Physical functioning and rehabilitative needs across the cancer continuum in patients with oesophageal cancer

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Declaration

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Summary

In recent decades, the incidence of oesophageal adenocarcinoma has dramatically increased, particularly in developed countries. Treatment for oesophageal cancer has traditionally been associated with poor outcomes and consequently a poor prognosis, however morbidity and mortality rates, in addition to long term survival post oesphagectomy have all dramatically improved over the past two decades. Notwithstanding progress in survivorship, curative treatments are complex and remain associated with risks of morbidity and mortality. Major surgery, in combination with preoperative chemotherapy and radiotherapy, can have an attritional impact on physical functioning. Poor physical functioning is associated with decreased overall HRQOL and an increased risk of disability and therefore is an important outcome to measure in any population.

A systematic review of the literature was carried to investigate the impact of curative treatment for oesophageal cancer on subjective and objective measures of physical functioning. Both neoadjuvant therapy and oesophagectomy were shown to have a significant negative impact on physical functioning in the acute phase post treatment. However there were inconsistencies in the literature regarding the long term recovery of physical functioning after successful completion of treatment for oesophageal cancer. In Study 1 in this thesis, survivors of oesophageal cancer (11-36 months post surgery) demonstrated significantly lower fitness and physical activity levels than age and gender matched control participants. A medical record review conducted as part of Study 1 revealed that the study cohort experienced a decrease in body weight and BMI at one, three and six months post-operatively with body weight continuing to be decreased up to three years post surgery. In addition, over 30% of the total study cohort was classified as sarcopenic prior to surgery. The second study in this thesis (Study 2) involved a qualitative exploration of the impact of treatment on physical functioning from the perspectives of survivors who were one to five years post surgery. This study aimed to further explore the potential reasons for the suboptimal physical functioning observed in Study 1 and to provide a more in-depth and contextualised understanding of the patient experience and patient needs. Participants in Study 2 reported physical changes and side effects of treatment which had impacted on their physical functioning and lifestyle. This cohort had poor knowledge and awareness of physical activity guidelines and the wide ranging benefits of exercise and faced a number of disease specific and general barriers to exercise and optimal activity levels. Overall Study 1 and Study 2 demonstrated the significant adverse impact treatment for oesophageal cancer can have on physical functioning, which can persist up to five years post-operatively. These findings provide data that suggest that a

comprehensive multidisciplinary rehabilitation programme may be a promising intervention to improve physical performance and HRQOL in survivorship. Study 2 examined participants' views on the development of such a programme. Participants expressed a high level of interest in rehabilitation and stated that they thought it would be beneficial for survivors of oesophageal cancer. Therefore interventional programmes appear feasible and would be well received in an oesophageal cancer population post completion of treatment.

In order to investigate when changes in physical functioning may occur across the cancer continuum, the third study in this thesis (Study 3) prospectively measured the acute impact of curative multimodal treatment for oesophageal cancer on physical performance. The preliminary results from this ongoing study suggest that oesophagectomy has a marked adverse impact on physical functioning but that chemotherapy and radiotherapy have a lesser impact. Fitness, hand grip strength and physical activity levels remained the same during neoadjuvant treatment. However a significant loss of hand grip strength was observed in participants four weeks post oesophagectomy as compared to baseline measures. Similarly, a clinically meaningful decrease in fitness levels was observed from pre surgery to four weeks post surgery. In addition, this study recorded low physical activity levels across the study period; at diagnosis, post neoadjuvant treatment and four weeks post surgery. The final study in this thesis, Study 4, qualitatively explored the patients' perspectives on their physical functioning from diagnosis and throughout their neoadjuvant treatment. This study gave a more in-depth evaluation of the impact of chemotherapy and radiotherapy on physical functioning and revealed that for most participants, neoadjuvant treatment did have some impact on physical functioning. However the majority of participants reported that the physical impact of neoadjuvant treatment was reasonably temporary and self limiting. While the objective measures of strength, fitness and physical activity levels were not significantly affected by chemotherapy and radiotherapy in Study 4, these measures were already low at diagnosis. As a result, this cohort may be an increased risk of post-operative complications. A prehabilitation intervention that would improve strength, physical activity and fitness pre-operatively may positively influence these complications. Study 2 examined participants' views on the development of a prehabilitation programme and the results overall indicated that a programme would be feasible between diagnosis and surgery. An important finding of this study however, was that the side effects of neoadjuvant treatment were experienced to varying degrees and at different times by participants. Therefore timing of interventions may have to be varied according to a patient's response to therapy and reasonably flexible in terms of timing, structure and components.

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List of Abbreviations

AC	Adenocarcinoma
ACSM	American College of Sports Medicine
AMNCH	Adelaide and Meath Hospital, Dublin, incorporating the National Children's Hospital
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BMR	Basal metabolic rate
CAQDAS	Computer assisted qualitative data analysis software
cm	Centimetre
CPET	Cardiopulmonary exercise test
CT	Computerised tomography
DEXA	Dual-energy X- ray absorptiometry
ECOG	Eastern Cooperative Oncology Group
EE	Energy expenditure
EG	Emer Guinan
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Oesophageal Cancer Module
FACT-E	Functional Assessment of Cancer Therapy – for patients with Esophageal cancer
HGS	Hand grip strength
HR	Heart rate
HRB	Health Research Board
HRQOL	Health related quality of life
ISWT	Incremental Shuttle Walk Test
JG	Jenny Gannon

kg	Kilogram
LON	Linda O'Neill
m	Metre
MDC	Minimal detectable change
MIO	Minimally invasive oesophagectomy
MRI	Magnetic resonance imaging
PA	Physical activity
PEACE	Physical Exercise Across the Cancer Experience
PET	Positron emission tomography
PIL	Participant information leaflet
PPC	Post-operative pulmonary complication
PROM	Patient reported outcome measure
QOL	Quality of life
RCT	Randomised control trial
RSCL	Rotterdam Symptom Checklist
SCC	Squamous cell carcinoma
SD	Standard deviation
SF-20	Medical Outcomes Study 20-Item Short Form Survey
SF-36	Medical Outcomes Study 36-Item Short Form Survey
SJH	St. James's Hospital
TCD	Trinity College Dublin
VATS	Video-assisted thoracoscopic surgery
VO_{2max}	Maximal oxygen uptake
WHO	World Health Organization
6MWT	Six Minute Walk Test
6MWD	Six Minute Walk Test distance

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Dissemination of research

Conferences/Published abstracts

Gannon J, Hussey J, Reynolds JV. 'Suboptimal physical activity levels at six months post oesophageal cancer surgery.'

- *Poster presentation*: Irish Cancer Society Survivorship Research Day, Aviva Stadium, Dublin, 19th September 2013. *(Winner of best poster presentation prize.)*

Gannon J, Hussey J, Reynolds JV 'Body composition, muscle strength and fitness levels in cancer survivors from six months post oesophageal cancer surgery.'

- *Poster presentation*: Irish Cancer Society Survivorship Research Day, Aviva Stadium, Dublin, 19th September 2013.

Gannon J, Guinan E, Hussey J, Reynolds JV. 'Physical activity levels after oesophageal cancer surgery: a case-control study.'

- *Poster presentation*: 9th International Cancer Conference, Trinity College Dublin, 17th-18th September 2014.

Gannon J, Guinan, E, Hussey J, Reynolds JV, 'Physical functioning post oesophagectomy.'

- *Platform presentation*: 9th International Cancer Conference, Trinity College Dublin, 17th-18th September 2014.
- *Poster presentation*: Irish Society of Chartered Physiotherapists Conference, Croke Park Conference Centre, Dublin, 7th & 8th November 2014.

Gannon J, Guinan, E, Hussey J, Reynolds JV. 'Physical functioning after oesophageal cancer surgery: a case-control study.' (2015) *Physiotherapy* (101 Supplement 1): e439-e440

- *Platform presentation*: World Confederation for Physical Therapy Congress, Singapore, 1st-4th May 2015.

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Chapter 1 Introduction

1.1 Oesophageal cancer

The oesophagus is a long muscular tube that connects the pharynx to the stomach and forms part of the gastrointestinal (digestive) system. It is approximately 25 cm long in adults and is divided into three parts; the cervical, thoracic and abdominal oesophagus. The oesophagus is composed of four distinct tissue layers: a mucosal lining, a submucosal layer, a muscular layer and an outer covering layer of cells called the adventitia. The oesophagus is involved in the processes of swallowing and peristalsis to move substances from the mouth to the stomach.

Cancer, also called malignancy, is an abnormal growth of cells. There are more than 100 types of cancer and each is classified by the type of cell that is initially affected. When altered cells divide uncontrollably, they form masses of tissue called tumors. Carcinomas develop from the epitheilial cells of organs and comprise at least 80% of all cancers. Other cancers arise from cells of the blood (leukaemias), immune system (lymphomas), and connective tissue (sarcomas). The lifetime prevalence of cancer is one in two for men and one in three for women (American Cancer Society, 2015). Cancer is one of the leading causes of morbidity and mortality worldwide.

Cancer in the form of a tumour can occur in the cells of any part of the oesophagus. There are two main histological subtypes of oesophageal cancer: adenocarcinoma (AC) and squamous cell carcinoma (SCC). More than 90% of oesophageal cancers fall into one of these subtypes (Daly et al., 2000). Rarely, other carcinomas, melanomas, leiomyosarcomas, carcinoids, and lymphomas may also develop in the oesophagus (Enzinger and Mayer, 2003). In SCC, the cancer starts in the squamous cells that make up the inner lining of the oesophagus. In AC, the cancer starts in the gland cells which form the mucus in the lining of the oesophagus. When the origin is unknown, the cancer is defined as undifferentiated. Approximately three quarters of all adenocarcinomas are found in the distal oesophagus, whereas squamous cell carcinomas are mainly found in the middle and upper third of the oesophagus (Siewert et al., 2001).

1.1.1 Incidence and aetiology

Oesophageal cancer is the eighth most common cancer worldwide and the sixth leading cause of cancer-related mortality (Ferlay et al., 2013). Ireland has one of the highest incidence rates of oesophageal cancer in Europe. According to the National Cancer Registry, an average of 386 oesophageal cancers, 139 (36%) in females and 247 (64%) in males, was registered in Ireland between 2010 and 2012. Oesophageal cancer has a male to female ratio of over 2:1 and a peak incidence in the 60-80 age group. The epidemiology of oesophageal carcinoma has changed markedly over the past several decades. The incidence of oesophageal SCC has decreased while oesophageal AC has dramatically increased, particularly in developed countries (Thrift and Whiteman, 2012, Bosetti et al., 2008). This increasing incidence has been attributed to a "western" lifestyle, particularly the rising rates of obesity and metabolic syndrome (Devesa et al., 1998, Melhado et al., 2010).

The exact aetiology and pathogenesis of oesophageal cancer is unknown but there are a number of risk factors associated with the disease (Table 1.1). Both increasing age and male gender are risk factors for oesophageal cancer. Smoking is the main avoidable risk factor for oesophageal cancer and is particularly associated with SCC. Alcohol consumption is also associated with SCC. Long term heavy drinkers of alcohol have an increased risk of oesophageal cancer and people who use both alcohol and tobacco are at an even greater risk. Overweight and obesity are associated with an increased risk of AC. In contrast, higher levels of body fat have been associated with a decreased risk of SCC (Vaughan et al., 1995). Diets that lack fruit and vegetables and vitamins A, C and riboflavin may increase the risk of oesophageal cancer. A history of gastro-oesophageal reflux disease has been associated with increased risk of AC, but not of SCC. Barrett's oesophagus is associated with long standing reflux and increases the risk of developing cancer. There is also evidence that physical inactivity increases the risk of oesophageal cancer (Behrens et al., 2014).

Table 1.1 Risk factors for oesophageal cancer, by direction of association and strength of evidence (Source: National Cancer Registry Ireland)

	Increases risk	Decreases risk
Convincing or probable	Tobacco smoking	Non-starchy vegetables
	Smokeless tobacco	Fruit
	Alcohol	Food containing beta-carotene
	Greater body fatness (AC)	Foods containing vitamin C
	Gastro-oesophageal reflux disease	*Helicobactor pylori* infection (AC)
	Low socio-economic status	Aspirin and other NSAIDS
Possible		
	Red meat	Gastric atrophy (AC)
	Processed meat	
	Pickled vegetables	
	High temperature drinks	
	Infection with human papilloma viruses (SCC)	
	Occupational exposure to hexavalent chromium	
	Gastric atrophy (SCC)	

Abbreviations: *AC* adenocarcinoma, *SCC* squamous cell carcinoma, *NSAIDS* non-steroidal anti inflammatory drugs.

1.1.2 Signs and symptoms

Oesophageal cancer is often diagnosed at an advanced stage because there are no early signs or symptoms. The most common presenting symptoms are dysphagia and weight loss. Less common symptoms include: odynophagia, gastro-oesophageal reflux, pain or discomfort (retrosternal or between the shoulder blades), hoarseness, persistent cough, vomiting, coughing up blood and chest pain. In addition, oesophageal cancer is associated with a relatively high frequency of malnutrition, sarcopenia and cachexia. Patients with oesophageal cancer are susceptible to developing malnutrition due to dysphagia and anorexia.

1.1.3 Diagnosis and staging

Oesophageal cancer is generally diagnosed using endoscopy (oesophagoscopy) and a barium swallow. Further tests including a computerised tomography (CT) scan, laparoscopy, an endoscopic ultrasound and a positron emission tomography (PET) scan are often carried out to stage the cancer. The TNM system is a widely recognised and accepted system used to stage cancers (Edge and Compton, 2010). Precise staging is essential to determine optimum treatment, as a baseline for response to treatment, and as a guide to the prognosis. T (tumour)

relates to the location and size of the cancer, N (nodes) refers to whether the cancer has spread to the lymph nodes and M (metastatic) describes whether the cancer has metastasised to other parts of the body. Oesophageal cancer can be staged as TX or T1-4, NX or T0-3 and M0-1 depending on how advanced it is. Numbered stages are also used to classify oesophageal cancer. These stages are briefly described in Table 1.2. The relationship between the numbered stages and the TNM system is described in Table 1.3.

Table 1.2 Stages of oesophageal cancer

Stage 0	Abnormal cells in mucosa or submucosa layer which may become cancerous. (High Grade Dysplasia)
Stage I	The cancer occurs in the superficial layers of cells lining the oesophagus.
Stage II	The cancer has invaded deeper layers of the oesophagus lining and may have spread to nearby lymph nodes.
Stage III	The cancer has spread to the deepest layers of the wall of the oesophagus and to nearby tissues or lymph nodes.
Stage IV	The cancer has spread to distant tissues or organs.

Table 1.3 Relationship between number and TNM stages for oesophageal cancer

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2	N1	M0
Stage IIIA	T4a	N0	M0
	T3	N1	M0
	T1, T2	N2	M0
Stage IIIB	T3	N2	M0
Stage IIIC	T4a	N1, N2	M0
	T4b	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

1.1.4 Treatment

The primary treatments for oesophageal cancer are surgery, chemotherapy and radiotherapy. Surgery is the primary curative treatment option and it is often carried out in conjunction with chemotherapy and radiotherapy. Oesophagectomy is the surgical removal of all or part of the oesophagus. There are two main types of oesophagectomy; transthoracic and transhiatal. A transthoracic oesophagectomy involves a thoracotomy and a laparotomy. Combined laparotomy and right thoracotomy is known as an Ivor Lewis procedure, or two stage oesophagectomy. A three incision transthoracic resection involving a laparotomy, thoracotomy and neck incision is known as a McKeown procedure, or three stage oesophagectomy. A transhiatal oesophagectomy involves a laparotomy and a neck incision. More recently, minimally invasive surgical techniques for oesophagectomy have also been introduced.

While it has been suggested that transhiatal oesophagectomy is associated with lower morbidity rates than transthoracic oesophagectomy, mortality rates are generally similar between the different surgical approaches and there is no strong evidence favouring one method of oesophageal resection over another. The histological tumour type, its location, the extent of the proposed lymphadenectomy, patient factors and the experience of the surgeon should determine the operative approach (Allum et al., 2011).

