A MULTIDISCIPLINARY TEAM APPROACH TO IMPROVING
LONG TERM OUTCOMES IN SARCOMA SURVIVORS

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ABSTRACT

Wide resection surgery is the preferred surgical option for sarcoma, regrettably resulting in significant functional disabilities persisting long term into survivorship. While research into the integration of exercise rehabilitation within cancer populations continues to grow, exercise within sarcoma populations remains very limited. This study investigates the benefit of an 8 week individualised exercise intervention focused on muscular strength, physical function and QOL in sarcoma survivors.

23 participants completed an 8 week fully supervised combined aerobic and resistance based exercise program at Hollywood Functional Rehabilitation Clinic. Given the unique presentation of sarcoma, all exercise programs were individualised to address each participants presenting functional deficits. Physical functioning was measured using the High Mobility Assessment Tool (HiMAT), Six minute walk test (6MWT) and lower limb strength tests. Patient reported QOL was assessed utilising the Short form 36 indices and Toronto Extremity Salvage Score (TESS).

Following the intervention, affected lower limb flexion and extension strength (peak torque) significantly improved by 98% and 67% respectively. This translated into significant improvements in function with HiMAT results increasing by 14% and 6MWTD increasing 76m from baseline evaluations. Little change was evident in patient reported QOL scores.

This study identified that gross functional deficits persisted in the participants even 5 years after surgery, as a consequence of invasive surgery and intensive curative treatments. Despite this, an individualised exercise programmes does improve muscular strength, which when coupled with improved ambulatory ability and exercise tolerance translated to improvements in physical functioning in sarcoma survivors. Future focus on post-operative rehabilitation programs needs to be directed to affected limb strength and gait training to promote improvements in functional activities of daily living.
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STATEMENT OF ORIGINAL CONTRIBUTION

This thesis is presented as an original compilation of research in the field of exercise rehabilitation. All hypotheses posed, and clinical trials undertaken throughout this thesis represent my own ideas, applications and writings. Other people that have significantly contributed to this thesis include my supervisors:

- Winthrop Professor Timothy Ackland (supervisor) has provided assistance with the research proposal, carrying out the research, general guidance, statistical analysis and writing the thesis.

- Dr Brendan Joss (supervisor) has provided assistance with the research proposal, carrying out the research, general guidance, statistical analysis and writing the thesis.

- Ms Jennifer Woodhouse (supervisor) has provided assistance with the research proposal, carrying out the research and general guidance.

- Professor David Wood has provided assistance with carrying out the research and general guidance.

This statement detailing the contribution of original work toward this thesis is accurate. This thesis has been compiled during my Masters candidature at the University of Western Australia and has not been previously used for any other degree.

Claire Munsie
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CHAPTER 1

THE PROBLEM

INTRODUCTION

Sarcomas are rare malignant neoplasms that arise in the mesodermal tissue, and can encompass large portions of muscles, bones, cartilage and fat as well as surrounding supporting structures (Skubitz and D'Adamo 2007). Previously, amputation was the most common treatment for lower extremity sarcoma. However, local recurrence rates with amputation remained at around 10%, thus patients continued to die from metastatic disease (Bickels, Wittig et al. 2002). In recent years the focus has been directed to more effective localised treatments, such as wide resection surgery, in combination with adjuvant therapies to reduce overall mortality rates and increase the likelihood of limb preservation and function (Rosenberg, Tepper et al. 1982, Pollock, Karnell et al. 1996).

With improvements in imaging capabilities as well as the combination of neo-adjuvant therapies, wide resectioning has become a safe and very viable option for a majority of sarcoma patients (Ghert, Alyami et al. 2005). Through a gradual decrease in safe surgical margins and a resultant improvement in post-operative functioning, wide resectioning is now the most commonly adopted practice for treatment of sarcoma patients. Currently it is estimated that 90-95% of all sarcoma patients will undergo wide resectioning as opposed to amputation, with comparable recurrence rates of 10-22% (Lewis, Leung et al. 1997, Yang, Chang et al. 1998, DeLaney, Spiro et al. 2003, Mc Kee, Liu et al. 2004).

Although the use of wide resectioning for sarcoma patients has been accepted as the primary treatment option, debate continues on the utilisation of neo-adjuvant and adjuvant radiotherapy and chemotherapy. Collectively, the use of both neo-adjuvant and adjuvant radiotherapy has shown similar benefits (Davis, O’sullivan et al. 2002, Abraham, Baldini et al. 2010). Although the use of neo-
adjuvant therapy has shown to significantly increase wound healing complications post-surgery, the local and regional control, distant metastases and overall survival rates are comparable between the two groups long term (Davis, O’sullivan et al. 2002, Abraham, Baldini et al. 2010). Similarly, the use of chemotherapy in both settings remains controversial, with greatest effects on disease control, recurrence and survival evident with doxorubicin-based chemotherapy with additional ifosfamide comparative to doxorubicin-based chemotherapy only (Pervaiz, Colterjohn et al. 2008).

Given the invasive nature of wide resection surgery patients can often be left with vast functional deficiencies and disabilities. Markhede and Stener (1981) investigated the functional impairment resulting from resection of the lower limb musculature. With removal of one, two, three or more quadriceps components, a resultant decrease in isometric extensor strength by 22, 33, 55 and 76% respectively was evident. Similarly, the loss of semimembranosus, biceps femoris, or all of the hamstrings group reduced isometric flexor strength by 24, 28 and 67% respectively (Markhede and Stener 1981). Thus, many authors have agreed that the greater proportion of resected muscles, the more functional deficit is observed (Markhede and Stener 1981, Capanna, Scoccianti et al. 2011).

More recently, these findings were supported by Pritsch et al. (2007) who investigated the reconstruction of the extensor mechanism of the anterior compartment of the leg following resection of soft tissue tumours. (Pritsch, Malawer et al. 2007). They concluded that wide resections of less than 850 cm² resulted in better functional outcomes than those greater than this volume of tissue. Hence collectively, these studies suggest that the degree of the disruption to the invaded structures by the sarcoma has direct implications on functional abilities, and should be carefully addressed post-operatively (Markhede and Stener 1981, Pritsch, Malawer et al. 2007, Capanna, Scoccianti et al. 2011)
Much of the literature involving cancer populations refer to 5-year survival rates. This 5-year mark has been considered to be a benchmark definition for long term survival, with survival expressed as 5 years post diagnosis (Foster, Wright et al. 2009). Similarly, Gotay and Muraoka (1998) suggested that 5-year survival is an effective time point, as most recurrence occurs within the first 5 years post diagnosis, with reduced mortality risk thereafter (Gotay and Muraoka 1998). Although these comments should be assessed with caution due to varying recurrence rates amongst different cancer types, it is generally accepted that 5 years post cancer diagnosis is considered long term survival.

Although there has been a progressive improvement in the safe surgical margin and resultant overall survival rates, sarcoma patients continue to suffer physically as a result of cancer treatment (Milne, Wallman et al. 2008). Consequently, exercise rehabilitation programmes are being incorporated into the lives of both sarcoma patients and cancer survivors generally. Potential benefits and harms of an exercise programme must be balanced against the deleterious effects of being physically inactive. Prolonged inactivity may lead to bone mineral loss, muscle atrophy, decrease cardiorespiratory capacity, worsening of glucose metabolism, insulin sensitivity, poor digestive and immune function, and increased cardiovascular risk factors (Schmitz, Holtzman et al. 2005).

