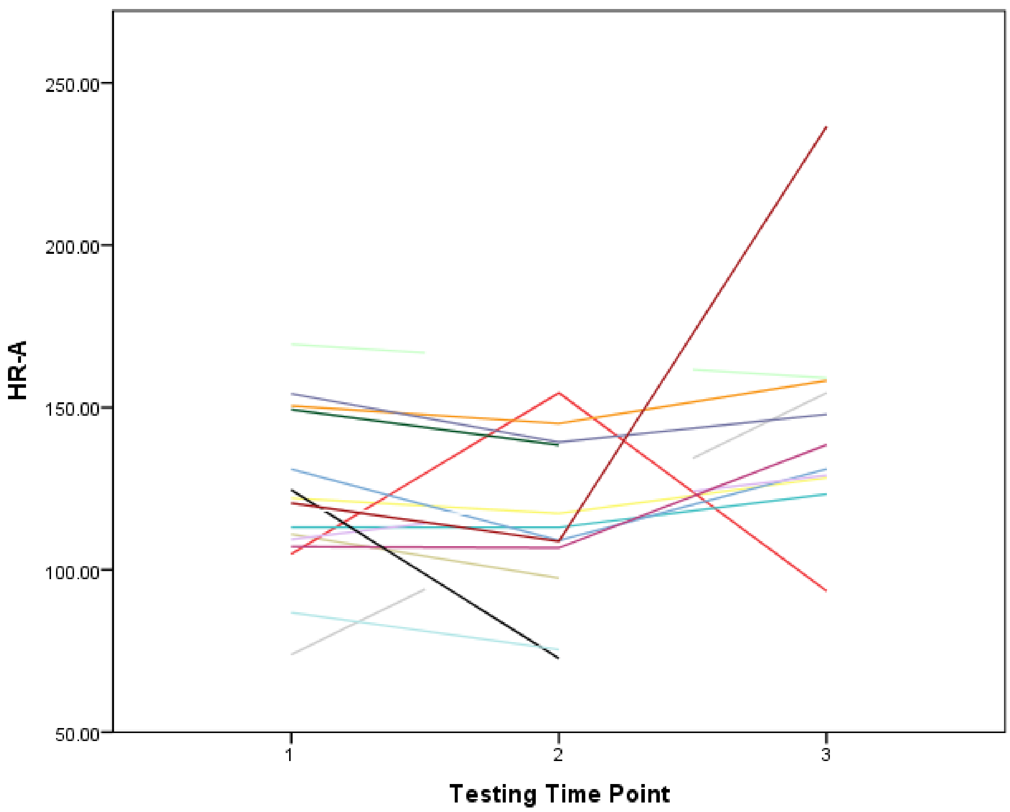


Figure 5.7 RPE Adjusted 6MW Scores

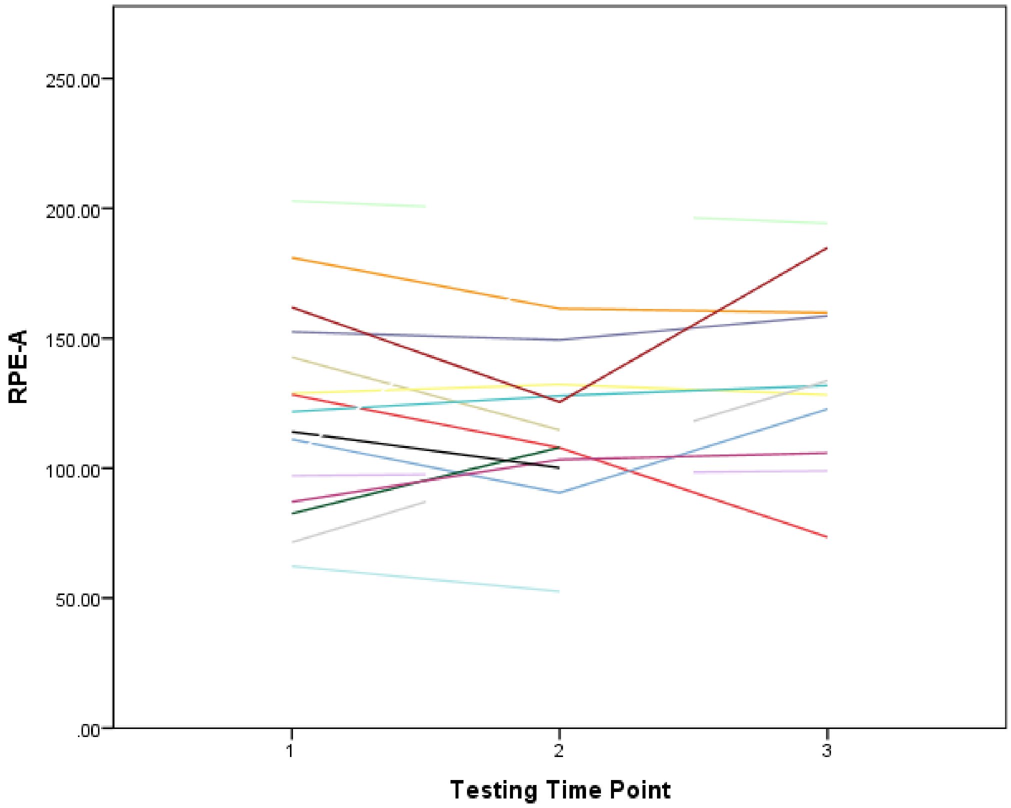


Figure 5.8 Heart Rate and RPE Adjusted 6MW Scores

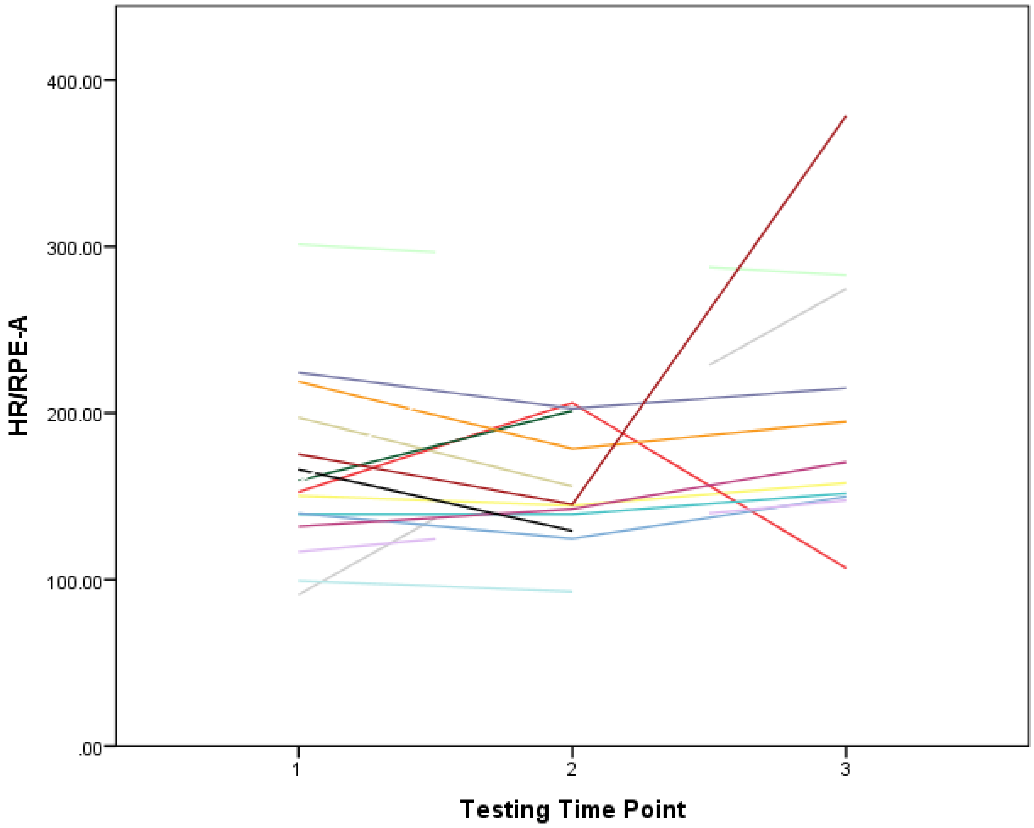
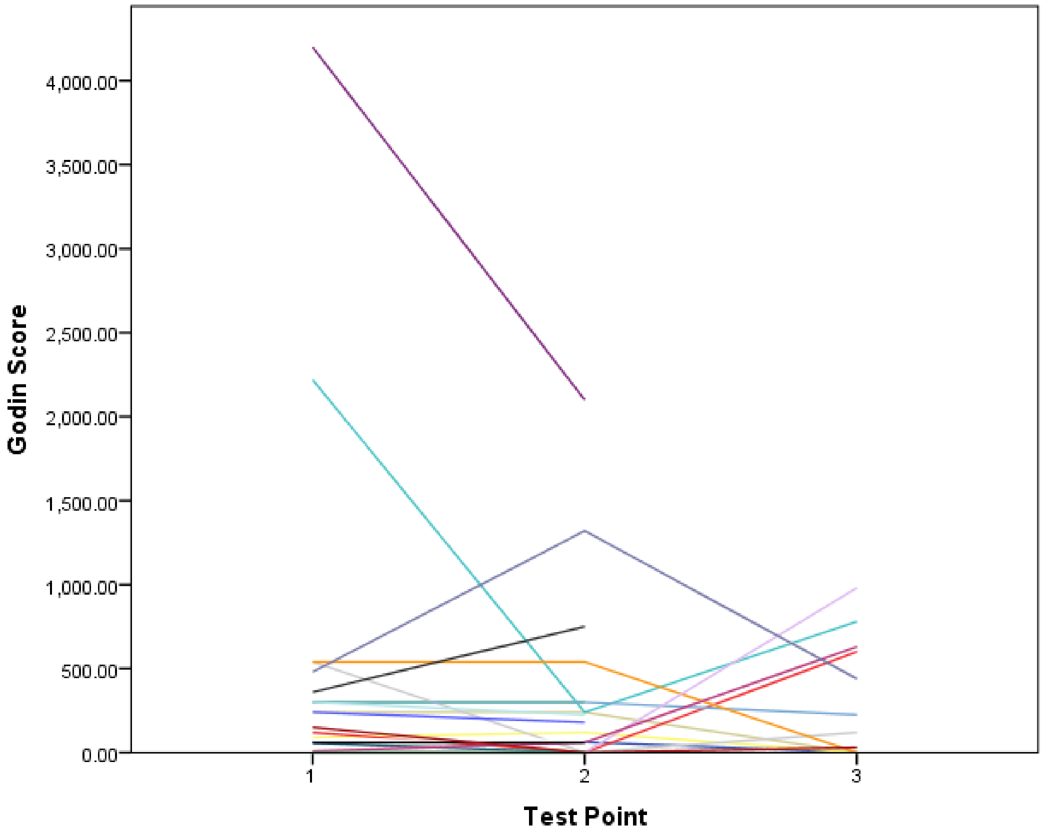


Figure 5.9 Godin Scores over Time



Appendices

Appendix A: 6MWT

1. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet.

2. Ensure client has put on the heart rate monitor and that it is working.

3. Take resting vitals: heart rate, blood pressure and oxygen saturation

4. Explain Borg scale to participant.

5. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.

6. Have the patient stand and rate their baseline perceived exertion using the Borg Scale.

7. Timer to set his/ her watch to zero.

8. Instruct the patient as follows:

- "The object of this test is to walk as far as possible for 6minutes.

- You will walk back and forth in this hallway.
- Six minutes is a long time to walk, so you will be exerting yourself.
- You will probably get out of breath or become exhausted.
- You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

- You will be walking back and forth around the cones.