Chemotherapy and radiotherapy treatment can be delivered either neoadjuvantly (prior to surgery to shrink the tumour size to facilitate surgery), adjuvantly (following surgery to reduce the risk of recurrence) or in metastatic disease to ease symptoms and prolong life. The primary neoadjuvant and adjuvant treatment regimens for oesophageal cancer are the CROSS protocol and the MAGIC protocol. The MAGIC regimen consists of three cycles of chemotherapy pre-surgery and a further three cycles of chemotherapy post-surgery. Each cycle of chemotherapy lasts three weeks. The drugs used in the MAGIC regimen include Epirubicin, Cisplatin and 5-Flourouracil/Capecitabine. The CROSS protocol involves a combination of chemotherapy and radiotherapy prior to surgery. It consists of five weeks of radiotherapy and five weekly cycles of chemotherapy delivered concurrently. The radiotherapy (41.4 Gy/23 fractions) generally commences on the 1st day of treatment and runs for five weeks: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. The chemotherapy drugs include Paclitaxel and Carboplatin. A trial is currently underway in SJH to compare these two regimens in terms of one, two and three year survival in addition to a number of other outcomes (Keegan et al., 2014).

Two recent meta-analyses have demonstrated a significant survival benefit of neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy over surgery alone (Gebski et al., 2007,

Kidane et al., 2015). Accordingly this increasingly constitutes the standard of care for patients with locally advanced tumours, who do not have contraindications against this approach (Stein et al., 2005). There is no clear evidence to date that neoadjuvant radiotherapy improves survival for patients with resectable oesophageal cancer (Arnott et al., 2005). For patients with localised oesophageal adenocarcinoma deemed unsuitable for surgery, definitive chemoradiation is a valid treatment option (Anderson et al., 2007). Toxicities arising from the treatments for oesophageal cancer will be discussed in Section 1.1.6.

1.1.5 Prognosis and survival

Treatment for oesophageal cancer has traditionally been associated with poor outcomes and consequently a poor prognosis, however morbidity and mortality rates post oesphagectomy have dramatically improved over the past two decades (Stein et al., 2005). Coinciding with a marked decrease in postoperative mortality, long term survival after oesophageal resection has also markedly improved in recent decades. Improved survival rates have been attributed to: changes in epidemiology, increased rate of early tumour stages, improved staging modalities, advances in surgical technique and perioperative management and an increased use of neoadjuvant treatment protocols (Stein et al., 2005). The improvement in five year survival rates in Ireland from 1994 – 2012 are shown in Table 1.4.

Table 1.4 Five year net survival rates for oesophageal cancer in Ireland (Source: National Cancer Registry Ireland)

Years	Net Survival (age standardised)	95% confidence intervals
1994 - 1999	11.3%	(9.6 – 12.9%)
2000 - 2006	13.7%	(12.0 – 15.5%)
2006 - 2011	18.6%	(16.5 – 20.8%)
2008 – 2012*	18.3%	(16.1 – 20.6%)

*hybid estimate

Notwithstanding this progress in survivorship, oesophageal cancer symptoms often present late in the progress of the disease and at diagnosis patients may already have an unresectable tumour or metastatic disease which results in continued poor survival rates for this particular group (Schlansky et al., 2006). Therefore a number of factors are important when considering

outcomes and survival rates associated with oesophageal cancer. Relevant factors include cancer stage, histological subtype, performance status and treatment type. For localised cancers, the five year survival rate is 40% or higher, for regional cancer the survival rate is approximately 20-30%, while for distant or metastasised cancers the survival rate is as low as 4% (Howlader et al., 2015). The five year stage specific survival rates in Ireland, between 2008 and 2012 are presented in Figure 1.1. In Ireland the five year survival rate for stage I cancer is almost 70%. The histological subtype of cancer has been identified as an independent prognostic indicator after oesophagectomy with the prognosis of resected ACs significantly better than that of resected SCCs (Stein and Siewert, 2004). Performance status or physical functioning is also an important consideration as higher fitness and physical activity levels prior to surgery have been shown to be associated with improved outcomes (Feeney et al., 2011, Murray et al., 2007, Moyes et al., 2013).

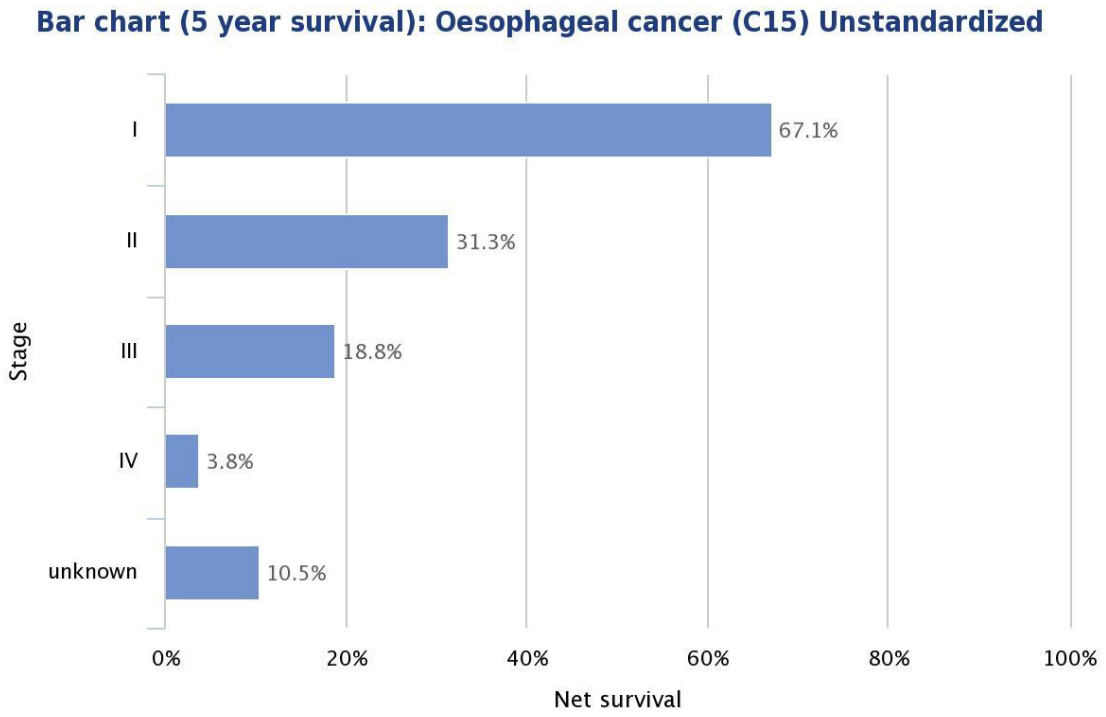

Figure 1.1 Five year stage specific survival rates for oesophageal cancer in Ireland between 2008 and 2012 (Source: National Cancer Registry Ireland)

1.1.6 Treatment side effects

Currently, oesophageal resection is associated with morbidity rates of approximately 30% and mortality rates of up to 5% (Metzger et al., 2004, Gockel et al., 2005, Courrech Staal et al., 2010). These rates are a vast improvement on the morbidity and mortality rates of 20 years ago which were approximately 50% and 20% respectively (Stein et al., 2005). Reasons for the improvement in outcomes after surgery are high hospital volumes, high surgeon volumes, patient selection, standardisation of surgical techniques and perioperative management and an aggressive approach to postoperative complications (Stein and Siewert, 2004). While current morbidity and mortality rates are a vast improvement on historical rates, treatment for oesophageal cancer is highly complex and continues to be associated with significant risks and side effects. The surgical trauma that oesophagectomy imposes is considered one of the greatest among general surgical populations. The surgery often involves the abdomen, chest, and neck, is technically complex and the margin of error is small (Law et al., 2004).

Anastomotic leakage is a frequent surgical complication after oesophagectomy and can contribute to substantial morbidity. The most common medical complication is cardiac arrhythmia; however in most cases this is benign. Post-operative pulmonary complications (PPCs), particularly pneumonias, are the most common serious morbidity after oesophagectomy (Law et al., 2004). The effects of anaesthesia, post-operative pain, prolonged recumbency, immobility and the administration of medications can all result in respiratory abnormalities in the form of reduced lung volumes, decreased mucociliary clearance and suboptimal respiratory muscle function. The incidence of PPCs can reach above 30%, even in high volume centres (Law et al., 2004). There is conflicting evidence regarding the impact of postoperative morbidity on long term survival. While some studies have found a significant association between technical surgical complications and poorer survival rates (Rizk et al., 2004, Rutegard et al., 2012, Luc et al., 2015), others have reported that surgical complications were not associated with a poorer overall survival (Hii et al., 2013, Ancona et al., 2006, Ferri et al., 2006). However, surgical complications have been shown to have a negative effect on several parameters of health related quality of life (HRQOL) in both short term (Rutegard et al., 2008, Viklund et al., 2005) and long term survivors of oesophageal cancer (Derogar et al., 2012) and therefore postoperative morbidity remains an important target for improvement.

There are numerous side effects associated with chemotherapy and radiotherapy treatments which depend on the individual and the dose used. Chemotherapy is a cytotoxic agent and therefore in the process of destroying cancer cells, treatments also damage healthy tissue. Chemotherapy drugs used in the treatment of oesophageal cancer include Epirubicin,

Cisplatin, 5-Flourouracil/Capecitabine, Paclitaxel and Carboplatin. These are all associated with a number of side effects including fatigue, nausea, vomiting, risk of infection, myelosuppression, anaemia, myopathies and neuropathies, as well as hepatic, renal and cardiac toxicities. Peripheral neuropathies are most often as a result of treatment with Cisplatin and taxanes such as Paclitaxel (Peedell, 2005). Cisplatin is the drug most responsible for nephrotoxicity. Anthracyclines, such as Epirubicin are particularly associated with cardiotoxicities, specifically cardiomyopathy and congestive heart failure (Volkova and Russell, 2011, Peedell, 2005). In addition, Paclitaxel can cause cardiac disturbances including ventricular arrhythmias, bradycardia, atrioventricular conduction block, bundle branch block and cardiac ischaemia while 5-Flourouracil can cause angina-like chest pain (Bovelli et al., 2010).

Side effects from radiotherapy can include fatigue, skin reactions, oropharyngeal mucocitis, oesophagitis, nausea and neuropathies. As radiation therapy for oesophageal cancer is carried out in the thoracic region it carries a particular risk of pulmonary side effects such as radiation pneumonitis and pulmonary fibrosis (Tsoutsou and Koukourakis, 2006). Late effects of gastrointestinal radiotherapy include strictures, obstruction, perforation, bleeding, diarrhoea and malabsorption (Peedell, 2005). Late effects are more common and severe with greater total doses of radiation, larger fraction sizes and larger treatment volumes (Peedell, 2005).

As discussed in Section 1.1.2, common symptoms of oesophageal cancer are dysphagia, weight loss and sarcopenia. Treatment for oesophageal cancer may further compound this earlier weight loss and muscle wasting. As oesophageal resection involves extensive reconstruction of the upper gastrointestinal tract, it carries a risk of malnutrition. In addition, problems with dysphagia due to stricture of the anastomosis and gastro-oesophageal reflux owing to resection of the lower oesophageal sphincter are common after surgery. Weight loss is one of the most pronounced side effects up to six months post surgery. Almost two-thirds of patients lose at least 10% of their preoperative BMI during the six months after operation, with one fifth losing at least 20% (Martin et al., 2007) and weight loss can continue up to three years post-operatively (Martin and Lagergren, 2009). Post-operative malnutrition can negatively influence the chance of survival, as well as the efficacy of treatment. It has been shown that malnutrition can double the risk for long term cancer recurrence (D'Journo et al., 2012).

As a result of the toxicities associated with treatments, patients with oesophageal cancer exhibit many symptoms and losses of functional ability which can have a significant impact on HRQOL. As the prognosis of oesophageal cancer remains quite poor, particularly for those diagnosed at later stages, HRQOL is an outcome of particular importance (Viklund et al., 2006,

Parameswaran et al., 2008). The measurement of HRQOL is useful for providing additional information which will enhance the usual clinical endpoints used in determining the benefits and toxicity of treatment. Therefore increased research is warranted to measure the impact of treatment on HRQOL and importantly, to develop strategies to optimise outcomes in this group.

1.2 Impact of cancer and cancer treatment on physical functioning

Physical functioning is an important component of HRQOL. HRQOL is defined as the functional effect of a medical condition and/or its consequent therapy upon a patient. It is a multidimensional concept which consists of physical, mental, emotional and social functioning (Figure 1.2). The measurement of HRQOL is particularly useful for elucidating the effects of various cancers and their treatments on patients' lives. While cancer survivors can experience losses in all functional domains, it has been shown that their losses are most profound in the area of physical functioning (Hewitt et al., 2003) and that HRQOL is more often influenced by physical issues than emotional problems (Weaver et al., 2012). Poor physical functioning is associated with decreased overall HRQOL and an increased risk of disability in cancer survivors and therefore is increasingly being recognised as an outcome of importance across the cancer continuum (Blanchard et al., 2004, Mosher et al., 2009). The measurement of physical functioning is described in Chapter 2.

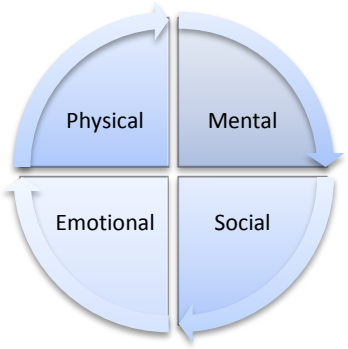

Figure 1.2 Components of HRQOL

A diagnosis of cancer and curative cancer treatments pose challenges for multiple body systems involved in overall physical functioning. Cancer and cancer therapy have the potential to affect the health-related components of physical fitness as well as neuromotor function (Pescatello, 2013). As described in Section 1.1.6, common physical side effects of cancer and its treatment include fatigue, myopathies, neuropathies, cachexia, sarcopenia and pain. These can all lead to deficits in aspects of physical functioning including physical activity, fitness and strength. Up to 90% of all survivors of cancer can experience cancer-related fatigue (Prue et al., 2006). Cancer related fatigue is particularly prevalent in patients receiving chemotherapy and radiotherapy and may persist for months or years after treatment completion. Cancer related fatigue is associated with a number of physiological and psychological mechanisms and persistent fatigue can have a considerable negative impact on physical functioning into survivorship (Hofman et al., 2007). Radiotherapy and chemotherapy can disturb muscle integrity and result in myopathies which can cause muscle imbalance and weakness. Similarly, decreased sensation and paraesthesia as a result of peripheral neuropathies can cause difficulties with walking. Cachexia occurs in up to 80% of patients with upper gastrointestinal cancers (Laviano and Meguid, 1996, Bruera, 1997) and is characterised by a loss of skeletal muscle mass. Decreased muscle strength, due to both decreased protein synthesis and increased muscle proteolysis, is a key feature of this condition (Strasser, 2008) and accordingly cachexia is associated with fatigue, weakness and poor physical performance (Donohoe et al., 2011b). Pain can be caused by surgery (incision sites), chemotherapy (painful neuropathies causing burning pain in hands and feet) or radiotherapy (irradiating skin, scarring nerves) and can be a barrier to optimal physical and functional recovery.

There is a growing body of evidence in the area of physical functioning in cancer survivorship. This research has identified suboptimal fitness and physical activity levels in survivors of breast, prostate, colorectal and lung cancer (Jones et al., 2008b, Lynch et al., 2011, Forbes et al., 2014, Broderick et al., 2014b). In addition, a large population based study of cancer survivors five years or more post treatment found that more than half report physical performance limitations including crouching/kneeling, standing for two hours, lifting/carrying 4.5kg and walking 0.4 km (Ness et al., 2006). The majority of research to date in this area however has been carried out in cancers such as breast, prostate and colorectal and less so in more complex cancers such as oesophageal. The aggressiveness of oesophageal cancer in addition to the complexity of its treatment may result in a more profound impact on physical functioning. Therefore in order to gain a greater understanding of the impact of treatment on physical functioning, specifically in patients with oesophageal cancer, a systematic review of all

the evidence currently available on this topic was completed, which is described in the following section.

1.3 Impact of oesophageal cancer treatment on physical functioning

A systematic review of the literature was carried out to investigate the impact of curative treatment for oesophageal cancer on physical functioning. Preliminary non systematic and informal searching of the literature by the researcher (JG) indicated that there was a paucity of published studies with objective data on physical functioning in patients with oesophageal cancer. There is, however, a large body of evidence regarding HRQOL in this population. For the purpose of this systematic review, both subjective and objective measures of physical functioning were included. Due to the large amount of HRQOL literature in this cohort, a meta-analysis of the results for subjectively measuring physical functioning was planned.