Conversely, numerous studies have demonstrated that exercise improves quality of life, aerobic fitness and treatment-related fatigue in cancer patients (Milne, Gordon et al. 2007, Stevinson 2010, Campbell, Stevinson et al. 2012). While proving efficacious in restoring effective physical and psychological functioning, exercise is also thought to offer protective benefits against recurrence or development of future cancers (Schmitz, Ahmed et al. 2005, Stevinson 2010). Although such positive findings have been identified, current research demonstrates that 50% of all adult sarcoma survivors do not meet the recommended minimum physical activity guidelines established by the United States Centre of Disease Control (Wampler, Galantino et al. 2012). This
suggests that exercise may need to be encouraged early in the cancer recovery timeline, to ensure long term adherence and benefits.

The greatest focus on exercise interventions for cancer populations to date has been with breast and prostate cancer patients (Courneya, Mackey et al. 2003, Ohira, Schmitz et al. 2006, Courneya, Segal et al. 2007, Courneya, Sellar et al. 2009, Schmitz 2010). As mentioned, such programmes have shown significant benefits both physically and psychologically. However, there is very little research into the effects of exercise in sarcoma patient populations. Given the individualised nature of sarcoma, it may be reckless to generalise results in breast and prostate cancer trials to these populations (Courneya, Sellar et al. 2009).

To my knowledge, only one study that has investigated the effects of exercise programming with STS patients (Mavros 2011). The nine participants in this study demonstrated significant improvements in affected lower limb range of motion (ROM), thigh flexion, adduction and abduction strength, six minute walk test distance (6MWT) and timed up and go (TUG) scores. These functional improvements were similarly evident the in statistical improvements in the Toronto Extremity Salvage Scores (TESS) and Short form 36 (SF-36) scores. Although limited by the small sample size, this study provides the knowledge that a combined resistance and aerobic exercise programme is not only tolerable and efficacious in sarcoma populations, but also beneficial for functional improvements (Mavros 2011). Consequently, this study fulfils a need for further research in exercise based interventions for sarcoma patients.

**STATEMENT OF THE PROBLEM**

Currently, formal medical management of sarcoma patients continues until 5 years post primary intervention. This 5-year mark is based upon the premise that local recurrence or metastases are most likely to occur within the first 2-5
years post diagnosis (Gotay and Muraoka 1998). Following this, recurrence rates drop from 28% to 14% at 5 and 10 years respectively (Krieg, Hefti et al. 2011) However, once patients are medically cleared and ‘free of cancer’ at 5 years post sarcoma treatment, major functional deficits remain and they are faced with the reality of coping with functional disabilities for the rest of their lives. The consequences from major tissue resection may include muscle weakness, affected ambulation patterns, major motor dysfunction, proprioceptive impairments and persistent pain (Markhede and Stener 1981, Bickels, Wittig et al. 2002, Capanna, Scoccianti et al. 2011). In order to overcome this disability, patients must learn to reactivate and strengthen the surrounding muscles to compensate for such negative changes, thus improving overall function.

Research has demonstrated that a formal exercise programme in the immediate post-operative period improves Sarcoma patients’ strength and joint ROM (Mavros 2011). These improvements translated to improved general functioning, endurance and psychological scores as measured by the High Mobility Assessment tool (HiMAT), SF-36, 6MWT and TESS. Although this study had a relatively small sample size, the results still demonstrated that exercise programmes can be well tolerated by sarcoma survivors. However, the follow up from the Mavros (2011) study concluded at 12 months with no projected outlook to 5 years or beyond. This highlights the lack of on-going care, or long term programmes that patients need once being medically cleared of sarcoma. Our research aims to provide a basis to begin the development of such programmes to be implemented into the Western Australian hospital system.

The aims of this research are:

1. To evaluate the effectiveness of an 8-week fully supervised exercise rehabilitation programme focusing on muscle strength, joint range of motion and cardiovascular fitness in patients who are at least 5 years post wide resection surgery for sarcoma.
2. To restore strength in the affected limb to 80% of non-affected limb values, or those of age-matched, normative functional scores.

3. To assess how any strength or ROM changes improve physical function as measured using HiMAT inventory.

4. To evaluate the effectiveness of a rehabilitation programme on improving overall participant quality of life (QOL) and psychological status as evaluated by the SF-36 questionnaire.

RESEARCH HYPOTHESIS

The following research hypotheses were developed and tested:

1. An 8-week fully supervised exercise programme for 5-year sarcoma survivors, will restore affected lower limb strength to a minimum of 80% of the non-affected limb strength.

2. Improvements in lower limb ROM and strength will result in improved physical functioning post intervention.

3. Collectively, these changes will result in improvements in overall participant QOL and psychological status post intervention.

LIMITATIONS

1. There will be no control group for comparison in this project. Due to the individualised nature of the surgery that each participant in this population has previously undergone, it is not feasible to match patients for the creation of a non-intervention group.

2. The amount and type of tissue excised from the initial surgery will vary between patients and cannot be controlled.

3. It is assumed that performance in functional tests is indicative of participants’ performance during normal activities of daily living.
DELIMITATIONS

1. Patients will only be included in the study if they meet the selection criteria outlined in the Methods section.

2. Patients with an ongoing presence of disease will be excluded.

3. Patients under 18 years of age will not be recruited for ethical reasons, although this age group does make up a large proportion of sarcoma patients, and should be investigated following this study.

DEFINITIONS OF TERMS AND ABBREVIATIONS:

1. Activities of daily living (ADL): activities which individuals may complete on a daily basis; including walking, lifting, sitting, standing and reaching.

2. Adjuvant therapies: are treatments that occur after surgery to prevent recurrence of cancer. Treatments can include radiation, chemotherapy or hormone therapy.


4. High level mobility assessment tool (HiMAT): is a measure of high level mobility suitable to a wide range of populations with motor and cognitive disabilities (Williams, Robertson et al. 2005).

5. Neo-adjuvant therapies: the treatments received before removal of a malignant tumour.

6. Physical activity (PA): any bodily activity that maintains or enhances physical fitness.

7. Quality of life (QOL): a measurement of participant’s behavioural functioning ability, or ability to complete daily activities.

8. Range of motion (ROM): the angular range to which a joint can be moved in a single plane.


11. Social physique anxiety (SPA): occurs when individuals perceive others to be negatively evaluating their physique (Milne, Wallman et al. 2008).

12. Soft tissue sarcoma (STS): are rare malignant tumours that may be present in muscles, fat, joints, nerves and blood vessels.

13. Timed up and go test (TUG): a test of physical function that requires a participant to stand up from a seated position, walk forward for 3 m, turn, walk back and sit down.

14. Toronto extremity salvage score (TESS): a questionnaire specific to limb salvage patients to determine physical functioning changes over time (Davis, Wright et al. 1996).

15. Wide resection: is the gross removal of a tumour with a surrounding margin of normal tissue (Mc Kee, Liu et al. 2004).
CHAPTER 2
LITERATURE REVIEW

The term sarcoma is derived from Greek origins: Sarkos translating to flesh and Sarkoma, fleshy substance (Skubitz and D'Adamo 2007). Sarcomas are rare malignant neoplasms that derive from mesodermal tissue resulting in a tumour or growth developing anywhere throughout the body (Skubitz and D'Adamo 2007). Sarcoma cellular origin can arise from many different tissues including cartilage, nerve, bone, muscle and fat mass; however, approximately 80% of all sarcomas arise in the soft tissue (Ilaslan, Schils et al. 2010).