- You should pivot briskly around the cones and continue back the other way without hesitation.
- Now I'm going to show you. Please watch the way I turn without hesitation." Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

- "Are you ready to do that? I am going to count your laps to keep track of the number of laps you complete.

- Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

- Start now, or whenever you are ready."

---

9. During the test:

After the first minute, tell the patient the following (in even tones): “You are doing well. You have 5 minutes to go.”

When the timer shows 4 minutes remaining, tell the patient the following: “Keep up the good work. You have 4 minutes to go.” Ask about perceived exertion, record HR.

When the timer shows 3 minutes remaining, tell the patient the following: “You are doing well. You are halfway done.”

When the timer shows 2 minutes remaining, tell the patient the following: “Keep up the good work. You have only 2 minutes left.” Ask about perceived exertion, record the HR.

When the timer shows only 1 minute remaining, tell the patient: “You are doing well. You have only 1 minute to go.”

Do not use other words of encouragement (or body language to speed up).
If the patient stops walking during the test and needs a rest, say this: “You can lean against the wall if you would like; then continue walking whenever you feel able.” Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: “In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you.”

When the timer rings (or buzzes), say this: “Stop!” Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

10. Post-test: Record the post walk Borg perceived exertion level and ask this: “What, if anything, kept you from walking farther?”

11. Take post-test vitals: **HR, blood pressure and pulse oximetry**.

12. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.

13. Congratulate the patient on good effort and offer a drink of water.

<u>SAFETY Procedures Six-minute Walk Test (6MWT)</u>

In the efforts to avoid a patient adverse event during the 6MWT the following procedures will be followed:

Layer 1: Screening for Eligibility

Patients will be excluded if they present with any of the following:

1) Serious non-malignant disease, such as cardiac failure or advanced arthritis of weight bearing joints, which would preclude daily treatment and follow-up;

2) Patients for whom physical activity or exercise is contraindicated;

3) Psychiatric or addictive disorders which preclude obtaining informed consent or adherence to the protocol;

Layer 2: Screening prior to, during and following the 6MWT

Set up:

1. Ensure hallway is clear of clutter
2. Ensure set-up includes 2 chairs: placed at each end of 30.57 metre walk distance; chair placed at halfway point.
3. Subjects will be excluded from the testing and study if any of the “Absolute and Relative Contraindications to Exercise Testing” are found prior to testing or at any point during the study.
4. Vitals: the 6MWT will not be performed if any of the following are found at rest:

a. Resting heart rate > 100 b/min
b. Resting systolic blood pressure > 145 mmHg
c. Resting diastolic blood pressure > 100 mmHg
d. Oxygen saturation room air: < 95%

Reasons for immediately stopping a 6MWT include the following:(*1*) chest pain, (*2*) intolerable dyspnea, (*3*) leg cramps, (*4)*staggering, (*5*) diaphoresis, (extreme sweating) and (*6*) pale or ashen appearance.

Physicians Dr. Chan and/or Dr. Barber will be available during the test should any medical issues arise.

Appendix B: Godin

For this questionnaire, we would like you to recall your average weekly exercise (prior to symptoms of your cancer/since your diagnosis/since your treatment). How many times per week on average did you do the following kinds of exercise over the past month?

When answering these questions please:

➢ consider your average over the past month.

➢ 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 line.

	Times Per Week	Average Duration
a. STRENUOUS EXERCISE	___________	___________
(HEART BEATS RAPIDLY, SWEATING)		
(e.g., running, jogging, hockey, soccer, squash, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling, vigorous aerobic dance classes, heavy weight training)		
b. MODERATE EXERCISE	____________	___________
(NOT EXHAUSTING, LIGHT PERSPIRATION)		
(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)		
c. MILD EXERCISE	____________	____________
(MINIMAL EFFORT, NO PERSPIRATION)		
(e.g., easy walking, yoga, archery, fishing, bowling, lawn bowling, shuffleboard, horseshoes, golf, snowmobiling)		

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