Commonly used HRQOL questionnaires often contain a subscale which relates specifically to physical functioning. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) is a frequently used HRQOL questionnaire in cancer populations. This measure is described in detail in Section 2.5.2. Other commonly used HRQOL measures include the Medical Outcomes Study 36-Item Short Form Survey (SF-36), the Medical Outcomes Study 20-Item Short Form Survey (MOS SF-20), the Rotterdam Symptom Checklist (RSCL) and the Functional Assessment of Cancer Therapy – for patients with Esophageal cancer (FACT-E). Both the SF-36 and the SF-20 have a 'physical functioning' subscale. The subscale consists of 10 items in the SF-36 and six items in the SF-20. Included items relate to the patient's ability to complete moderate and vigorous activities, bend, lift, walk, walk uphill and to complete self care activities. The RSCL measures physical functioning using the 'activity level' subscale which consists of eight items. Items included are self care, walking, light housework, climbing stairs, heavy housework, walking outdoors, going shopping and going to work. The FACT-E assesses physical functioning primarily with the 'physical well-being' subscale. The subscale consists of seven items which include: energy levels, nausea, pain, treatment side effects, and needing bed rest.

1.3.1 Aims and objectives

The aim of this systematic review was to investigate the effect of neoadjuvant therapy (chemotherapy and/or radiotherapy) and surgery on physical functioning in oesophageal cancer patients.

The objectives of this review were:

- To measure the effect of curative treatment for oesophageal cancer on subjectively reported physical functioning.
- To investigate the effect of curative treatment for oesophageal cancer on objectively measured physical functioning.

1.3.2 Methods

1.3.2.1 Inclusion/Exclusion criteria

Studies were eligible and included in the review only where they reported on:

- ***P**articipants:* Patients with oesophageal cancer undergoing treatment with a curative intent.
- ***E**xposure:* Primary neoadjuvant therapy (chemotherapy and/or radiotherapy) or surgery with a curative intent.
- ***O**utcomes:* Physical functioning measured subjectively as a domain of a psychometrically validated, multidimensional, patient-reported outcome measure (PROM) or objectively using a measure of fitness, muscle strength or physical activity.
- ***S**tudy type:* Randomised controlled trials (RCTs) or longitudinal studies where outcome was assessed at baseline (pre-treatment) and at one or more time points post treatment.

Studies were excluded that (1) reported on questionnaire development or validation, (2) assessed HRQOL as a predictive or prognostic indicator of clinical outcomes, (3) reported on cost analyses, (4) assessed interventions in addition to primary neoadjuvant therapy and surgery (e.g enhanced nutritional support during chemotherapy), (5) assessed treatments for cervical oesophageal cancer or (6) reported on oesophageal cancers not amenable to oesophagectomy. Non English language texts and non full text articles (e.g. conference abstracts) were also excluded.

1.3.2.2 Search and selection strategies

The search strategy was developed in consultation with a medical librarian, which was tailored to each individual database. One author (JG) conducted searches using EMBASE, PubMed, CINAHL, Scopus and PsycINFO databases to include publications from inception of the database up to 1st April 2015. The following key words (among others) were used in various combinations: "o/esophageal cancer", "o/esophageal neoplasm", "o/esophageal adencarcinoma" "o/esophageal carcinoma" o/esophagectomy"," o/esophagogastrectomy, "o/esophageal surgery", "o/esophageal resection", "neoadjuvant treatment", "chemotherapy", "radiotherapy", "radiation therapy", "chemoradiotherapy", "combined modality therapy", "multimodal treatment", "physical function/ing", "physical activity", "fitness", "physical performance", "physical capacity", "exercise", "strength", "quality of life", "health status", and "functional status". In addition, similar subject terms, relevant to each individual database were searched. Full details of the search strategies for each database can be found in Appendix I.

The titles and abstracts of all studies identified through the search strategy were reviewed and assessed for eligibility by two authors (JG and LON). All potentially relevant articles were then independently reviewed as full text articles by two authors (JG and LON). Disagreements between the reviewers were resolved through discussion to achieve consensus. Failing agreement, a third reviewer (EG) arbitrated.

1.3.2.3 Quality assessment of included studies

For the studies to be included the meta-analyses the "Checklist for Measuring Study Quality" (Downs and Black, 1998) was used to measure study quality. The "Checklist for Measuring Study Quality" can be used to assess the quality of both randomised and non-randomised studies and contains 27 'yes'-or-'no' questions across five sections. The tool provides both an overall score for study quality and a numeric score out of a possible 30 points. The five sections include questions about: (1) study quality (10 items) – the overall quality of the study, (2) external validity (3 items) – the ability to generalise findings of the study, (3) study bias (7 items) – to assess bias in the intervention and outcome measure(s), (4) confounding and selection bias (6 items) – to determine bias from sampling or group assignment and (5) Power of the study (1 items) – to determine if findings are due to chance. This instrument has been shown to be both valid and reliable (Downs and Black, 1998) and has been recommended for assessing risk of bias in non-randomised studies (Deeks et al., 2003). A copy of this checklist is

included in Appendix II. For question 27, which relates to power and sample size, the question was simplified to a yes or no answer indicating whether or not a power calculation was carried out. Therefore in this review, scores for the quality assessment were calculated from a maximum of 28. The following cut points to categorise studies by quality have been proposed and used in the literature: excellent (26-28), good (20-25), fair (15-19) and poor (≤14) (Silverman et al., 2012, Kennelly, 2011, Hooper et al., 2008).These categories were applied to the scores from the quality assessment in this review to give a broad evaluation of overall study quality. The quality assessment of studies included in the meta-analyses was carried out by two authors (JG and LON). Disagreements between the reviewers were resolved through discussion to achieve consensus or consultation with a third reviewer (EG). Consultation with a third reviewer was necessary for two studies.

1.3.2.4 Data extraction

A pre-defined data extraction sheet was used by two authors (JG and LON) to record data on study design and results. Items that were extracted included: key study characteristics, patient characteristics, treatments carried out, instrument(s) used to measure physical functioning and the number and timing of the assessments of physical functioning. Where email addresses were provided, authors were contacted for additional results and information in the case of insufficient data in the original manuscript. Where studies compared different treatment regimes (e.g definitive chemoradiation vs surgery only), only the group that met the inclusion criteria was included.

1.3.2.5 Data synthesis and analysis

Meta-analysis of subjectively measured physical functioning

Due to the large amount of HRQOL data available, meta-analyses were used to measure the impact of treatment on subjectively reported physical functioning. The EORTC-QLQ was the most widely used subjective measure of physical functioning and therefore studies using this measure were included in the meta-analyses. Inclusion criteria for the meta-analyses were: numerical results for the physical functioning subscale of the EORTC-QLQ measured at baseline (pre-surgery) and at either; 1-3 months, 4-6 months or 10-12 months post treatment. Studies were excluded from the meta-analyses where the specific results needed were not detailed in the paper and it was either: impossible to contact the author, there was no response from the

author or the author was not able to provide the relevant data. Studies using a HRQOL questionnaire other than the EORTC-QLQ were too few to be analysed separately and therefore were also excluded from the meta-analysis.

For the purpose of the meta-analyses in this review, results for open surgery (transhital or transthoracic oesophagectomy) and minimally invasive oesophagectomy were analysed separately. Heterogeneity was measured using the I^2 statistic which describes the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins et al., 2003).

Narrative review of subjectively measured physical functioning

The studies which subjectively measured physical functioning but were not suitable for inclusion in the meta-analysis were included separately in a narrative review.

Narrative review of objectively measured physical functioning

The studies which objectively measured physical functioning were included in a narrative review.

1.3.3 Results

1.3.3.1 Identification and selection of studies

The systematic database search identified 3244 citations (1682 from EMBASE, 783 from PubMed, 89 from CINAHL, 670 from Scopus and 20 from PsychINFO). After removing duplicates, 1899 unique citations were screened by title and abstract and, of these, 1787 citations were excluded as they did not meet the inclusion criteria for the review. Full-text papers of the remaining 112 citations were obtained and reviewed. Sixty nine of these were excluded for reasons detailed in Figure 1.3. This resulted in 43 papers for inclusion in the review. Of the included studies, 16 were suitable for inclusion in the meta-analysis of subjectively measured physical functioning, 20 were included in the narrative review of subjectively measured physical functioning and seven were included in the narrative review of objectively measured physical functioning.

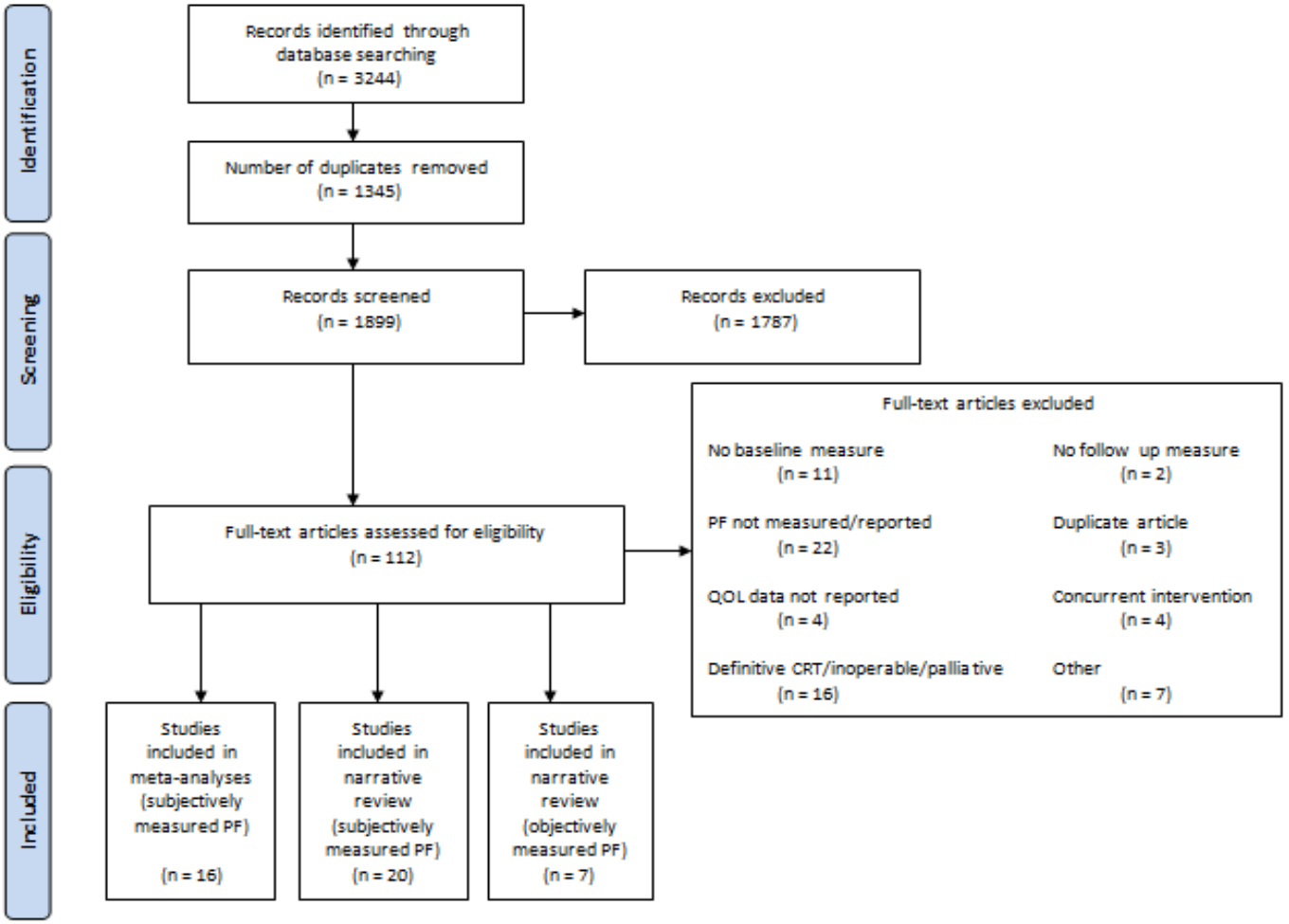

Figure 1.3 Flow chart of publication identification (*PF* physical functioning)

1.3.3.2 Meta-analyses of subjectively measured physical functioning

Study design and characteristics

Sixteen studies were suitable for inclusion in the meta-analyses (Chang et al., 2014, Barbour et al., 2008, Hong et al., 2013, van Meerten et al., 2008, Ramakrishnaiah et al., 2014, Reynolds et al., 2006, Parameswaran et al., 2010, Nafteux et al., 2011, Wang et al., 2010, Wang et al., 2011, Wang et al., 2015, Lv et al., 2014, Leibman et al., 2006, Teoh et al., 2011, Lagergren et al., 2007, Avery et al., 2007a) Included articles were published between 2006 and 2015. Of the 16 studies suitable for inclusion in the meta-analysis, there were 13 longitudinal studies, one RCT, one phase II trial and one longitudinal study where the participants were randomly assigned to either open or minimally invasive surgery. All studies measured physical functioning as a subsection of the EORTC-QLQ. Sample sizes ranged from 25 to 444 participants and the studies included a mixture of patient groups with regards to cancer histology (AC, SCC and others) and stage (stage 0-IV). The studies evaluated patients who had received multimodal treatment or surgery only. Surgery types evaluated included open (transthoracic and transhiatal) and minimally invasive oesophagectomy (MIO). Characteristics of the included studies are detailed in Table 1.5.

Table 1.5 Study and patient characteristics for the studies included in the meta-analyses of subjectively measured physical functioning

Author (year)	Study period	Type of study	Sample size*	Me(di)an age (SD/range)	Histology	Stage	Surgery type(s)	Neoadjuvant/ adjuvant treatment
Chang et al., (2014)	2008-2011	Prospective longitudinal	99	55.5 (32-83)	AC, SCC	0-III	Open	NACRT: 70%
Barbour et al., (2008)	2000-2003	Prospective longitudinal	43	60 (9)	Siewert type I-III AC	TX,T1-3, NX, N0-1, M0	Open - TTO	NACT or NACRT: 84%
Hong et al., (2013)	2009-2011	Retrospective longitudinal†	Open: 59 MIO: 55	Open: 55.56 (10.84) MIO: 56.13 (10.73)	Siewert type I AC	II-III	Open - TTO, MIO	ACT: 59% (open) & 65% (MIO)
van Meertan et al., (2008)	2001-2004	Prospective phase II	50	59 (40-75)	AC, SCC, other	T2-3, N0 -1	Open	NACRT: 100%
Ramakrishnaiah et al., (2014)	2007-2009	Prospective longitudinal	55	52.6 (10.9)	AC, SCC, other	0-III	Open - THO & TTO	NART: 49.1%, NACT: 3.6% ACT or ACRT: 22%
Reynolds et al., (2006)	1999-2004	Prospective longitudinal	147	61 (29-79)	AC, SCC	I-IV	Open - TTO & THO	NACRT: 51%
Parameswaran et al., (2010)	2005-2007	Prospective longitudinal	55	67 (49-80)	AC, SCC, HGD	0-III	MIO	NACT: 77%
Nafteux et al., (2011)	2005-2010	Retrospective longitudinal	Open: 101 MIO: 65	Open: 64.1 (29-82) MIO: 63.1 (41-82)	AC, SCC, other	T<2, N0, MO	Open-TTO, MIO	None
Wang et al., (2010)	2007-2008	Longitudinal	Open: 29 VATS: 27	Open: 60.7 (9.3) VATS: 58.2 (11.5)	AC, SCC, undifferentiated	0-III	Open-TTO, VATS	None
Wang et al., (2011)	2007-2009	Retrospective longitudinal	97	61 (8.25)	AC, SCC, undifferentiated	0-III	MIO	None

Author (year)	Study period	Type of study	Sample size*	Me(di)an age (SD/range)	Histology	Stage	Surgery type(s)	Neoadjuvant/ adjuvant treatment
Wang et al., (2015)	2004-2013	Retrospective longitudinal	Open: 444 MIO: 444	Open: 56 (38-76) MIO: 56 (32-77)	SCC	0-IV	Open -TTO, MIO	NACT or NACRT: 17% (open) 18% (MIO)
Lv et al., (2014)	2011-2013	Longitudinal	50	<65: 56% ≥65: 44%	AC, SCC, other	0-IV	Open - TTO	None
Leibman et al., (2006)	1998-2000	Prospective longitudinal	25	61 (38-77)	AC, SCC, HGD	0-III	MIO	NACRT: 32%
Teoh et al., (2011)	2000-2004	Prospective RCT	45	62 (9.15)	SCC	T1-4, N1, M1	Open - TTO	None
Lagergren et al., (2007)	2000-2003	Prospective longitudinal	47	63 (44-79)	AC, SCC, HGD	0-III	Open - TTO & THO	NACT or NACRT: 62%
Avery et al., (2007)	2000-2004	Prospective longitudinal	69	62.4 (8.5)	AC, SCC	II-III	Open - TTO	NACT or NACRT: 100%

*Number who completed baseline questionnaires. † Randomly assigned to surgery type. § Information not available in article. Abbreviations: *RCT* randomised controlled trial, *AC* adenocarcinoma, *SCC* squamous cell carcinoma, *HGD* high grade dysplasia, *TTO* transthoracic oesophagectomy, *THO* transhiatal oesophagectomy, *MIO* minimally invasive oesophagectomy, *VATS* video assisted thoracoscopic surgery, *NACT* neoadjuvant chemotherapy, *NART* neoadjuvant radiotherapy, *NACRT* neoadjuvant chemoradiotherapy, *ACT* adjuvant chemotherapy, *ACRT* adjuvant chemoradiotherapy.