Sarcomas are a relatively small, complex, heterogeneous group of cancers, with an impact on upon the community disproportionate to its incidence (Thomas, Whyte et al. 2009). Sarcomas account for approximately 1-2% of all adult malignancies, increasing to approximately 7-15% of all childhood malignancies (Morrison 2003). Approximately 800 new sarcoma cases are diagnosed in Australia each year; an average increase of 40% over the past decade (Australian Institute of Health and Welfare, 1998).

The World Health Organisation (WHO) has identified more than 70 histologically and biologically distinct sarcoma subtypes. However, they are commonly grouped into Soft Tissue Sarcomas (STS) and Primary Bone Sarcomas according to the adult tissue they resemble (Pollock, Karnell et al. 1996, Shmookler, Bickels et al. 2001). The three most common soft tissue sarcomas are malignant fibrous histiocytoma (MFH), commonly found in the extremities, liposarcoma originating in the retroperitoneum, and leiomyosarcoma, generally occurring in the abdominal cavity. Ewing Sarcoma, Osteosarcoma and Chondrosarcoma are the most commonly occurring primary bone sarcomas (Shmookler, Bickels et al. 2001). The majority of primary lesions occur in the lower limb extremities, with an overall incidence of 46%, of which 30-50% of these are located in the thigh (Justesen, Kelly et al. 2004). Comparative
incidence rates in the trunk are approximately 19%, with 13% in the upper extremity, 12% in the retroperitoneum, 9% in the head and neck and 1% in other locations respectively (Shmookler, Bickels et al. 2001).

While Sarcomas are heterogenous in nature, they contain common clinical features and pathologies. It has been agreed in the literature that size, histological grade and location in relation to the deep fascia are the most important clinical diagnostic features (Pollock, Karnell et al. 1996). In addition, the presence or not of lymph node and/or distant metastases are also very important clinical features (Pollock, Karnell et al. 1996, Johnson 2001). Johnston et al. (2001) determined that a tumour of greater than 5 cm, with associated pain, increasing size and location below the deep fascia increased likelihood of malignancy to 81%, thus potentially affecting survival rates (Johnston 2001). Early diagnosis and treatment, to stunt tumour growth beyond 5 cm, increases the likelihood of a positive prognosis long term (Johnston 2001).

CURRENT TREATMENT OPTIONS

Over the past two decades, treatment focus has shifted from unimodal radical surgery and amputation, to multi-modal treatment including tissue conserving surgery, such as wide resectioning, combined with adjuvant therapies (Rosenberg, Tepper et al. 1982, Pollock, Karnell et al. 1996). Previous research has supported this trend showing a three-fold increase in wide local excision, to 45.2% of all patients, with a converse reduction in amputation from 35.5% to 11.1% over a 5-year period (1988-1993) (Pollock, Karnell et al. 1996). This trend has continued with rates of wide resectioning currently at 90-95% in all STS patients (Yang, Chang et al. 1998, DeLaney, Spiro et al. 2003). Wide resection surgery not only enables limb preservation, but addresses local recurrence issues, with rates of 10-22% comparable to amputation, which is estimated to be 10% (Lewis, Leung et al. 1997, Bickels, Wittig et al. 2002, Mc Kee, Liu et al. 2004). This control of local recurrence is essential, as it has been demonstrated
Several prognostic factors have been identified to be predictors of survival at 5 years post cancer diagnosis. Five-year sarcoma survival rates are 45-55%, with the lowest proportion of survival in osteosarcoma patients (19%) (Kawai, Healey et al. 1998, Wirbel, Schulte et al. 2000, Jawad, Haleem et al. 2011). These prognostic factors affecting survival include the safe surgical margin and clinical stage of the disease progression (Wirbel, Schulte et al. 2000). In addition, Jawad et al. (2001) suggested age; stage, grade and size of tumour; histopathology; and use of surgical technique to be independent predictors of survival at 5 years (Pollock, Karnell et al. 1996, Jawad, Haleem et al. 2011).

This 5-year post diagnosis is considered the benchmark definition for long term survival in cancer patients (Foster, Wright et al. 2009). Gotay and Muraoka (1998) explained that 5-year survival is an effective time point, as most recurrence occurs within the first 5 years after diagnosis, with reducing mortality risk thereafter (Gotay and Muraoka 1998). Although these comments should be assessed with caution due to varying recurrence rates amongst different cancer types, it is accepted that 5 years post cancer diagnosis is considered to be long term survival (Hankey and Steinhorn 1982).

**WIDE RESECTION SURGERY**

Wide resection surgery is defined as resection of the gross tumour with a surrounding margin of normal-appearing tissue (Justesen, Kelly et al. 2004). Whilst wide resectioning aims to improve the likelihood of limb preservation and function comparative to amputation, it may still result in significant disruption to functioning structures and surroundings. Over the previous two decades, there has been marked improvement in imaging quality, as well as the use of neo-adjuvant therapies, to increase the likelihood of limb preservation that is vital to limb function.
Several authors have identified surgical margin to be an important prognostic factor for local recurrence, with negative margins being favoured, meaning no tumour tissue being present at the margin (Rosenberg, Tepper et al. 1982, Justesen, Kelly et al. 2004, Mc Kee, Liu et al. 2004). McKee and colleagues (Mc Kee, Liu et al. 2004) suggested that for optimal reduction in local recurrence, a negative margin of greater than 10 mm (10 mm of tumour-free tissue) is essential (Rosenberg, Tepper et al. 1982). McKee also suggested that patients with negative margins of less than 10 mm had similar local recurrence rates to those with positive margins (Mc Kee, Liu et al. 2004). Similarly, the presence of a positive margin nearly doubles the risk of local recurrence to 28%, compared to 15% in negative margin cases (Stojadinovic, Leung et al. 2002). Although negative margins are preferred in wide resectioning, it must be accepted that this is not always achievable. If tumours are adjacent to motor nerves and bones, they are generally avoided in order to preserve function (Mc Kee, Liu et al. 2004).

The National Cancer Institute (NCI) affirms that equivalent local control, disease-free survival (DFS) and overall survival (OS) rates can be achieved with wide local excision with adjuvant therapies (Korah, Deyrup et al. 2012). However, unlike many other types of cancer, sarcomas are far less sensitive to chemotherapy and/or radiation, which must be taken into consideration when deciding on treatment protocols. Although the sarcoma can be insensitive to such adjuvant therapies, they are commonly adopted for treatments of micrometastases, preoperative cytoreduction (reducing the size of the primary tumour) and local recurrence (Justesen, Kelly et al. 2004). The theoretical advantage of neo-adjuvant chemotherapy, is this potential reduction in tumour size, thereby facilitating less radical surgery and leading to decreased functional deficits (Eilber, Rosen et al. 2001).

The optimal timing of radiation therapy remains under investigation. Authors have debated the benefits of neo-adjuvant versus adjuvant therapy on local and regional control, distant metastases and overall survival for many years and have agreed that both protocols can adequately address these issues (Davis,
O'sullivan et al. 2002, Abraham, Baldini et al. 2010). However, although both protocols demonstrate similar benefits, a significant difference in wound complication rates has been identified (Davis, O'sullivan et al. 2002, O'Sullivan, Davis et al. 2002), with 35% of preoperative (neo adjuvant) radiation cases resulting in wound complication compared to 17% in post-operative radiation cases. These wound complications, coupled with tumour characteristics were identified to affect limb function and resultant quality of life and so, must be taken into consideration when deciding on RT administration (O'Sullivan, Davis et al. 2002).