Study quality

All of the studies included in the meta-analysis were categorised as fair or good quality, with an average score of 18 out of 27 in the Downs and Black Checklist. As no study was deemed of poor quality, all suitable studies were included in the meta-analyses. Appendix III contains the details of the quality assessment for each study. The majority of the studies were clear about their main objective, outcomes to be measured, interventions of interest, main outcomes, estimates of variability and loss of participants. The most common areas where studies demonstrated poor quality was internal validity; in particular the lack of blinding of the participants and assessors to the intervention and the lack of randomisation to the intervention. However this was to be expected due to the small number of RCTs included in the review. In addition the majority of included studies did not carry out a power calculation.

Meta-analysis results

Impact of open surgery on physical functioning

Thirteen studies measured the impact of open surgery (transthoracic or transhiatal oesophagectomy) on physical functioning. These studies compared physical functioning scores at baseline with scores at 1-3 months, 4-6 months and 10-12 months. Of the 13 studies included overall, 11 measured physical functioning at 1-3 months, 10 measured physical functioning at 4-6 months and five measured physical functioning at 10-12 months. The meta-analyses were completed as planned, however heterogeneity between studies was high and therefore the results presented here should be interpreted with caution. This is discussed further below. The mean difference (standard deviation (SD)) scores from baseline to post surgery for the studies included at each time point are illustrated in the following forest plots: Figure 1.4, Figure 1.5 and Figure 1.6.

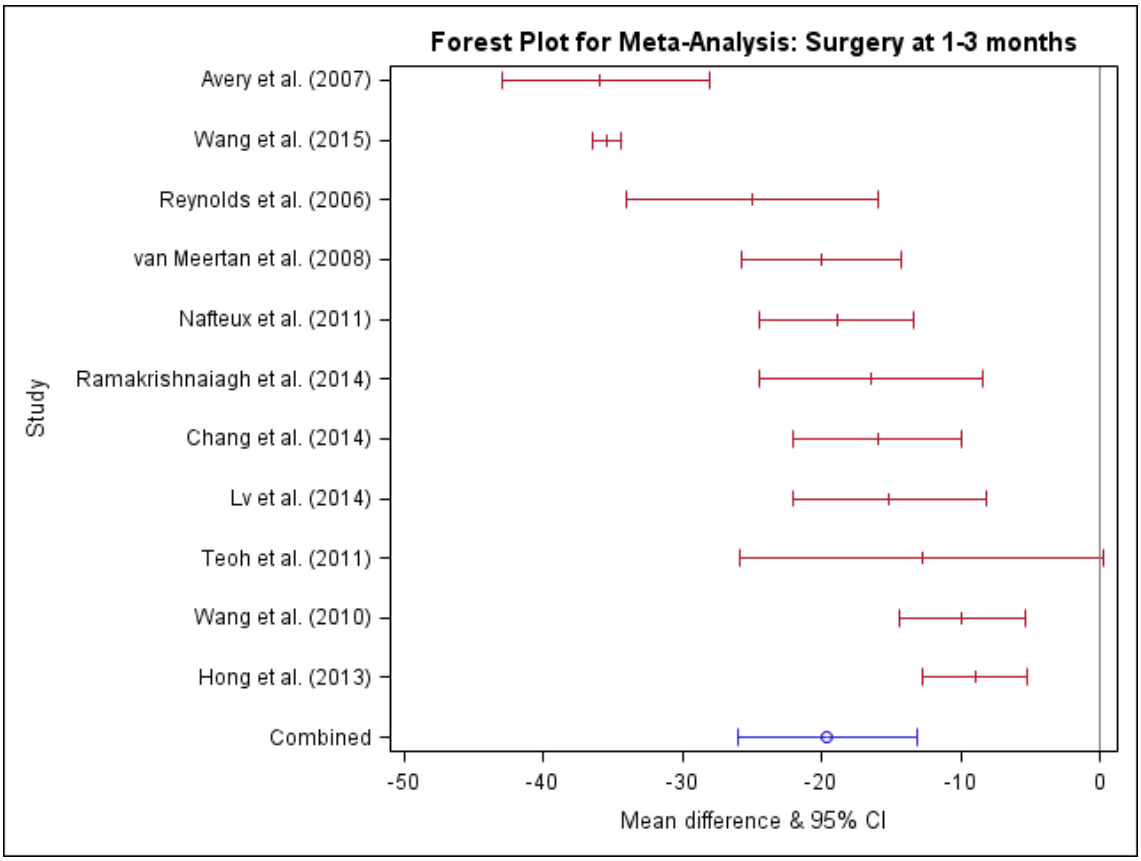

Figure 1.4 Mean difference in physical functioning scores at 1 - 3 months post open surgery (I^2 for heterogeneity = 97.55%)

At 1 - 3 months post surgery all included studies recorded a decrease in physical functioning scores from diagnosis. The mean (SD) decrease ranged from 9 (14.04) points (Hong et al., 2013) to 36 (26.23) points (Avery et al., 2007b).

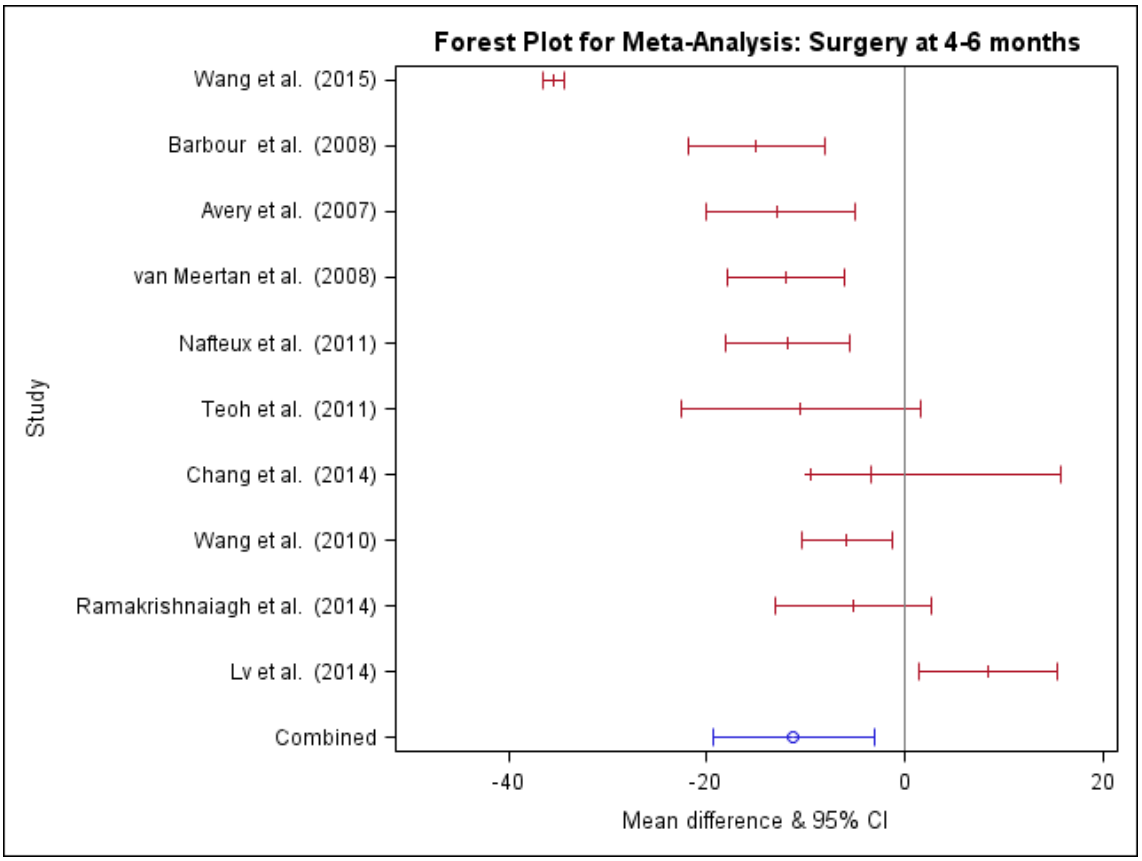

Figure 1.5 Mean difference in physical functioning scores at 4 - 6 months post open surgery (I^2 for heterogeneity = 98.4%)

At 4 - 6 months post surgery 10 of the 11 included studies recorded a decrease in physical functioning scores from baseline. The mean (SD) decrease ranged from 5.2 (23.15) points (Ramakrishnaiah et al., 2014) to 35.4 (11.84) points (Wang et al., 2015). In contrast, one study reported a mean increase of 8.4 (24.47) points as compared to baseline (Lv et al., 2014).

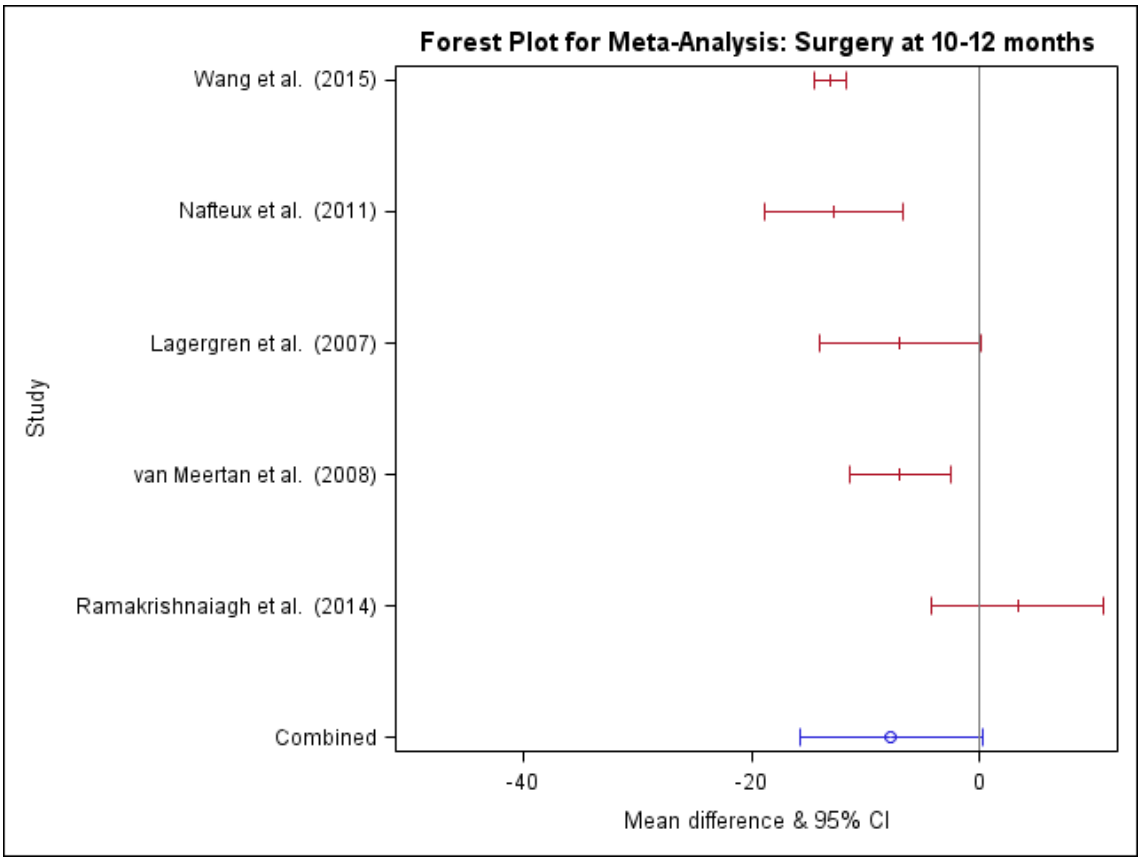

Figure 1.6 Mean difference in physical functioning scores at 10 - 12 months post open surgery (I^2 for heterogeneity = 85.6%)

At 10 - 12 months post surgery four of the five included studies recorded a decrease in physical functioning scores from baseline. The mean (SD) decrease ranged from 7 (13.83) points (van Meertan et al., 2008) to 12.78 (24.60) points (Wang et al., 2015). In contrast, one study reported a small increase of 3.35 (17.77) points as compared to baseline (Ramakrishnaiah et al., 2014).

Impact of minimally invasive surgery on physical functioning

Seven studies measured the impact of minimally invasive oesophagectomy on physical functioning. These studies compared physical functioning scores at baseline with scores at 1 - 3 months, 4 - 6 months and 10 - 12 months. Of the seven studies included overall, six measured physical functioning at 1 - 3 months, five measured physical functioning at 4 - 6 months and four measured physical functioning at 10 - 12 months. The meta-analyses were completed as planned, however heterogeneity was high for some of the meta-analyses and therefore the results presented here should be interpreted with caution. The mean difference (SD) scores

from baseline to post surgery for the studies included at each time point are each illustrated in the following forest plots: Figure 1.7, Figure 1.8 and Figure 1.9.

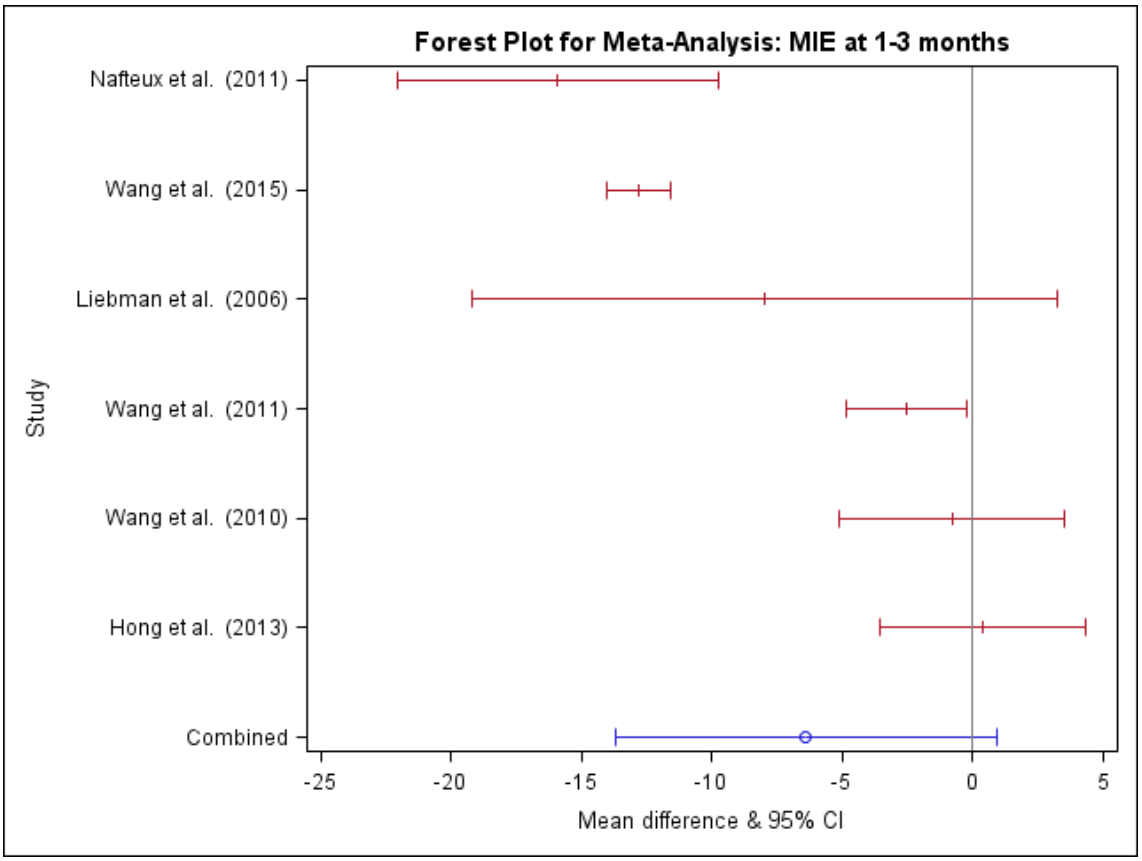

Figure 1.7 Mean difference in physical functioning scores at 1 - 3 months post minimally invasive surgery (I^2 for heterogeneity = 95.5%)

At 1 - 3 months post surgery five of the six included studies recorded a decrease in physical functioning scores from baseline. The mean (SD) decrease ranged from 0.8 (10.65) points (Wang et al., 2010) to 15.92 (22.12) points (Nafteux et al., 2011). In contrast, one study recorded a very minor increase of 0.4 (14.04) points in the physical functioning score as compared to baseline (Hong et al., 2013).