The role of neo-adjuvant and adjuvant chemotherapy for patients with STS remains controversial. The first collaborative paper investigating the role of chemotherapy in sarcoma treatment was the Sarcoma Meta-Analysis Collaboration (SMAC) (1995), which analysed 1,568 patients, randomised to adjuvant chemotherapy versus no chemotherapy controls. This analysis demonstrated a significant reduction in risk of local or distant recurrence in patients who received doxorubicin-based chemotherapy compared to no chemotherapy controls. Although overall survival at 10 years was not significantly different (54% for patients who received chemotherapy; 50% who did not), the trend was still evident and may be clinically relevant. (Tierney, Mosseri et al. 1995).

More recently, the European Organisation for Research and Treatment of Cancer (EORTC) (2008) conducted a further meta-analysis to determine the benefits of adjuvant chemotherapy in 1,953 sarcoma patients (Pervaiz, Colterjohn et al. 2008). This meta-analysis supported previous research showing a risk reduction in local recurrence, distant recurrence and overall recurrence in these sarcoma patients (Pervaiz, Colterjohn et al. 2008). Similar to the SMAC study (1995) which showed trend towards risk reduction in overall survival at 5 years with doxorubicin-based chemotherapy, the EORTC reached statistical significance in overall survival rated with adjuvant chemotherapy (Tierney, Mosseri et al. 1995, Pervaiz, Colterjohn et al. 2008). It must be noted, however, that the latter protocol was a combination of doxorubicin-based
chemotherapy with additional ifosfamide. Although both studies demonstrated positive associations for chemotherapy as an adjuvant therapy with wide resectioning, the authors of both studies mentioned the need for chemotherapy treatment to be assessed on an individual basis, considering other factors in particular tumour size, grade and histological type. (Tierney, Mosseri et al. 1995, Pervaiz, Colterjohn et al. 2008).

**CONSEQUENCES OF SARCOMA TREATMENT**

Given the invasive nature of sarcoma, large portions of tissue, adjacent nerves and blood vessels often become compromised. With advances in anatomic imaging and the use of adjuvant therapies, decreased safe surgical margins are occurring, thereby increasing the likelihood of preservation of vital structures that are key to every day function (Ghert, Alyami et al. 2005). Several authors have suggested three factors contribute to poor function post limb preservation surgery, including tumour size, nerve resection and other complications (Brooks, Gold et al. 2002, Davis, O’sullivan et al. 2002).

Unfortunately, the preservation of vital structures is not always possible in aggressive tumour presentation, thus major nerves, large portions of muscles, bones and blood vessels may need to be resected. Markhede and Stener (1981) investigated the functional impairment resulting from resection of the lower limb musculature. As expected, a greater proportion of resected muscles is associated with an increased functional deficit (Markhede and Stener 1981). With removal of one, two, three or more quadriceps components, a resultant decrease in isometric extensor strength by 22, 33, 55 and 76% respectively, was evident. Similarly, the loss of semimembranosis, biceps femoris, or both of these hamstring muscles reduced isometric flexor strength by 24, 28 and 67% respectively (Markhede and Stener 1981). This was further supported by Capanna et al (1991) who reported that the degree of the resection had implications on post-operative functional results (Capanna, Scoccianti et al. 2011). Furthermore, Pritsch et al. (2007) investigated the reconstruction of the extensor mechanism of the anterior compartment of the leg following resection...
of soft tissue tumours (Pritsch, Malawer et al. 2007). They concluded that wide resections of less than 850 cm$^2$ resulted in better functional outcomes than those of greater volume (Pritsch, Malawer et al. 2007). In summary, it has been stated by several authors that the degree of the disruption to the invaded structures by the sarcoma has implications for ongoing functional abilities.

One of the major concerns of limb salvage surgery relates to neurovascular involvement by the tumour (Ghert, Alyami et al. 2005). Vascular resection and reconstruction as a consequence of wide resection surgery has been shown to result in an increased likelihood of patients requiring muscle transfers, wound complications, deep vein thrombosis and clinically significant limb oedema. As resection of large vessels implies the loss of contralateral vessels and disruption of lymphatic draining, resulting in further wound complications, with potentially increased risk of amputation. Although vascular resection has increased prognostic risk factors, Ghert et al. (2005) demonstrated only slight differences in limb function at 1 year post-surgery compared to those who did not have vascular resection as part of their wide resection surgery.

While preservation of limbs through wide resectioning of muscles, bones and even vascular structures continues to be accepted as functionally viable, resection of major motor nerves remains a controversial issue (Brooks, Gold et al. 2002). Few studies have investigated the surgical management of sarcomas encompassing motor nerve involvement and the resultant functional deficits (Brooks, Gold et al. 2002). Brooks et al. (2002) reviewed the functional abilities of 11 patients who had undergone motor nerve resection in the lower limb, and determined that sciatic nerve resection was a functionally viable option. This resection would result in a balanced flail foot, with no equinus deformity, but also no ability to push off through the plantar flexion muscles of the foot. The authors noted, however, that this could be managed with a sciatic ankle brace (Brooks, Gold et al. 2002). Similar findings were reported by Bickles et al. (2002), whereby sciatic nerve resection resulted in a good functional outcome in 11 patients, moderate in three and poor in one patient. However, Kawai et al. (2002) concluded, through case study evaluation, that patients who underwent
sciatic nerve resection faced significant functional deficits and poor gait patterns at 5 years post-surgery. Although each of these studies has presented important facts on nerve resections, they each had very small samples and the results must be interpreted with caution.

The functional consequences of resecting the femoral nerve through wide resection surgery for sarcoma treatment has not been greatly evaluated (Jones, Ferguson et al. 2010). Previously, femoral nerve resections were thought to be well tolerated and less debilitating than sciatic nerve resections. However, Jones et al. (2010) suggested a greater morbidity with femoral nerve resections than was previously thought. Through sacrifice of the extensor mechanism in the anterior thigh, patients had an increased risk of falls, with Jones et al.(2010) documenting six out of 10 patients suffering fractures as result of falling after femoral nerve resection (Jones, Ferguson et al. 2010). To my knowledge this study is the only published research on femoral nerve resections, and whilst limited by a small sample size, it highlighted the need to consider further the functional consequences of femoral nerve resection for sarcoma patients.

Despite the continual advances in anatomic imaging and resultant accuracy of wide resectioning surgery, patients continue to suffer from extensive functional deficits. Several studies have identified the level of deficit that patients incur is dependent on the extent of invasion to the surrounding structures and resultant volume of resectioning (Markhede and Stener 1981, Pritsch, Malawer et al. 2007, Capanna, Scoccianti et al. 2011). Similarly, resection of vital nerves and vascular structures is associated with significant consequences for patient function. Vascular resection and reconstruction is now widely accepted, with promising results. However motor nerve resection continues to be a controversial issue, with further research required in this field (Bickels, Wittig et al. 2002, Brooks, Gold et al. 2002, Jones, Ferguson et al. 2010).

Although the direct aetiology of sarcoma is unknown, sarcoma patients tend to exhibit several co-morbidities to the cancer itself, and are twice as likely to
inherit them as healthy matched individuals (Brown, Byers et al. 2003). While these co-morbidities are independent of prognosis, they are clinical indicators of the complexity of the patients’ needs and must be considered during the recovery phase. The common comorbidities are cardiovascular disease (33%), respiratory disease (10%) and diabetes (7%). The most common sarcoma-related symptom is fatigue, which may be accompanied by depression (6%) and anemia (6%), and so are similarly identified as co-morbidities. (Ness, Mertens et al. 2005, Herk-Sukel, Shantakumar et al. 2012). Collectively these co-morbidities can influence a patient’s ability to cope with the rigorous treatment for sarcoma, as well as the many years of rehabilitation that follow.

Cancer related fatigue (CRF) is the most commonly reported adverse side effect among cancer treatment populations, affecting 70-90% of all cancer patients (McNeely and Courneya 2010). CRF has been defined as the persistent, subjective, sense of tiredness related to cancer or cancer treatment that interferes with usual functioning (Janaki, Kadam et al. 2010). It is a complex and multi-factorial problem with unknown etiology. CRF may be due to the cancer treatment itself, cancer related anemia (caused by bone marrow involvement, blood loss, nutritional deficiencies, chemo or radiotherapy), deconditioning and high levels of cytokines (Watson and Mock 2004). CRF may continue for long periods of time post cancer treatment, with a profound impact on patient’s QOL, as they become too tired to participate in usual activities and normal social roles (McNeely and Courneya 2010). Therefore, not only do multi-disciplinary teams need to treat the cancer itself, they may be required to consider co-morbidities, or cancer treatment-related symptoms throughout the treatment process to ensure quality of life is maintained.

EXERCISE AS TREATMENT FOR CANCER SURVIVORS

“Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it” — Plato (427–347 BC)
Although cancer treatments can prove efficacious in managing the cancer itself, they are not site specific. Due to widespread physiological affects, structural and functional changes may occur, affecting physical performance, resulting in long term implications for sarcoma survivors (Ness, Mertens et al. 2005, Schmitz 2010). As previously highlighted, there are significant functional consequences as a result of wide resectioning. Physiological effects including pain, nausea, vomiting, anemia and lymphedema are common in cancer populations, thus significantly affecting a patient’s ability to function independently (Ness, Mertens et al. 2005, Herk-Sukel, Shantakumar et al. 2012, Siegel, DeSantis et al. 2012). These implications can result in increased dependence on others, reduced self-esteem, increased psychological stress, inability to manage self-care, and limitations in social and work situations (Dimeo, Thomas et al. 2004, Ness, Mertens et al. 2005). Such limitations have been reported in approximately 69% of childhood cancer survivors (Ness, Mertens et al. 2005). Therefore, improving functional performance status through exercise programmes may increase quality of life and reduce psychological stress (Dimeo, Thomas et al. 2004).

Exercise rehabilitation for patients, both during cancer treatment as well as the recovery phases, has been widely reviewed. Historically, physicians had recommended rest and avoidance of any strenuous activity for cancer patients to ensure optimal recovery from treatment (PANEL 2010). However, in recent years, evidence has emerged to suggest that physical activity does not cause excessive harm to cancer patients but rather, can improve their health status and overall quality of life (Brown, Byers et al. 2003, Courneya, Mackey et al. 2003, PANEL 2010, Rock, Doyle et al. 2012). Potential benefits of physical activity must be balanced against the negative effects of being inactive. Inactivity may lead to bone mineral loss, muscle atrophy, decrease cardiorespiratory capacity, worsening of glucose metabolism, insulin sensitivity, digestive function, immune function, and cardiovascular risk factors and can result in further deconditioning. Consequently, a self-perpetuating condition results, with diminished activity leading to de-conditioning and vice versa (Dimeo, Stieglitz et al. 1999, Schmitz, Holtzman et al. 2005, Courneya, Sellar et al. 2009).
Whilst research evidence supporting the positive benefits of exercise both during and after cancer treatment is growing, participant involvement does not currently reflect this. Current physical activity (PA) guidelines for healthy Australians recommend adults need to accumulate at least 30 minutes of moderate intensity exercise on most days of the week, with additional vigorous intensity exercise for extra health and fitness benefits (Australian Government, department of health and ageing). However, Milne, Gordon et al. (2007) indicated that overall PA levels declined during active treatment for breast cancer, and a majority of participants were not exercising enough to accrue important health benefits. This decrease in PA is most likely due to the side effects that survivors experience during treatment, such as pain, fatigue and nausea. Equally, this reduction in PA may be due to psychological, socio-economic and domestic changes that result as a consequence of cancer diagnosis (Milne, Gordon et al. 2007). Thus, PA initiation and adherence seems to pose a problem for cancer survivors, and this issue requires further investigation.

Although the body of research in exercise and cancer populations is growing, there are currently no specific, published guidelines to suggest the most efficient mode, duration and intensity for interventions. Brown et al. (2003) suggested patients should engage in at least 30 minutes of moderate intensity exercise on five or more days per week (Brown, Byers et al. 2003). Likewise, Rock et al. (2012) supported these recommendations, with an additional inclusion of two days of strength training per week (Rock, Doyle et al. 2012). Rock et al. (2012) also stated that cancer patients should avoid prolonged inactivity and return to normal activities as soon as possible following diagnosis (Rock, Doyle et al. 2012). Furthermore, guidelines suggested by the American College of Sports Medicine (ACSM) and the American Heart Association for healthy individuals also indicate that cancer treatments should not hinder participation in regular PA (Haskell, Lee et al. 2007).
AEROBIC EXERCISE PROGRAMMES

Aerobic exercise tends to be the preferred intervention for cancer survivors (Conn, Hafdahl et al. 2006). However, a meta-analysis in 2006 demonstrated vast differences in the exercise mode prescribed in each aerobic intervention (Conn, Hafdahl et al. 2006). A majority of studies in cancer populations have used walking and cycling for aerobic intervention due to ease of accessibility (Segal, Evans et al. 2001, Courneya, Mackey et al. 2003, Conn, Hafdahl et al. 2006, Mutrie, Campbell et al. 2007); however, stair climbing machines and interval training have also been evident.

Aerobic exercise has been shown to improve physical performance, health related quality of life (HRQOL), psychological scores and cancer related physical and mental fatigue in cancer populations when compared to non-exercising groups (Dimeo, Tilmann et al. 1997, Courneya, Mackey et al. 2003, Dimeo, Thomas et al. 2004, Mutrie, Campbell et al. 2007). Dimeo et al. (2004) demonstrated that an aerobic exercise programme post-adjuvant therapy resulted in clinically relevant improvements in maximal physical performance for 72 cancer patients (Dimeo, Thomas et al. 2004). Furthermore, the aerobic programme resulted in improved emotional stability and elevated mood states (Dimeo, Thomas et al. 2004). This supports previous findings that indicated improvements in mental state and reduced psychological stress in patients undergoing active chemotherapy (Dimeo, Stieglitz et al. 1999). Collectively, these papers suggest aerobic training in both the adjuvant and post-adjuvant settings may be beneficial for physical and psychological health.

Although Segal et al. (2003) and Dimeo et al (2004) both reported that aerobic exercise resulted in improvements in physical performance, they also identified that it lacked resultant changes in cognitive fatigue states (Segal, Reid et al. 2003, Dimeo, Thomas et al. 2004). Furthermore, this was supported by Segal et al. (2009) who demonstrated a lack of significant change in fatigue long term with aerobic training comparative to resistance training (Segal, Reid et al. 2009). Although several studies have demonstrated improved benefits with
aerobic training, they may be negated by the lack of improvement in fatigue states.
RESISTANCE EXERCISE PROGRAMMES

Despite our understanding of cancer-related muscle wasting, and the potential beneficial role of resistance exercise, a majority of reported exercise rehabilitation interventions only incorporated aerobic exercises (De Backer, Schep et al. 2009). This continued focus on aerobic exercise for cancer survivors resulted in limited knowledge and research on the subject. Emerging in 2003 (Segal, Reid et al. 2003), was a study investigating the effects of resistance exercise in men receiving androgen deprivation therapy for prostate cancer. This study was the first to demonstrate that resistance exercise assisted with reducing the symptoms of CRF. The authors also demonstrated that resistance exercise improves health related QOL and muscular fitness in men with prostate cancer (Segal, Reid et al. 2003). These results were supported by Schmitz et al. (2005) who demonstrated that resistance training was safe and behaviourally feasible in breast cancer survivors (Schmitz, Ahmed et al. 2005). This study also demonstrated a reduction in body fat and an increase in lean muscle mass following the intervention (Schmitz, Ahmed et al. 2005).