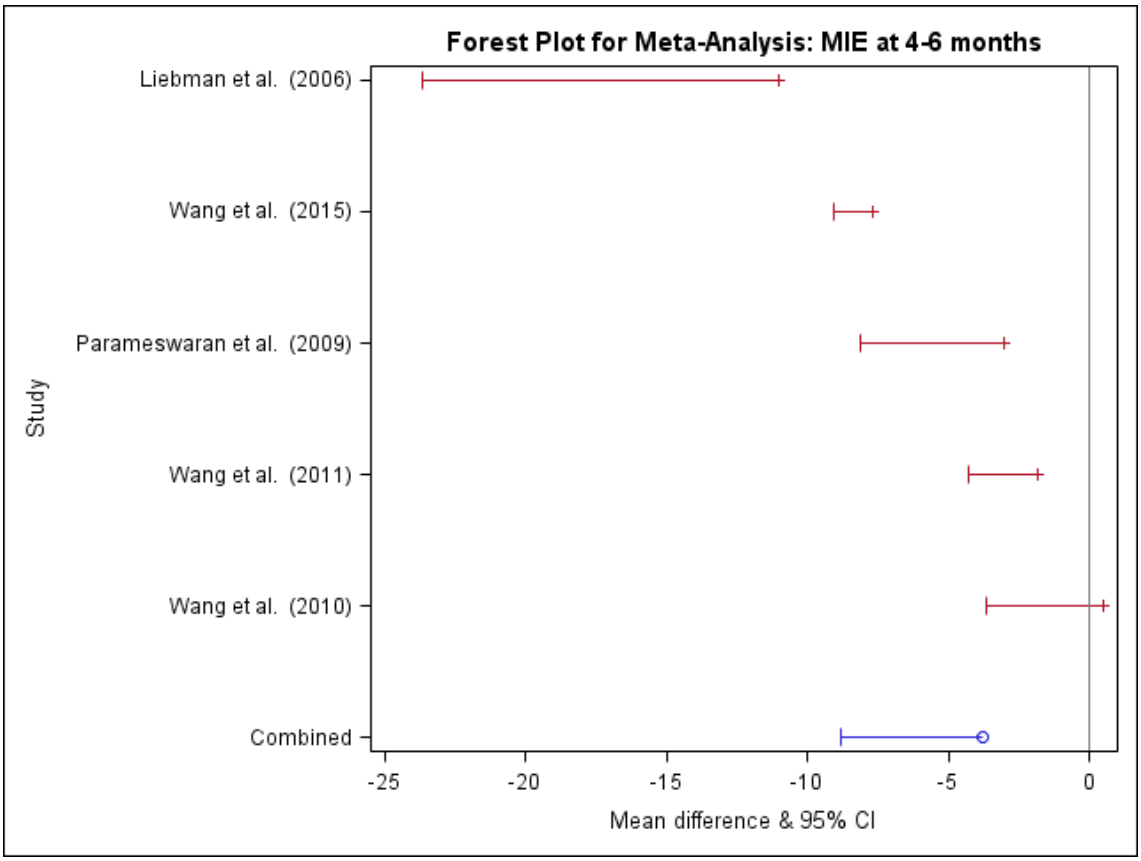

Figure 1.8 Mean difference in physical functioning scores at 4 - 6 months post minimally invasive surgery (I^2 for heterogeneity = 86.5%)

At 4 – 6 months post surgery four of the five included studies recorded a decrease in physical functioning scores from baseline. The mean (SD) decrease ranged from points 1.8 (11.92) (Wang et al., 2011) to 11 (27.79) points (Leibman et al., 2006). In contrast, one study recorded a very minor increase of 0.5 (10.34) points in the physical functioning score as compared to baseline (Wang et al., 2010).

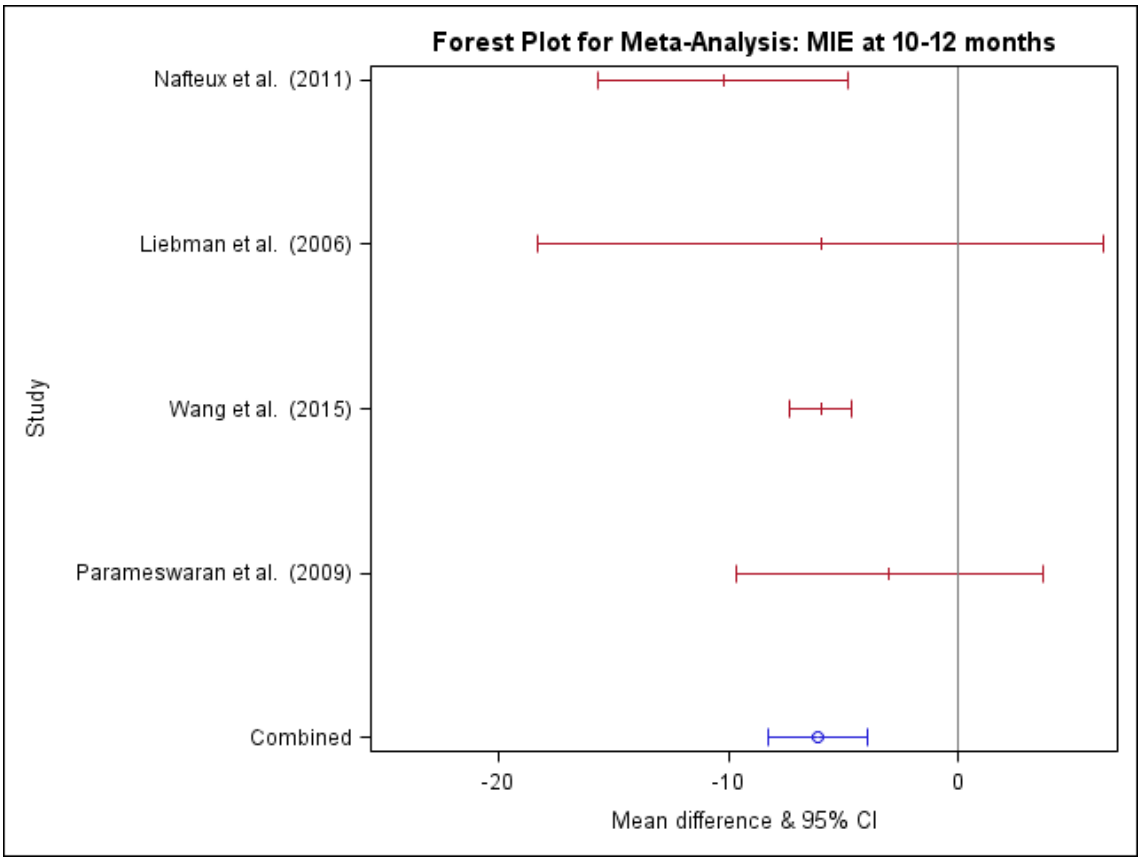

Figure 1.9 Mean difference in physical functioning scores at 10 - 12 months post minimally invasive surgery (I^2 for heterogeneity = 6.74%)

At 10 - 12 months post surgery all included studies recorded a decrease in physical functioning scores from diagnosis. The mean (SD) decrease ranged from 3 (20.97) points (Parameswaran et al., 2010) to 10.23 (18.77) points (Nafteux et al., 2011).

Meta-analyses limitations

There was a very high level of heterogeneity in the meta-analyses included in this review ranging from 85.6% to 97.55% (Figures 1.4 - 1.8) as measured by the I^2 statistic. Just one meta-analysis of the difference in physical functioning from baseline to 10 - 12 months post minimally invasive oesophagectomy had a low level of heterogeneity (6.74%) (Figure 1.9). Therefore for five of the six meta-analyses there appears to be a significant inconsistency between the treatment effects as measured by each study. These findings limit the generalisation of the results of the meta-analyses. Therefore for the purposes of this review, the forest plots are primarily presented for descriptive purposes.

1.3.3.3 Narrative review of subjectively measured physical functioning

Study design and characteristics

The remaining studies identified for inclusion in this review were not suitable for inclusion in the meta-analyses and are described in this section. These studies subjectively measured physical functioning and the majority reported the results graphically. Included articles were published between 1992 and 2015. Of the 20 studies included in the narrative review, there were 14 longitudinal studies, two RCTs, one phase II trial and three studies which measured physical functioning pre and post treatment, one of which randomly assigned participants to receive chemotherapy or not. Fourteen studies measured physical functioning using a subscale of the EORTC-QLQ. The remainder of the studies measured physical functioning as a subscale of other HRQOL questionnaires. Two studies used both the MOS SF-20 and the RSCL, one used the RSCL only, one used the SF-36 and another two used the FACT-E. Sample sizes ranged from 24 to 199 participants and the studies included a mixture of patient groups with regards to cancer histology (AC, SCC and others) and stage (stage 0-IV). The studies evaluated patients who had received multimodal treatment or surgery only. Surgery types evaluated included open (transthoracic and transhiatal) and minimally invasive oesophagectomy. Characteristics of the included studies are detailed in Table 1.6.

Table 1.6 Study and patient characteristics for studies included in the narrative review of subjectively measured physical functioning

First author (year)	Study period	Type of study	Sample size	Me(di)an age (SD/range)	Histology	Stage	Surgery type(s)	Neoadjuvant/ adjuvant treatment	HRQOL questionnaire used
Huang et al., (2015)	2012-2013	Prospective longitudinal	196	≤60: 49% >60: 51%	SCC, other	0-III	Open -TTO, MIO	ACT or ACRT: 14%	EORTC-QLQ
Blazeby et al., (2000)	1993-1995	Longitudinal	55	67 (51-79)	AC, SCC	II-III	Open	NACT: 9%	EORTC-QLQ
Zeng & Liu (2012)	2010	Prospective longitudinal	90	62.4 (9.53)	SCC	I-III	Open -TTO, MIO	None	EORTC-QLQ
Shen et al., (2015)	2005-2007	Longitudinal	62	<60: 27% ≥60: 73%	AC, SCC	0-III	Open - TTO, HVATS	None	EORTC-QLQ
Gradauskas et al., (2006)	§	Longitudinal	49	59.68 (9.58)	AC, SCC	I-III	Open	§	EORTC-QLQ
Egberts et al., (2008)	1998-2006	Prospective longitudinal	105	62.4 (9.1)	AC, SCC, other	I-IV	Open-TTO	NACRT: 42% ACT: 36%	EORTC-QLQ
Hauser et al., (2014)	1998-2009	Prospective longitudinal	131	62.4 (9.1)	AC, SCC	I-IV	Open -TTO	NACT or NACRT: 36%	EORTC-QLQ
Kataria et al., (2012)	2004-2005	Longitudinal (pre & post measures) ‡	30	52 (35-70)	§	§	Open -THO	NACT: 50% ART: 100%	EORTC-QLQ
Scarpa et al., (2013)	2009-2011	Prospective longitudinal	126	60.5 (53-67)	AC, SCC, other	T0-4, N0-3, M0-1	Open -TTO	NACT or NACRT: 77% ACT: 70%	EORTC-QLQ
Schneider et al., (2010)	2001-2005	Longitudinal	24	59 (52-75)	AC, SCC	§	Open	§	EORTC-QLQ
Donohue et al., (2011)	1985-2009	Longitudinal (pre & post measures)	67	§	AC, SCC, other	I-IV	Open – TTO & THO	§	EORTC-QLQ

First author (year)	Study period	Type of study	Sample size	Me(di)an age (SD/range)	Histology	Stage	Surgery type(s)	Neoadjuvant/ adjuvant treatment	HRQOL questionnaire used
Cense et al., (2006)	1994-2003	Prospective longitudinal	92	63 (35-78)	AC	0-IV	Open-TTO	None	MOS SF-20 & RSCL
de Boer et al., (2004)	1994-2003	RCT	199	62 (23-78)	AC	§	Open –TTO & THO	None	MOS SF-20 & RSCL
Aly et al., (2010)	2004-2007	RCT	56	64.5	§	I-III	Open - TTO	NACT or NACRT: 33%	EORTC-QLQ
Luketich et al., (2003)	1996-2002	Prospective longitudinal	57	66.5 (39-89)	AC, SCC. HGD	§	MIO	§	SF-36
Safieddine et al., (2009)	2002-2005	Prospective phase II	52	60 (33-79)	AC, SCC, other	II-IV	Open - TTO	NACRT: 100%	FACT-E
van Knippenberg et al., (1992)	1984-1987	Longitudinal (pre & post measures)	62	58.1 (9.9)	§	§	Open	NART: 43%	RCSL
Brooks et al., (2002)	1998-2000	Longitudinal	38	62.4 (42-82)	AC, SCC, HGD, other	0-III	Open	NACT or NACRT: 53%	FACT-E
Blazeby et al., (2005)	2000-2003	Prospective longitudinal	103	63.83 (8.73)	AC, SCC	I-IV	Open - TTO	NACRT: 33% NAC: 47%	EORTC-QLQ
Zieren et al., (1996)	§	Longitudinal	30	57 (10)	AC, SCC	§	Open-TTO, THO	None	EORTC-QLQ

§ Information not available in article. ‡Randomly assigned to chemotherapy. Abbreviations: *RCT* randomised controlled trial *AC* adenocarcinoma, *SCC* squamous cell carcinoma, *HGD* high grade dysplasia, *TTO* transthoracic oesophagectomy, *THO* transhiatal oesophagectomy, *MIO* minimally invasive oesophagectomy, *HVATS* hand video assisted thoracoscopic surgery, *NACT* neoadjuvant chemotherapy, *NART* neoadjuvant radiotherapy, *NACRT* neoadjuvant chemoradiotherapy, *ACT* adjuvant chemotherapy, *ACRT* adjuvant chemoradiotherapy, *EORTC-QLQ* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, MOS SF-20 Medical Outcomes Study 20-Item Short Form Survey, *SF-36* Medical Outcomes Study 36-Item Short Form Survey, *RSCL* Rotterdam Symptom Checklist, *FACT-E* Functional Assessment of Cancer Therapy – for patients with Esophageal cancer.

Narrative review results

Impact of neoadjuvant treatment on physical functioning

Four studies included in the narrative review measured physical functioning pre and post neoadjuvant therapy, two used the EORTC-QLQ (Scarpa et al., 2013, Blazeby et al., 2005) and two used the FACT-E scale (Safieddine et al., 2009, Brooks et al., 2002). A significant decrease in the physical functioning and physical well-being subscales was observed after neoadjuvant treatment and prior to surgery in three studies (Safieddine et al., 2009, Brooks et al., 2002, Blazeby et al., 2005). Two studies included in the meta-analysis also evaluated the impact of neoadjuvant treatment on physical functioning and recorded a significant mean decrease of 13 points ($p=0.004$) (Reynolds et al., 2006) and 22 points ($p<0.05$) (van Meerten et al., 2008) from baseline scores using the EORTC-QLQ. In contrast, Scarpa et al., (2013) reported that physical functioning measured using the EORTC-QLQ remained stable pre and post neodjuvant treatment.

Impact of open surgery on physical functioning

The acute negative impact of transthoracic or transhiatal oesophagectomy on physical functioning, demonstrated by the meta-analyses, is supported by these additional studies which also subjectively measured physical functioning. Thirteen studies measured the short term effect of open surgery on physical functioning using the EORTC-QLQ and all of these reported a decrease in physical functioning scores from pre to post surgery (Huang et al., 2015, Zeng and Liu, 2012, Shen et al., 2015, Schneider et al., 2010, Gradauskas et al., 2006, Blazeby et al., 2005, Zieren et al., 1996, Aly et al., 2010, Egberts et al., 2008, Hauser et al., 2014, Blazeby et al., 2000, Scarpa et al., 2013, Kataria et al., 2012). Similarly, significant decreases in the physical functioning subscale of the MOS SF-20 and the activity level subscale of the RSCL post surgery were observed from pre to post surgery (Van Knippenberg et al., 1992, de Boer et al., 2004, Cense et al., 2006). Physical well-being, as measured by the FACT-E questionnaire was also significantly decreased after surgery compared to baseline values (Brooks et al., 2002, Safieddine et al., 2009). One exception to this was a subgroup within a study by Kataria et al., (2012) where the physical functioning score increased from prior to neoadjuvant chemotherapy to post surgery and adjuvant radiotherapy. However the other subgroup in this study who received surgery and adjuvant radiotherapy only, experienced a deterioration in physical functioning at 16 weeks post treatment.

While all studies recorded a decrease in physical functioning initially post surgery there were inconsistent results in relation to the return of physical functioning scores to baseline levels. Five studies found that physical functioning did not return to baseline values within the study periods of six months (Shen et al., 2015, Zeng and Liu, 2012), one year (Scarpa et al., 2013) or two years post surgery (Hauser et al., 2014, Egberts et al., 2008). In contrast, eight studies reported that physical functioning returned or almost returned to baseline values within the study periods of three to six months (Gradauskas et al., 2006, Safieddine et al., 2009), six to nine months (Huang et al., 2015, Blazeby et al., 2005, Zieren et al., 1996, de Boer et al., 2004, Brooks et al., 2002) or nine to eighteen months post operatively (Cense et al., 2006).

Longer term physical functioning, beyond two years post surgery, was only measured in two studies. Blazeby et al., (2000) compared those who survived longer than two years with those who survived less than two years post surgery and found that physical functioning had returned to baseline levels by nine months for the long term survivors, however for those who did not survive longer than two years, physical functioning never returned to baseline values after surgery. Finally, one study investigated long term physical functioning in disease free survivors who were one – twenty three years post surgery (Donohoe et al., 2011a). This study found that the long term scores on the physical functioning subscale of the EORTC-QLQ were significantly lower than baseline ($p<0.001$), indicating a prolonged negative effect of oesophagectomy on physical functioning.

Impact of minimally invasive surgery on physical functioning

Four studies included in this narrative review included participants who had undergone minimally invasive oesophagectomy. Two studies (Zeng and Liu, 2012, Shen et al., 2015) measured the impact of minimally invasive oesophagectomy on physical functioning using the EORTC-QLQ and reported similar outcomes: physical functioning scores were decreased in the initial post-operative period but returned or almost returned to baseline levels within three to six months. In contrast, the majority of the studies included in the meta-analysis reported that physical functioning did not return to baseline scores at three to six months or ten to twelve months post surgery. One study investigated the impact of MIO on physical functioning using the SF-36 and found no change in the physical component score pre and post surgery indicating preservation of physical functioning (Luketich et al., 2003). Finally, the study by Huang et al., (2015) included both minimally invasive and open surgery but did not report separate results for the surgery groups. As approximately 80% of participants in this study

underwent open surgery, the results are included in the section for open surgery.

1.3.3.4 Narrative review of objectively measured physical functioning

Study design and characteristics

Seven studies published between 2001 and 2015 objectively measured physical functioning before and after curative treatment for oesophageal cancer. Of the seven studies included in the narrative review, one was a longitudinal study with multiple assessments, one was a cohort study within a prospective randomised trial and five studies measured physical functioning pre and post treatment. Sample sizes ranged from 27 to 51 participants and the studies included a mixture of patient groups with regards to cancer histology (AC and SCC) and stage (stage 0-IV). The studies evaluated patients who had received multimodal treatment or surgery only. Surgery types evaluated included open (transthoracic and transhiatal) and minimally invasive oesophagectomy. Characteristics of the included studies are detailed in Table 1.7.

Four studies (Jack et al., 2014, Lund et al., 2015, Tatematsu et al., 2013a, Liedman et al., 2001) measured the impact of neoadjuvant treatment on objective measures of physical functioning and two studies (Taguchi et al., 2003, Tatematsu et al., 2013b) measured the effect of surgery on physical functioning. The final study (Rawat et al., 2011) measured physical functioning pre neoadjuvant radiotherapy as well as three, six and nine months post completion of treatment including surgery for a percentage of participants.

The primary outcome in all of the studies reviewed was fitness. Four studies used maximal exercise tests on cycle ergometers, two carried out a cardiopulmonary exercise test (CPET) (Jack et al., 2014, Taguchi et al., 2003) and two carried out a maximal working capacity test (Liedman et al., 2001, Lund et al., 2015). Three studies carried out the Six Minute Walk Test (6MWT) (Rawat et al., 2011, Tatematsu et al., 2013a, Tatematsu et al., 2013b). Fitness assessed using cycle ergometer tests was measured by maximal oxygen uptake (VO_{2maz}/VO_{2peak}) (Jack et al., 2014, Taguchi et al., 2003) and working capacity (Watts) (Lund et al., 2015, Liedman et al., 2001), while 6MWT results were measured by changes in the distance achieved on the test. In addition to the fitness assessments, the studies by Tatematsu and colleagues (Tatematsu et al., 2013a, Tatematsu et al., 2013b) measured isometric knee strength using an isometric knee-extensor muscle strength machine.

Table 1.7 Study and patient characteristics for studies included in the narrative review of objectively measured physical functioning

First author (year)	Study period	Type of study	Sample size	Me(di)an age (SD/range)	Histology	Stage	Surgery type(s)	Neoadjuvant/ adjuvant treatment
Jack et al., (2014)	2007-2009	Longitudinal (pre & post measures)	39	64.86 (9.06)	Oesophageal or Gastric Ca	T1, T4	Open	NACT: 100%
Lund et al., (2015)	2008-2013	Cohort within a prospective randomised trial	NACT group: n=23 NACRT group: n=17	NACT group: 62 (46-71) NACRT group: 66 (56-76)	AC, SCC	T1-3, N0-1	Open -TTO	NACT: 57.5% NACRT: 42.5%
Rawat et al., (2011)	2008-2009	Prospective longitudinal	45	<50 yrs: 26% >50 yrs: 73%	AC, SCC	§	Open - THO & TTO†	NACRT: 100%
Taguchi et al., (2003)	1993-1998	Longitudinal (pre & post measures)	VATS group: n=22 Open surgery group: n=29	VATS group: 61.6 (47-79) Open surgery group: 61.7 (43-74)	SCC	0-III	Open – TTO, VATS	None
Tatematsu et al., (2013a)	2009-2010	Longitudinal (pre & post measures)	27	63.4 (6.8)	SCC	II-IVA	Open	NACT: 100%
Tatematsu et al., (2013b)	2009-2010	Longitudinal (pre & post measures)	30	63.6 (7.1)	SCC	0-III	Open – TTO	NACT: 70%
Liedman et al., (2001)	1996-1998	Longitudinal (pre & post measures)	Study group (NACRT & surgery): n= 29 Control groups (surgery only): n=10	Study group: 63 (45-78) Control group: 62 (46-76)	AC, SCC	T2-3, N0-1	Open - TTO (study group) & THO (control groups)	NACRT: 100% (study group)

§ Information not available in article. †55% of study cohort underwent surgery. Abbreviations: *AC* adenocarcinoma, *SCC* squamous cell carcinoma, *TTO* transthoracic oesophagectomy, *THO* transhiatal oesophagectomy, *VATS* video assisted thoracoscopic surgery, *NACT* neoadjuvant chemotherapy, *NACRT* neoadjuvant chemoradiotherapy.

Narrative review results

Impact of neoadjuvant treatment on physical functioning

Three studies investigated the effect of neoadjuvant chemotherapy on fitness (Jack et al., 2014, Lund et al., 2015, Tatamatsu et al., 2013). Two of these studies reported a negative effect of treatment on fitness with significant decreases in VO_2 ($p<0.001$) (Jack et al., 2014) and working capacity ($p=0.03$) (Lund et al., 2015) observed. Conversely, the study by Tatamatsu and colleagues (2013) found no significant changes in fitness pre and post chemotherapy as measured by the 6MWT. Furthermore, this study revealed no change in muscle strength after chemotherapy. The impact of neoadjuvant chemoradiotherapy was measured by two studies (Lund et al., 2015, Liedman et al., 2001) and both revealed a significant decrease in working capacity, as measured using a CPET, after this treatment ($p=0.001$ and $p<0.0001$ respectively). In addition, Liedman et al., (2001) compared the study group to a control group awaiting surgery and not receiving neoadjuvant treatment. The significant changes recorded in the study group contrasted with the stable physical performance of the control group in the preoperative period. The study group demonstrated a significantly lower working capacity ($p<0.001$) than the control group prior to surgery. In the study by Rawat et al., (2011) a decrease in the mean distance achieved on the 6MWT was recorded at three and nine months post treatment, however a statistical significance value for this decrease was not reported.

The study by Tatematsu et al., (2013) also subjectively measured physical activity levels using the International Physical Activity Questionnaire and reported no significant difference from pre to post neoadjuvant chemotherapy.

Impact of surgery on physical functioning

A highly significant reduction in VO_{2max} ($p<0.0001$) and 6MWT distance ($p<0.001$) post surgery was demonstrated by two studies (Taguchi et al., 2013 and Tatamatsu et al., 2012) indicating the considerable negative impact of oesophagectomy on fitness levels. This reduction in fitness was demonstrated for both open surgery and VATS (Taguchi et al., 2003). Surgery was also shown to have a negative effect on muscle strength with a significant reduction in knee extensor muscle strength observed ($p<0.001$) (Tatamatsu et al., 2012).The results of these studies are summarised in Table 1.8.

Table 1.8 Main results of studies which objectively measured physical functioning pre and post treatment

First author (year)	Test/Tool	Measure(s)	Timepoints	Comparison	Results
Jack et al., (2014)	CPET on cycle ergometer	VO_2 (ml kg^{-1} min^{-1}) at LT VO_2 (ml min^{-1}) at LT O_2 pulse at LT O_2 pulse at peak VO_2peak (ml kg^{-1} min^{-1}) VO_2peak (ml min^{-1}) V_E/ VCO_2 at LT V_E/ VCO_2 at peak	Pre and post NACT	None	Significant decrease in absolute and relative VO_2 at LT ($p<0.001$)& peak ($p<0.001$) Significant decrease in O_2 pulse at LT ($p<0.001$) and peak ($p=0.002$) V_E/ VCO_2 significantly increased at LT ($p=0.014$) and peak ($p=0.052$)
Lund et al., (2015)	Maximal working capacity test on cycle ergometer	Maximum work capacity (WC) (Watts)	Pre and post neoadjuvant therapy	NACT vs NACRT	Significant decrease in WC in both NACT ($p=0.03$) and NACRT ($P=0.001$) groups
Rawat et al., (2011)	6WMT	6MWD (m)	Pre NART and 1, 3, 6, 9 months post treatment	None	Decrease in 6MWD at 3 & 9 months post treatment
Tatematsu et al., (2013)	6MWT Isometric knee-extensor muscle strength machine I-PAQ*	6MWD (m) Max isometric knee strength (N m/kg) Physical activity levels over previous 7 days	Pre and post NACT	None	No significant changes in any measure

First author (year)	Test/Tool	Measure(s)	Timepoints	Comparison	Results
Liedman et al., (2001)	Maximal working capacity test on cycle ergometer	Working capacity (Watts)	Pre and post NACRT	NACRT (study group) vs surgery only (control group)	Significant decrease in WC ($p<0.0001$) in study group. Significant decrease in WC in study group as compared to control group ($p<0.001$)
Taguchi et al., (2003)	CPET on cycle ergometer	VO_{2max} Resting VO_2/HR AT	Pre and 3 months post surgery	VATS vs open surgery	Significant decrease in VO_{2max} & AT in both groups ($p<0.0001$) Significant decrease in resting VO_2/HR in VATS ($p=0.016$) and open surgery ($p=0.04$) groups
Tatematsu et al., (2012)	6MWT Isometric knee-extensor muscle strength machine	6MWD (m) Max isometric knee strength (N·m/kg)	Pre and post surgery	None	Significant decrease in knee extensor muscle strength ($p<0.001$) and 6MWD ($p<0.001$)

*Subjective measure. Abbreviations: *CPET* cardiopulmonary exercise test, *6MWT* Six Minute Walk Test, *6MWD* Six Minute Walk Distance, *I-PAQ* International Physical Activity Questionnaire*, N* newton, *m* metre, *kg* kilogram, *ml* millilitre, *min* minute, *WC* working capacity, *NACT* neoadjuvant chemotherapy, *NART* neoadjuvant radiotherapy, *NACRT* neoadjuvant chemoradiotherapy, *VO_2* oxygen uptake, *VO_2peak,* highest VO_2 achieved during CPET, *LT* lactate threshold, *peak* peak exercise, *V_E/ VCO_2* ventilatory equivalents for O_2 and CO_2: ventilatory requirement for a given metabolic rate, *O_2 pulse* VO_2/HR, *AT* anaerobic threshold, *HR* heart rate, *VATS* video assisted thoracosopic surgery,

1.3.4 Discussion of systematic review

The aim of this systematic review was to examine the impact of treatment for oesophageal cancer (chemotherapy, radiotherapy and surgery) on both subjectively and objectively measured physical functioning. Physical functioning was subjectively measured as a subscale of patient reported HRQOL questionnaires and was objectively evaluated using measures of strength and fitness. Of the large number of studies which subjectively measured physical functioning, the vast majority examined the effect of surgery on physical functioning, with a small minority investigating the impact of neoadjuvant treatment. In contrast, five of the seven studies of objectively measured physical functioning investigated the impact of neoadjuvant treatment on physical functioning, while only two studies measured the effect of surgery.

Overall the studies included in this review revealed an acute negative effect of neoadjuvant chemotherapy and/or radiotherapy on physical functioning. Five of the six studies which subjectively measured physical functioning reported a significant decrease in this outcome from pre to post neoadjuvant treatment. These subjective reports are supported by the objective measures of physical fitness. Three studies reported significant reductions in fitness, as measured using a CPET or maximal working capacity test, from pre to post neoadjuvant treatment (Jack et al., 2014, Lund et al., 2015, Liedman et al., 2001). In contrast, two studies recorded no changes in fitness from pre to post neoadjuvant as measured by the 6MWT (Tatematsu et al., 2013, Rawat et al., 2011). Tatematsu and colleagues (2013) found no significant change in distance achieved on the 6MWT by the study cohort after completion of neoadjuvant chemotherapy. Similarly, while Rawat et al. (2011) recorded a mean decrease in the distance achieved on the 6MWT, the significance of this change was not reported and the mean difference was less than would be considered clinically meaningful (Perera et al., 2006). Therefore it is unlikely this study cohort experienced any clinically meaningful changes in fitness from pre to post neoadjuvant treatment.

While the 6MWT has shown moderate to high correlations with VO_{2max} (Ross et al., 2010), it may be less sensitive to treatment effects than a CPET. It has been suggested that walking tests might not be sensitive enough to assess changes in exercise capacity in patients with early-stage disease or in those without concomitant comorbid disease because they may not sufficiently stress the cardiovascular system (Jones et al., 2008a).

In a comparable finding to the impact of chemotherapy and radiotherapy, oesophagectomy was shown to have an acute negative impact on physical functioning in the acute post-operative phase. The scores for subjectively reported physical functioning were found to be

decreased in the initial weeks and months post surgery as compared to pre-operative levels. This negative impact of surgery was observed in both open and minimally invasive oesophagectomy cohorts. The magnitude of this decrease however was difficult to determine due to the significant heterogeneity between studies reflected in the large I^2 values in the meta-analyses. Accordingly while there was a clear trend towards a negative impact of surgery on subjectively measured physical functioning, a pooled estimate and confidence interval for this treatment effect could not be reported with confidence. Objectively, the impact of surgery was measured using a CPET and the 6MWT, and a significant decrease in both VO_{2max} and distance achieved on the 6MWT was observed indicating a significant reduction in fitness levels post surgery (Taguchi et al., 2003, Tatematsu et al., 2012). Furthermore, the study by Tatematsu and colleagues (2012) reported a significant loss of muscle strength from pre to post surgery.

While there was general agreement between studies regarding the negative impact of surgery on physical functioning in the acute post-operative phase, there was conflicting evidence regarding the return of physical functioning scores to baseline levels. In the meta-analyses, for both open and minimally invasive surgery, the majority of studies included continued to report lower scores for physical functioning as compared to baseline at four to six months and ten to twelve months (Figures 1.5, 1.6, 1.8, 1.9). However in the narrative review, the majority of studies report a return of physical functioning scores to baseline levels within a range of three to 18 months post-operatively.