Resistance training has also been prescribed for breast cancer patients with positive results (Schmitz, Ahmed et al. 2009). A 1-year resistance programme reduced the number and severity of arm and hand symptoms of breast cancer-associated lymphedema, as well increased muscular strength and reduced lymphedema exacerbations (Schmitz, Ahmed et al. 2009). These results were support by Ohira et al. (2006), who identified improvements in physical and psychological QOL scores, which were associated with increases in lean muscle mass and upper body strength. Similarly, an earlier study by Schmitz et al demonstrated decreases in body fat percentage, as well as insulin-like growth factor II (IGF-II) (Schmitz, Ahmed et al. 2005). Collectively, these studies suggest important improvements in several aspects of QOL may be achieved through resistance based training for cancer patients.
COMBINED RESISTANCE AND AEROBIC PROGRAMMES

Whilst debate continues as to which modality of exercise produces the best rehabilitation results in cancer populations, combined resistance and aerobic exercise programmes become more commonly prescribed. Milne and colleagues demonstrated improvements in physical and psychological factors as a result of a 12-week, supervised, combined resistance and aerobic programme in 58 breast cancer survivors. (Milne, Wallman et al. 2008). Meaningful improvements in QOL, fatigue, Social Physique Anxiety (SPA), aerobic fitness and muscular strength were evident at an interim testing point (6 weeks) and at the conclusion of the intervention at 12 weeks (Milne, Wallman et al. 2008).

These results were similarly reflected by Mutrie et al, who found improvements in physical and psychological scores in an combined modality exercise based intervention group compared to a control group (Mutrie, Campbell et al. 2007). However, it must be noted that this study was conducted in a group setting, and the authors suggested that the physical and psychological benefits may be attributed to the exercise, the group experience, or by a combination of both (Mutrie, Campbell et al. 2007).

SPECIFIC EXERCISE INTERVENTIONS FOR SARCOMA PATIENTS

As previously mentioned, exercise training improves health outcomes in breast cancer patients (Courneya, Mackey et al. 2003, Courneya, Segal et al. 2007, Milne, Gordon et al. 2007) and prostate cancer patients (Segal, Reid et al. 2003, Segal, Reid et al. 2009), but minimal research has been conducted on sarcoma populations. Given the individualised nature of sarcoma, we must be cautious not to generalise results from breast and prostate cancer trials to sarcoma patients (Courneya, Sellar et al. 2009).

To my knowledge, only one paper exists investigating the direct effects of a combined, progressive, aerobic and resistance exercise programme on
Sarcoma patients. Mavros (2011) concluded that a 12-week exercise programme was not only safe and tolerable in nine sarcoma patients, but also resulted in improvements in strength and functional scores. This study demonstrated that the patients’ affected limb strengths were restored to within 80% of that measured in the non-affected limb, with no statistical difference in strength evident between the two limbs following the intervention. These improvements in strength translated to statistical improvements in 6MWT and TUG scores, but remained well below age-matched normative data (Gibbons, Fruchter et al. 2001). Furthermore, significant improvements in function were evident between baseline and 6 weeks and through to 12 weeks in this cohort as measured by the HiMAT. Statistical improvements were also evident for both the TESS and SF-36 scores, suggesting subjective evaluation of patient coping (both physically and mentally) was also met (Mavros 2011).

While it is evident from the results of Mavros’ (2011) study that sarcoma patients benefit from an exercise intervention, they must be interpreted with caution. This study had a very small sample size, with only nine participants completing the total intervention. However, it also highlights the need for further research in this field to enable a greater generalisation of results.

**SUMMARY**

Wide resection surgery, combined with adjuvant therapies, is now commonly accepted as a safe, feasible and effective treatment for the majority sarcoma diagnoses (Yang, Chang et al. 1998, DeLaney, Spiro et al. 2003) While the use of neo-adjuvant and adjuvant therapies, along with improvements in imaging is slowly decreasing the safe surgical margins for sarcoma patients, significant disruption to functional structures remain (Ghert, Alyami et al. 2005). Consequently, major disruption to physical functioning continues to be an ongoing problem for sarcoma patients during their recovery from surgery.
Numerous studies have investigated the feasibility of exercise rehabilitation programmes in cancer survivors. A majority of the current literature available involves implementation of exercise programmes in breast and prostate cancer populations, with very promising results. The published studies varied greatly in terms of recruit populations and intervention characteristics such as mode, intensity and duration, thus making generalisation to other cancer populations difficult.

Previous research has identified significant improvements in strength, aerobic fitness, QOL, fatigue and psychological scores through aerobic, resistance or combined programmes in a variety of cancer populations. However, given the individualised nature of sarcoma, it would be inappropriate to generalise the results from these studies to sarcoma populations. More recently, a pilot study identified significant improvements in strength, functioning and QOL scores through a combined resistance and aerobic programme in nine sarcoma patients. The small sample size of this study lessens the ability to generalise these results and highlights the need for further research in this field.
CHAPTER 3
METHODS AND PROCEDURES

This study is part of a larger research project, funded by the Hannah Chance Foundation courtesy of the Australian Sarcoma Study Group, currently being undertaken at Edith Cowan University and The University of Western Australia. A team of experts in orthopaedic and plastic surgery, musculo-skeletal rehabilitation, and psychology examined the benefits of a multidisciplinary approach to improving long term outcomes for patients following wide resection surgery of sarcomas. Specifically, this masters project aimed to evaluate the effectiveness of an 8-week fully supervised exercise rehabilitation programme focusing on muscle strength, joint range of motion and cardiovascular fitness in patients who are at least 5 years post wide resection surgery for sarcoma. This chapter will focus on the methods and procedures used in this study.

SAMPLE

Participants who had previously undergone wide resection surgery for lower limb sarcoma were identified through a sarcoma registry database. Patients were only recruited from two orthopaedic surgeons, operating at three hospitals in Perth. Following identification from the registry, a covering letter and information package was sent to each potential participant, inviting them to take part in the study (Appendix A).

Participants were given 2 weeks to respond to this initial invitation to join the study. All non-responders were contacted by telephone to confirm if they had received the package and to ascertain if they would be interested in participating in the study. Those who registered interest in joining the study were then contacted by telephone to assess inclusion and exclusion criteria. An initial baseline test was scheduled if participants met all the inclusion criteria and did not violate any of the exclusion criteria.
The following inclusion criteria were met for each participant:

5. At least 5 years post treatment for sarcoma involving wide resection surgery on the lower limb;

6. Male or female between the ages of 18-65 years;

7. Live in the Perth metropolitan area;

8. Provided voluntary, written informed consent to participate in this investigation and permitted de-identified data from this study to be published; and

9. Capable of completing an exercise based programme.

Participants were excluded from the study if they met any of the following criteria:

- Currently engaged in a formal rehabilitation programme at an alternate institution;

- Estimated life expectancy of less than 1 year;

- A concurrent orthopaedic condition(s) to that being treated;

- Cognitive disturbances, serious psychopathy or emotional instability that may hinder participation in the study;

- Not competent in speaking, reading and understanding questions, and providing responses in English; and

- Presence of severe cardiovascular disease or a life threatening illness.