The discrepancy in the study results could be due to a variety of factors. As a result of an increase in specialist centres, improved patient selection, standardisation of surgical techniques and an aggressive approach to addressing postoperative complications, outcomes after treatment for oesophageal cancer have continually improved over recent decades. Therefore as the studies included in this review were carried out over the last three decades, a degree of inconsistency in long term treatment effects across study cohorts could be expected. Furthermore the study populations included in this review included a variety of histological subtypes of oesophageal cancer and participants underwent a range of treatment combinations and surgery types. All of these factors can have an impact on outcomes and potentially explain some of the non-uniformity in study results.

This review considered the impact of open and minimally invasive surgery on physical functioning separately. MIO has emerged in recent years as an alternative to open surgery. Due to the smaller incisions involved, minimally invasive surgery is often associated with lower morbidity, less blood loss, reduced post-operative pain, lesser scarring, faster recovery and

decreased length of hospital stay. The benefits of minimally invasive surgery over open surgery have not yet been proven in an oesophageal cancer population (Allum et al., 2011), however the results of this review indicate that physical functioning may be less adversely affected by MIO than by open oesophagectomy. In the meta-analyses, while the overall trends in the changes in physical functioning scores from baseline were similar for open and minimally invasive surgery cohorts, the mean decrease in scores were lower in those who underwent MIO than those received open surgery. For example, at one to three months post-operatively the decrease in physical functioning scores from baseline ranged from 9 to 36 points in the open surgery cohorts and 0.8 to 16 points in the minimally invasive surgery cohorts. Furthermore six studies included in either the meta-analyses or the narrative review compared HRQOL outcomes between open surgery and MIO. Five of these studies suggested that patients in the MIO groups recovered more quickly than the open surgery group. The physical functioning scores in the MIO groups were significantly better than the open surgery group at various time points from two weeks up to 18 months post-operatively (Wang et al., 2010, Wang et al., 2015, Hong et al., 2013, Shen et al., 2015, Zeng and Liu, 2012). In contrast one study found no significant difference between open and minimally invasive surgery groups from one to twelve months post-operatively (Nafteux et al., 2011). Due to the limited number of studies currently available regarding the effect of MIO on physical functioning, no definite conclusion can be reached, however the results in this review suggest that this is an area which merits further research.

1.3.5 Limitations of systematic review

As discussed in Section 1.3.3.2 there was a very high level of heterogeneity in the meta-analyses included in this review, indicating significant inconsistency between the treatment effects as measured by each study. This may have been as a result of differences in treatment effects due to medical and surgical advances in recent decades or as a result of the differences in study populations included in the review; the study populations included a variety of histological subtypes of oesophageal cancer and participants received a range of treatment combinations and surgery types. However, as all the studies contained in the meta-analyses met the specific inclusion criteria for the systematic review and accordingly provide a relevant and valid contribution to the body of evidence on this topic, there was no valid reason to exclude these studies and they were included in the review. Due to the high level of heterogeneity the forest plots are included in this thesis for descriptive purposes only; in order

to provide the reader with a visual representation of the trends in study results. A pooled estimate and confidence interval for the treatment effect has not been reported and the conclusions are based solely on the common trends seen in the study results.

1.3.6 Conclusion of systematic review

To conclude, the results of this systematic review reveal that both neoadjuvant therapy and oesophagectomy can have a significant negative impact on physical functioning in the acute phase post treatment. However it is unclear how long it takes for physical functioning to return to baseline levels or whether it returns at all. Therefore more research is warranted in this population to determine how physical functioning recovers after chemotherapy, radiotherapy and surgery, particularly as treatment outcomes in this group are currently evolving and improving.

The small number of studies which objectively measured physical functioning included in this review highlight the need for more studies of this nature. Objective data on fitness, strength and physical activity levels across the oesophageal cancer continuum would provide a more comprehensive overview of the physical functioning of this group and help to identify specific areas which could be targeted with interventional programmes. Finally, with the improving five year survival rates in this cohort there is a need for more research into longer term physical functioning, beyond the initial post-operative year.

1.4 Role of physiotherapy for people with cancer

Physiotherapy can play an important role to ameliorate the impact of treatment on physical functioning throughout the cancer trajectory. People with cancer may present with a wide range of needs, including respiratory, neurological, lymphatic, orthopaedic, musculoskeletal and pain, and may benefit from physiotherapeutic intervention. Within the context of cancer, the primary goal of physiotherapy intervention is to assist the patient achieve maximum physical, psychological and vocational functioning within the limits imposed by disease or treatment (Cromes, 1978).

It is well established that exercise can improve quality of life (QOL) for cancer patients regardless of the type and stage of their disease (Mishra et al., 2012a, Mishra et al., 2012b).

The Physical Exercise Across the Cancer Experience (PEACE) Framework, first described in 2001 by Courneya and Friedenreich, describes six cancer related time points where exercise and activity can play a key and developed role. Based on these six time periods this framework describes eight general cancer control outcomes which are amenable to physical exercise interventions (Figure 1.10). There is evidence to support the beneficial role of exercise in each of these cancer control categories (Courneya and Friedenreich, 2007).

Physiotherapists are exercise specialists and therefore are ideally placed to provide interventions to improve strength, fitness and activity levels across the cancer continuum. Furthermore, physiotherapy can play a vital role in maintaining healthy weight and preventing muscle wasting in patients with cancer. In particular, physiotherapy can optimise physical functioning prior to treatment with prehabilitation programmes or restore optimal physical functioning after treatment through rehabilitation programmes.

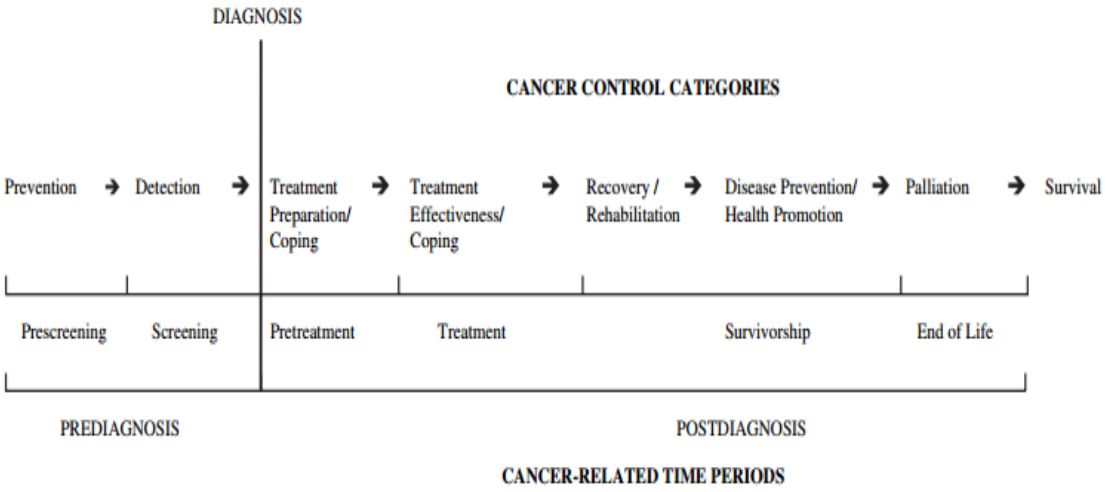

Figure 1.10 PEACE Framework

The process of enhancing the functional capacity of the individual to enable him/her to withstand an upcoming stressor has been termed 'prehabilitation' (Topp et al., 2002, Ditmyer et al., 2002). There is a growing body of scientific evidence that supports prehabilitation as a method of optimising health and functioning before the often toxic and disabling effects of cancer treatments (Silver and Baima, 2013). Cancer prehabilitation may involve unimodal or multimodal approaches including exercise, nutritional, and psychological strategies. Exercise therapy as a component of prehabilitation is an area where physiotherapists can play a key role. Prehabilitation involves physical assessments that establish a baseline functional level,

identifies impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments (Silver and Baima, 2013).

Rehabilitation involves preventing and addressing the late and long-term effects of cancer and its treatment. It aims to restore patient's physical functioning, independence and QOL; some or all of which may have been affected throughout the treatment trajectory. In cancer survivors, a healthy diet and regular participation in moderate-vigorous intensity activity is associated with a higher quality of life, prolonged survival and diminished treatment side effects (Lynch et al., 2013, Mosher et al., 2009). Therefore there is huge potential for exercise and diet interventions post treatment to improve the overall health and well being of cancer survivors.

Prehabilitation and rehabilitation programmes in an oncology population are areas which are still very much in development. As cancer survivors are a heterogeneous group with respect to medical as well as socio-demographic factors, their complex prehabilitation and rehabilitation needs can vary considerably. Therefore in order to design evidence based and targeted interventional programmes it is first necessary to measure the physical functioning and investigate the specific needs of each individual cancer group.

1.5 Preliminary work

An initial aim of this PhD was to carry out a randomised control trial to examine if an exercise intervention preoperatively could influence postoperative outcomes in patients post oesophagectomy. This proposal was developed following previous work in this department which demonstrated that those who developed post-operative pulmonary complications following oesophagectomy had lower pre-operative physical activity levels than those who did not develop complications (Feeney et al., 2011). This lead to the suggestion that increasing physical fitness and activity preoperatively could potentially lead to a decrease in postoperative complications, a shorter hospital stay and improved patient outcomes. The theoretical basis for this effect is that higher levels of fitness would increase the patient's ability to withstand the demands of surgery.

1.5.1 Study design

This was a prospective single blind RCT. The study design consisted of a preoperative exercise intervention during which the participants in the intervention group performed a graded walking programme in the time period from the beginning of neoadjuvant therapy to surgery. The inclusion criteria were: (1) >18 years of age and (2) undergoing multimodal treatment (neoadjuvant therapy and surgery) for oesophageal cancer with a curative intent. Exclusion criteria included: (1) a neurological or musculoskeletal condition limiting independent mobility (2) medically unsuitable to participate in an exercise intervention or (3) contraindications to exercise testing as per the American College of Sports Medicine guidelines (Pescatello, 2013).

1.5.2 Study procedure

Eligible participants were identified at multidisciplinary team meetings and upper gastrointestinal surgical clinics at St. James's Hospital. These patients were informed of the study at clinics by either the surgical team or nurse specialist. If the participant was agreeable, the study investigator then met or telephoned him/her to further explain the study and establish his/her interest in participation. When participants agreed to take part, an appointment was made for the initial assessment. On entry to the study each participant was randomly assigned to either the control or intervention group using computer generated random numbers. Randomisation was stratified according to gender. Participants who were assigned to the intervention group completed the exercise intervention. Participants who were assigned to the control group received usual care.

The study assessments were performed by the lead investigator (JG) who was blind to the group allocation and the exercise intervention was supervised by an independent physiotherapist. Baseline measures were performed on entry to the study. Follow up measurements were performed the day before surgery, one month post surgery and three months post surgery. Body composition was measured using the Tanita MC 180 machine. Exercise tolerance was measured using the Incremental Shuttle Walking Test. Physical activity levels were measured objectively using the RT3 accelerometer (Stayhealthy Inc, Monrovia, CA). A portable micro medical spirometer (Micro Medical Ltd., Rochester, Kent, U.K.) was used to measure pulmonary function. Quality of life was measured using the EORTC QLQ-C30. The incidence of postoperative pulmonary complications was recorded, as defined by Benzo et al., (2011): pneumonia (new infiltrate + either fever (>38.5°C) and white cell count >11,000 or

fever and purulent secretions), severe atelectasis (requiring bronchoscopy), prolonged chest tubes (>seven days), and prolonged mechanical ventilation (>24h). Length of hospital stay was also recorded.

1.5.3 Exercise intervention

The exercise intervention was completed in the time period from commencement of neoadjuvant treatment to the time of surgery. Participants were counselled to complete 40 minutes of walking per day either in one session or in two sessions of 20 minutes. Where participants were found to engage in less than 10 minutes of physical activity per day during the initial assessment, the exercise target commenced at 20 minutes and increased weekly by 10 minutes up to 40 minutes. The target zone of the walking programme was that of a moderate intensity (40-59% of heart rate reserve or a rating of perceived exertion of 4). Each participant was provided with a polar heart rate monitor to wear while performing the exercise intervention. This was to demonstrate to the participant the intensity of the exercise they were engaging in at home. Participants were instructed on the use of the polar heart rate monitor and the heart rate target zone to work within.

Participants were required to attend once weekly throughout the study intervention. During the weekly attendance they performed 40 minutes of walking on the treadmill and had an opportunity to discuss with the physiotherapist any issues with completing the walking programme at home. In addition these participants were contacted by the physiotherapist on a separate day each week to monitor progress and promote adherence. Participants in the control group received usual care and were advised by the physiotherapist to maintain regular physical activity levels during their neoadjuvant therapy. In addition, the participants in both the intervention and control group were asked to keep an activity diary over the intervention period. This diary was subdivided into days and hours and a record of the type of activity performed was documented.

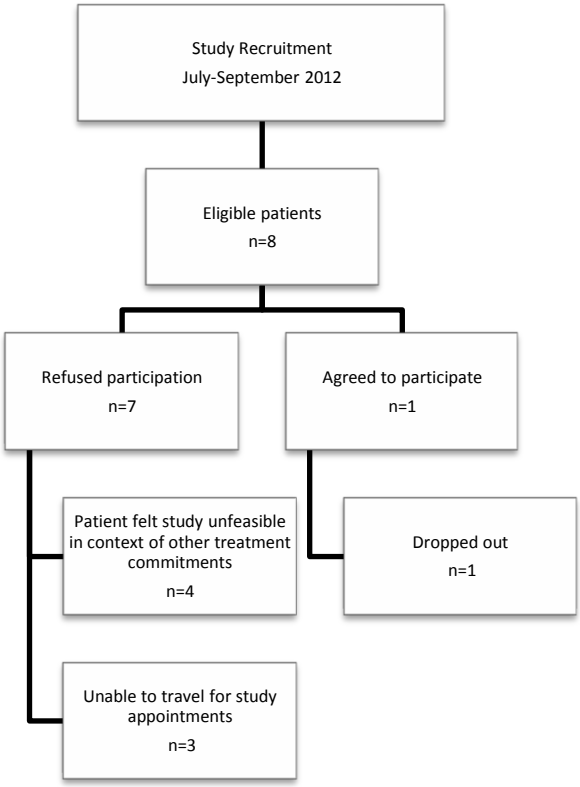

Figure 1.11 Recruitment details for preliminary work

1.5.4 Recruitment strategies

Recruitment for the RCT took place at weekly clinics from July 2012 to September 2012. Recruitment for this study was poor in the initial weeks of the trial. Accordingly some amendments were made to the recruitment strategy with the aim of improving recruitment rates. This consisted of increased weekly communication between the research and clinical staff to ensure all members of the multidisciplinary team present knew the specific criteria for potential participants for the study. In addition, a patient list was introduced which identified each patient that needed to be informed about ongoing research and potentially meet research staff. Both clinical and research staff at the clinic had a copy of the list and aimed to ensure that each patient met each professional marked on the list before leaving the clinic.

Despite the changes made to the recruitment strategy, during the recruitment period only eight potential participants were identified as suitable and were informed of the study. The study was explained to these eligible patients at clinic and patients were followed up with phone calls to determine interest. Seven of the patients declined to take part in the study

(Figure 1.11). One patient was interested in participation and was recruited into the study. This participant completed an initial assessment and was assigned to the intervention group, however subsequently dropped out as he felt unable to continue the exercise intervention while undergoing chemotherapy.

The reasons for both refusal to participate and for study drop out indicated that the study appeared unacceptable to potential participants. This may have been due to the need to commit to a daily exercise intervention soon after receiving a complex cancer diagnosis and commencing treatment. In addition to the daily home based walking programme, the exercise intervention consisted of a weekly session with the physiotherapist in St. James's Hospital. All potential or included participants either felt unable to commit to the exercise intervention while undergoing treatment or felt that they would be unable to attend the weekly sessions as they lived outside Dublin and would have to travel long distances for the study appointment.