The initial baseline assessment was conducted at Hollywood Functional Rehabilitation Clinic (HFRC) and lasted approximately 1 hour. Following this assessment, a second baseline assessment was scheduled for 1 week later. This second baseline assessment was utilised to ensure that patients’ physical and psychological state was stable. If participants’ second baseline results differed by more than 10% from the initial baseline scores, then a third baseline
assessment was conducted. Otherwise, their performance was considered stable and participants were approved to commence the rehabilitation programme.

For this study 25 participants with a previous malignant diagnosis (sarcoma) and minimum of 5 years following wide resection surgery were recruited. This was based on results derived from a power analysis, using the HiMAT as the primary outcome measure and information from a previously conducted sarcoma pilot study (Mavros 2011). Twenty-two participants were necessary to find statistical differences (p=0.05) with 80% power. Therefore, we accounted for a potential 10% dropout by recruiting 25 participants in total. Two participants dropped out due to travel constraints. There was no control group for this study as this is not a homogenous participant population. Given the individualised nature of each wide resection surgery, it would be impossible to match tumour size, growth, location and treatment type, in order to match pairs of individuals for a treatment versus control group design. Therefore, outcomes were compared over time, and between affected and non-affected limbs, as well as to aged matched normative data.

Prior to commencing the study participants were required to read a patient information sheet, and provide informed consent to participate in this study (Appendix B). This study was approved by the University of Western Australia’s Human Research Ethics committee (HREC) (Appendix C). This research project was funded by the Australian Sarcoma Study Group.

METHODS

Outcome measures and assessments

Primary and secondary outcome measures were recorded twice at baseline, once at the conclusion of the program at 8 weeks, and again at 8 weeks post intervention. The primary outcome measure of this study was participant physical function, as measured by the HiMAT. Other outcome measures
assessed perceived physical function and QOL, as well as key factors influencing these variables. These secondary outcome measures were the TESS, SF-36, muscular strength, 6MWT and knee, ankle and hip ROM.

**Baseline testing procedure**

The initial baseline assessment commenced with a comprehensive interview to obtain information about current and previous treatments, current physical activity level, pain scales, goals, medications and past medical history. The patient then completed the SF-36 and TESS questionnaires on their own, and without assistance from study investigators. Participants then completed a series of objective tasks, as follows:

- **Stature** was assessed using an anthropometer attached to the wall. Participants were instructed to stand without shoes or socks as straight as possible, with feet, buttocks, shoulders and head remaining in contact with the wall.
- **Body weight** was measured on a set of calibrated electronic scales, with participants wearing light clothing but no shoes.
- **Body mass index** was calculated using body weight in kilograms divided by stature in metres squared.
- **Blood pressure** was measured manually using a sphygmomanometer and stethoscope.

**Primary outcome measures and assessments**

The primary outcome measure for this study was the assessment of physical function as measured by the HiMAT. The HiMAT is a uni-dimensional measure of high level mobility that was originally developed for people with traumatic brain injury (Williams, Robertson et al. 2005). The test consists of 13 items that assess high-level walking tasks. Each item is scored and values are summed for a total score; higher scores indicate better mobility (maximum score = 54). Each task is measured by either a stopwatch or measuring tape and the test
takes approximately 5-15 minutes to complete. The test has high inter-rater reliability, retest reliability and internal consistency (Williams, Robertson et al. 2005, Williams, Robertson et al. 2006, Williams, Greenwood et al. 2006). Although this test was developed to assess patients who had suffered traumatic brain injuries it has, more recently, been employed to assess mobility in limb salvage patients (Mavros 2011). An outline of the testing protocol is listed below.

4. Walking forwards and backwards: the participant was instructed to walk “as quickly and as safety as possible” between two points marked 20 m apart. The middle 10 m was timed and recorded. Participants were then instructed to repeat this test walking backwards.

5. Walking on “toes”: Measured as for the walking tasks above, but with participants walking on the balls of their feet. Any heel contact throughout the test was recorded as a fail.

6. Walking over an obstacle: Measured as for the walking tasks above, but with an object the size of a house brick placed at the mid-point. Participants were instructed to step over the brick without contacting it. A fail was recorded if the participant contacted the brick or walked around it.

7. Run: Time to cover the middle 10 m of a flat, carpeted, 20 m course was recorded. A fail was recorded if participants did not have a consistent flight phase while running during the trial.

8. Skip: As for the run test, but with participants skipping.

9. Hop: Participants stood on their more affected leg and hopped forward. The time taken to hop 10 m was recorded.

10. Bound (affected leg): A bound is a jump from one leg to the other with a flight phase. Participants were instructed to stand behind a line on their less affected leg, hands on hips, and jump forward to land on their more affected leg. The average distance covered of three trials was recorded.

11. Bound (less affected leg): Participants stood behind a line, hands on hips, and jumped forward to land on their less affected leg. The average of three trials was recorded.
12. Up-stairs: Participants walked up a flight of 14 stairs at their normal, self-selected pace. The elapsed time was recorded from when the participant started climbing until both feet were at the top. Participants who used the rail or a non-reciprocal stepping pattern were scored as ‘upstairs dependent’. Participants who ascend the stairs reciprocally without the rail were scored in ‘upstairs independent’ and were allocated an additional five points for this task.

13. Down stairs: Measured as for upstairs, but with participants beginning at the top of the staircase and descending at a normal, self-selected pace.

**Secondary outcome measures and assessments**

The secondary outcome measures were subjective assessments of perceived physical function and QOL using the SF-36 and TESS. Key variables that affect these measures, including lower limb strength, ROM and 6MWTD were also recorded.

The TESS is currently the only disease-specific subjective, measure developed to assess physical disability in patients who had undergone limb salvage surgery of the extremities (Davis, Wright et al. 1996). The TESS accounts for the relative heterogeneity of sarcoma populations and reflects the disability of the extremity as a whole, rather than to joint-specific disabilities. It may also be used to evaluate the change in function over time due to different therapeutic interventions. There is an upper and lower limb version of this questionnaire, each comprising 32 items, which were completed by the participant without assistance.

The SF-36 is a multi-purpose, short form health survey consisting of 36 questions. It is a multi-item scale measuring eight separate domains; which are physical functioning, role limitations due to physical health problems, bodily pain, social functioning, general mental health, role limitations due to mental health problems, vitality and general health perceptions (Ware Jr and Gandek
These eight domains are combined to create summary scores - the physical component summary score (PCS) and the mental component summary score (MCS). Values are assigned to each health concept, which are summed and converted to a score out of 100, whereby zero represents the lowest possible score and 100 represents the highest. Higher scores represent better perceived health. This scale has been used frequently to study a broad variety of populations, including chronic pain, cardiac rehabilitation and joint pain. The summary scores for the test were calculated using the algorithm published at: www.sf-36.org/demos/SF-36.html.

The 6MWT is a test of mobility, while taking into account any limitations imposed by cardiovascular or musculoskeletal systems (Enright 2003). The primary outcome for the 6MWT is 6-minute walk distance, which is the distance covered by the patients over the 6-minute period. Patients were instructed to walk between two points 50 m apart, as quickly and comfortably as they safely could manage for the duration of the test. The tester provided standardised phrases, with no encouragement given, but did not walk with the participant. This protocol ensures the patient was not influenced to perform better. Distance covered, pain in affected limb and dypsnea were recorded at the completion of the test.

Lower limb strength measurements

Lower limb strength was measured bilaterally to evaluate strength deficits on the affected limb compared to the non-affected limb. Strength was evaluated using a Keylink isokinetic dynamometer (Isosport international, isokinetic dynamometer, Gepps Cross, South Australia) and a three repetition maximum (3RM) testing protocol. Leg flexor and extensor strength was measured using the isokinetic dynamometer, while thigh abduction, adduction and flexion was assessed using the 3RM protocol. In addition, where leg flexion and extension was not possible participants were required to complete hip abduction and adduction only. Isokinetic dynamometry permits the isolation of muscle groups, and provides accommodating resistance to maximal exercise throughout the
range of motion. It provides reliable, quantifiable data for peak torque, total work and power. Pincivero et al. (1997) determined that ICC coefficients for peak torque, total work and power using the dynamometer ranged from r=0.86 to r=0.97, with r=>80 as an acceptable reliability level (Pincivero, Lephart et al. 1997).

Participants were instructed to sit on the dynamometer, with the back rest adjusted to ensure knee joint line and the fulcrum of the machine were in line. Participants were then secured to the chair with a Velcro belt, and their upper leg also secured. A full knee joint ROM was evaluated and recorded to ensure their greatest flexion and extension points were attained with each repetition. The participants were then instructed to extend the leg maximally, then flex maximally, at a predetermined speed of 60 deg/s². ‘Easy up, easy back’ were the instructions given for the first two repetitions, the third was ‘as hard as you can push up, and as hard as you can pull back’, then two ‘easy up, easy back’ to finish the set. This procedure was repeated for a second time. The process was then repeated on the affected leg. The maximal torque was recorded from the third repetition for each set. If participants were unable to complete the isokinetic strength test due to limited ROM, their leg flexor and extensor values were recorded as 0.

Lower limb ROM

Lower limb ROM was measured using a standard, long arm goniometer and bubble inclinometer. Both affected and non-affected limbs were assessed and trials repeated to ensure reliability of results. Below are the measurement protocols utilised for each joint ROM.

- Thigh flexion/extension ROM: The bubble inclinometer was positioned 2 cm proximal to the superior boarder of the patella, at the midpoint of the thigh and reset to 0 degrees prior to commencing thigh flexion movement. Patients were instructed to ‘flex at the hip, lifting your leg, bending the knee, bringing it in to your chest as far as possible’. For the measurement of thigh extension, the patient was instructed to stand
facing a wall, with pelvis and lumbar spine in neutral. The bubble inclinometer was placed 5 cm proximal from the popliteal fossa on the posterior aspect of the thigh. The participant was then instructed to extend their leg posteriorly, keeping the knee extended and ensuring their pelvis and lumbar spine remain in a neutral alignment.

- **Leg flexion/extension ROM:** The patient was instructed to lie supine on the plinth, with hips and knees in a neutral position. The goniometer axis was aligned with the lateral epicondyle of the femur, with the proximal arm parallel to the long axis of the femur, pointing towards the greater trochanter of the femur. The distal arm was aligned parallel to the long axis of the fibula and pointed to the lateral malleolus. The thigh and leg were flexed as the heel moved towards the buttock, placing the foot down on the plinth at maximal leg flexion. Leg extension required the participant to place the ankle on a foam bolster to permit full leg extension.

- **Foot dorsi/plantar flexion ROM:** A bubble inclinometer was placed between the first and second metatarsal bones on the dorsal aspect of the foot, with the ankle in neutral, and was set to zero. Participants were then asked to “point your toes” bringing the foot into full plantar-flexion, then returning to neutral. From neutral, they were asked to “pull your toes towards your face”. Maximal dorsi-flexion was measured at this point.

**Exercise Intervention**

The exercise rehabilitation intervention consisted of an 8-week fully supervised, combined resistance and aerobic programme. Participants were required to attend the clinic twice per week for 1 hour each session. The programme progressed through three phases, with each participant being required to achieve certain tasks prior to progressing to subsequent phases (Appendix D). Given the individualised nature of wide resection surgery, each participant’s programme was individually tailored to account for variations in ability to complete all tasks. The three phases (with aims and a brief rationale) are outlined below, with specific exercises outlined in Appendix D.
Phase One (1-2 Weeks)

Aims:

- Muscle isolation and activation of lower limb musculature
- Completion of home exercises programme
- Encourage the return to full lower limb ROM
- Introduction to aerobic exercises

Exercise Prescription:

- Active and passive ROM exercises
- Non-weight bearing exercises; limb weight against gravity or resistance machines
- Basic upper body and core stability exercise for general deconditioning
- Hydrotherapy for gait re-education, stretching and light strengthening using a flotation device.

Phase Two (2-4 weeks)

Aims:

- Further improvements in lower limb strength
- Commence weight bearing gait retraining

Exercise Prescription:

- Introduction to modified closed kinetic chain exercises
- Addition of hip abduction and adduction exercises
- Proprioception and balance exercises
- Gait retraining in front of a mirror, to enhance understanding of body position in space.*
• Increased cardiovascular exercise to at least 10 minutes continuous

Phase Three (weeks 4-8)

Aims:
• Progression to higher demand functional exercise
• Replication of activities of daily living
• Closed kinetic chained exercise with incorporation of proprioception

Exercise Prescription:
• Weighted squats and lunges on a balance ball (Bosu)
• Ambulation on an unstable surface
• Incorporation of several multi-joint exercises, including upper and lower limb movements

*Gait retraining utilised subjective assessment of participants’ gait patterns. Utilising clinical judgement and visual assessment, participants were educated on correct technique and gait improvement strategies. Using visual feedback and cueing, each participant’s gait was subjectively modified.

Data Analysis and Statistics

The effectiveness of an 8-week, fully supervised, exercise rehabilitation programme focussing on muscle strength, joint ROM, functional movements and QOL, was assessed in patients post wide resection surgery for sarcoma treatment. Participants were assessed twice at baseline (to ensure stability of their condition), once immediately following the intervention at 8 weeks, and at 8 weeks post-intervention (16 weeks). To ensure patients physical and mental status was stable prior to commencing the intervention, their second baseline assessment results were to be within 10% variance of initial baseline results. If patients were deemed stable, and participated in the intervention, their second baseline results were used to for final statistical comparisons.
A series of one way repeated measures ANOVAs was used to assess the significance of changes in the primary outcome variables. Each subject's primary and secondary outcome measures were assessed at three time points: baseline, 8 weeks and at 8 weeks post intervention. In the occurrence of significant main or interaction effects, post-hoc test analyses were conducted using pairwise comparisons to identify the specific time points at which these differences occurred. Additionally, paired samples t-tests were used to compare strength and joint ROM measures between the affected and unaffected limbs, at baseline, 8 weeks and 16 weeks. Significance was accepted at $P<0.01$ to accommodate for multiple comparisons being made in ANOVA analyses. In order to determine the key contributors to physical function outcome (HiMAT), stepwise multiple regression analysis was utilised. Predictor variables identified through correlation analysis were entered one at a time based on statistical criteria formulated in SPSS. At each step, the predictor variable that contributed most to the prediction equation in terms of increasing the multiple correlations ($R$) was entered first. When no additional predictor variables added anything statistically meaningful to the regression equation, the analysis ceased.