The poor recruitment rates in addition to the issues with maintenance of participation highlighted that this study design appeared unfeasible in its current format and the study was postponed while other projects in this PhD were commenced. This preliminary work highlighted the potential difficulties in setting up prehabilitation programmes in this limited complex cohort and indicated that preoperative exercise interventions of this nature may need to be revised prior to the successful completion of an RCT. For example interventions may need to be more flexible or less intensive in terms of participant commitment and include an alternative home based exercise intervention option for those living a distance from the primary research site. In addition a multi-site study may be a useful opportunity to increase recruitment potential.

As a result of this preliminary work the focus of this PhD shifted from an interventional study to a comprehensive investigation of patient functioning and needs throughout the oesophageal cancer continuum. This work aimed to gain a greater understanding of the physical functioning of patients with oesophageal cancer, in particular in relation to the physical impact of treatment. The data generated was used in the design and implementation of evidence based and specifically targeted intervention programmes in this group. This may lead to improved recruitment and maintenance rates in this population in future interventional studies.

1.6 Thesis aims and objectives

Historically the aggressive nature of oesophageal cancer meant that outcome was assessed solely through mortality and disease free survival rates. However recent advances in treatment and the resultant improvements in survival have allowed HRQOL to emerge as an outcome of importance in this cohort. The systematic review in Section 1.3 revealed the adverse effect treatment for oesophageal cancer can have on physical functioning. This effect has primarily been subjectively reported and there is a lack of objective measures of physical performance outcomes in this cohort, particularly into longer term survivorship. Objective data on body composition, strength, fitness and physical activity levels in this group will establish the physical functioning of this cohort throughout the cancer trajectory and identify any physical deficits or rehabilitative needs.

While there is some subjective and objective quantitative data on the physical functioning of patients with oesophageal cancer, there is a lack of research approaching the same area from a qualitative perspective. When planning interventions to optimise outcomes in this cohort it is important to gain an understanding of the patients' subjective experiences and investigate their perceptions of the impact of treatment on physical functioning. Therefore in order to gain an in-depth and contextualised understanding of the physical functioning of patients with oesophageal cancer, both quantitative and qualitative research methods were used in this thesis.

The overall aim of this thesis was to examine physical functioning and rehabilitative needs throughout the treatment trajectory and into survivorship in patients with oesophageal cancer. The overall aim of each individual study is presented in Figure 1.12.

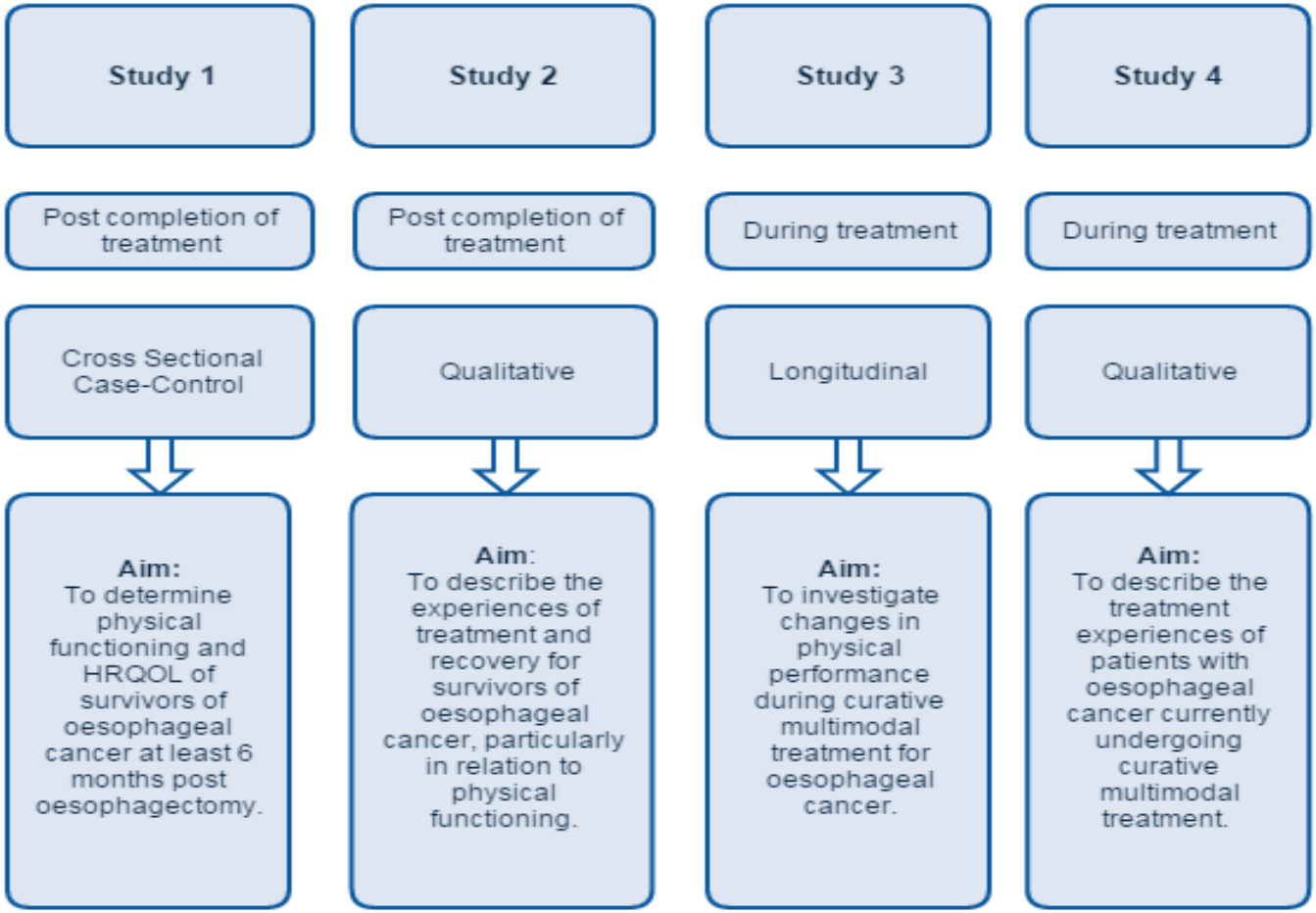

Figure 1.12 Study types and overall aims

Chapter 2 Quantitative Methods

2.1 Introduction

This chapter will describe study designs, sampling methods, data analysis and background to the quantitative assessments used in this thesis. Some of the assessments are common to both quantitative studies (Study 1 and Study 3) included in this thesis and subsequent chapters will refer back to the relevant sections when describing individual study methods. Qualitative methods will be discussed in Chapter 3.

2.2 Background research methods

2.2.1 Study designs

There are a number of methods available for carrying out investigative or experimental research. The type of study design that is employed depends on the specific research question being asked. Broadly, studies can be either experimental or observational. Observational studies are further categorised into those with and without a comparison group. If the study has a comparison or control group it is termed analytical. If there is no comparison group, it is a descriptive study (Grimes and Schulz, 2002). Generally observational studies describe a certain population but do not try to quantify a relationship or measure interventions or exposures. Examples of analytical studies include, cohort studies and case control studies. Examples of descriptive studies include case series and case reports. Cross sectional studies can be either analytical or descriptive. Experimental studies include randomised and non randomised controlled trials. In this thesis, quantitative work takes the form of analytical study design.

In a cross-sectional study, a sample of individuals is selected from a previously defined population and contacted at a particular point in time to obtain simultaneously information on both the exposure and outcome of interest. Cross-sectional studies are primarily used to determine prevalence of a disease or condition, however they are also used to describe characteristics of a particular group at a particular time. In case-control studies people with the outcome of interest are matched with and compared to a control group who do not. The most

common use of case-control studies is to retrospectively compare cases and controls to assess whether there were any differences in their past exposure to presumed risk factors. Case-control studies are also used to measure matched groups at one point in time and compare one or more outcomes of interest. A case report or case series study usually describes a new mechanism, or a new aetiological or therapeutic observation in one or a few patients (Stel et al., 2007). Cohort studies are observational studies which establish links between risk factors and health outcomes. These studies may be prospective or retrospective and sometimes two cohorts are compared. A group with the exposure of interest and a group without the exposure are identified at the outset of the study. The exposed and unexposed groups are then followed up over time to observe whether or not they develop the outcome of interest. This type of observational study is the one that most closely resembles intervention studies; as exposure is identified at the outset, it can be assumed that it preceded the outcome (Grimes and Schulz, 2002). However a drawback of cohort studies is that allocation of subjects to the exposure is not controlled by the investigator.

The major limitation of observational studies is the inability to control for confounding variables. There is always a risk that observed effects may be due, not to the condition under study, but to other factors, which are unknown to those carrying out the work. A confounding variable is independently associated with both the variable of interest and the outcome of interest and may provide an explanation for the result (Mann, 2003). The list of potential confounders is virtually infinite, however common examples include; age, socio-economic background, health status, smoking and alcohol habits. Another limitation of observational studies is that temporal associations between supposed causes and effects might be unclear. While case control and cohort studies have some potential to make causal inferences, case reports and cross sectional studies which do not have a comparison group do not allow assessment of associations (Jager et al., 2007). Despite their limitations, descriptive studies have several important roles in medical research and are very useful as early descriptors in under researched populations. Furthermore through documenting the health of certain populations, observational studies can help researchers develop hypotheses about cause which often prompts more rigorous studies.

In an experimental study, investigators study the impact of varying some factor which they can control, on the outcome of interest. Experimental studies allow the most control over the conditions under which the data are collected. The randomised control trial (RCT) is considered the gold standard of experimental research. An RCT is a particular type of cohort study where participants are randomly assigned to the experimental group (with exposure) and control

group (without exposure) (Stel et al., 2007). Although RCTs are the gold standard, this study design does have some drawbacks depending on the research question and how the studies are conducted. RCTs can have poor external validity. Often RCTs employ strict inclusion and exclusion criteria which limits the extent to which results can be generalised to a broader population (Grimes and Schulz, 2002). Furthermore RCTs can be prohibitively expensive, unethical, inadequate or unnecessary (Grimes and Schulz, 2002). For example, it may be considered unethical to compare well-accepted best practice with a treatment with an unknown or probably less favourable outcome or it may be considered unnecessary to carry out an RCT where the effects of health interventions are dramatic and observational studies are sufficiently adequate to demonstrate the effectiveness of an intervention (Jager et al., 2007).

2.2.2 Sampling

In quantitative research it is important that sampling methods and sample size are adequate to ensure that statistical results can be detected and that the findings have external validity, i.e. are generalisable to the population of interest. Unless a condition is particularly rare, testing all patients with a particular condition is usually very expensive or impossible. Therefore it is necessary to find some way of reducing the number of subjects in the study without biasing the findings. Random or probability sampling is one way of doing this. With probability sampling, a random sample is selected from a target population, referred to as the sampling frame. In a random sample every individual in the population must have an equal probability of being selected (Fox, 2007). Random sampling techniques include simple random sampling, systematic sampling and stratified sampling.

Simple random sampling is the simplest form of random sampling, where a table of random numbers, a computer random number generator, or a mechanical device is used to select the sample. With systematic sampling, numbers are allocated to everybody in the population frame, the first individual is picked using a random number table and then subsequent subjects are selected using a fixed sampling interval, e.g. every 10th person (Fox, 2007). For this method to be effective it is essential that the units in the population are randomly ordered, at least with respect to the characteristics that are being measured. Stratified random sampling involves dividing the population into homogenous subgroups and then taking a simple random sample in each subgroup. Stratified sampling is a way of ensuring that particular strata or categories of individuals are represented in the sampling process.

When probability sampling is not possible, non-probability sampling techniques can be used. Unlike probability sampling, non-probability sampling does not involve random selection. While non-probability sampling may be representative of the sampling frame, it cannot depend on the rationale of the probability theory and therefore these studies have an inherent bias. Common non-probability sampling methods include; convenience sampling, quota sampling, purposive sampling and self selection sampling. A convenience sample is simply one where the units that are selected for inclusion in the sample are the easiest to access. In quota sampling people are selected non randomly according to some fixed quota. For example if the target population has 40% men and 60% women, sampling will continue until these percentages are achieved. In purposive sampling, one or more specific predefined groups are sought. Self selection sampling occurs when participants choose to take part in research of their own accord. Non-probability sampling can be particularly useful in exploratory research where the aim is to find out if a problem or issue even exists in a quick and inexpensive way. In this thesis, non probability sampling was used as this was deemed the most feasible for exploratory research in a limited clinical population.

A key consideration when planning a study is to decide how many observations are required. Too many observations may lead to a waste of resources while too few will reduce the power of the study, making it impossible to detect true significant results (Suresh and Chandrashekara, 2012). The determination of sample size involves balancing the risk of failing to detect important differences when they are present, with the risk of falsely concluding that effects are present when, in fact, they are not. Larger sample sizes will tend to reduce the influence of chance variation, but this often comes at a greater expense.

When calculating sample size a number of factors need to be considered and defined as outlined below:

- It must be specified whether a one or two sided statistical test will be used.
- To provide an estimate of the magnitude of the chance variation, the standard deviation (σ) is obtained from previous studies or a pilot study. The larger the standard deviation, the larger the sample size required for the study.
- The level of significance (α) must be defined. This is the probability of a type I error occurring i.e. detecting a significant difference when there is none present. The conventional values used for α are 0.05 and 0.01.
- The minimal difference that would be considered important to detect must be specified (δ).

- The power of the study (β) must be specified. This is the risk of failing to detect a difference between groups if it does exist (type II error). The ideal power for any study is considered to be 80% or higher (Suresh and Chandrashekara, 2012).

2.2.3 Reliability and validity

2.2.3.1 Reliability

Reliability is the ability of a test to yield stable and consistent results across trials over time. Each observed score on an outcome measurement is the composite of the true score and of random error. Reliability refers to the degree to which an outcome measurement is free of random (McDowell, 2006). Random errors may occur during any part of the measuring process and may be a product of inaccuracy, fatigue or inattention.

Reliability can be described as relative and absolute. Relative reliability is the extent to which individuals maintain their position in a sample over repeated measurements (Bruton, 2000). Relative reliability is measured through intra-rater reliability, inter-rater reliability and internal consistency (Stokes, 2011). Intra-rater reliability indicates the agreement between two points in time and inter-rater reliability indicates the agreement between raters. Internal consistency is a measure of the homogeneity of the instrument as it assesses the relationship between items and their relationship with the overall score. Reliability can be quantified by calculating the level of agreement between two sets of data. For continuous data, the level of agreement can be measured using inter-class correlation coefficients. Inter-class correlation coefficients measure percentage agreement between and within raters and are usually presented with kappa co-efficients (K) or weighted kappa co-efficients (kw). The K accounts for agreement that could only exist between raters by chance, while the Kw allows for partial agreement between raters. There are numerous versions of inter-class correlation coefficients with each form being appropriate to specific situations. The most common statistical expression of internal consistency is Cronbach's alpha (Stokes, 2011) which is calculated from pairwise correlations between items, to compare individual items to the overall score.

Absolute reliability is the degree to which repeated measurements vary for individuals and is expressed in terms of the actual unit of the original measurement as the standard error of the measurement. The standard error of measurement can be used to calculate the minimal detectable change (MDC) of an outcome measure. The MDC is the minimal amount of change in the score of an instrument that must occur to be sure that the change in score is not simply

attributable to measurement error (Stokes, 2011). Other methods of measuring reliability include coefficient of variation, repeatability coefficient and Bland and Altman 95% limits of agreement (Bruton, 2000). The Bland and Altman method plots the mean of two sets of scores against the differences of the two sets of scores and can measure whether error changes over the range of the scale (Stokes, 2011).

2.2.3.2 Validity

Validity refers to the extent that an instrument or tool measures what it intends to measure (Finch, 2002). There are numerous domains of validity which can be assessed including face, content, criterion and construct validity. Validity encompasses the entire experimental concept and establishes whether the results obtained meet all of the requirements of the scientific research method.

Face validity examines whether on the surface of the outcome measure, it measures what it intends to measure (Stokes, 2011). An instrument with good face validity will likely be more acceptable to users. Content validity is the extent to which the elements within a measurement procedure are relevant and representative of the construct that they will be used to measure (Haynes, 1995). Face and content validity are often defined by consensus based on expert opinion. Criterion validity considers the performance or accuracy of a measure by comparing it to a gold standard. The gold standard may often be a more expensive, inaccessible or time consuming measure. Criterion validity includes a timing component and can be either concurrent or predictive. Concurrent validity assesses how the measure compares to the gold standard at a given point in time, while predictive validity refers to the relationship with a future assessment (Stokes, 2011). Construct validity can be described as the experimental demonstration that a test is measuring the construct that it claims to be measuring. It is an overarching term which incorporates all other forms of validity (i.e., content validity, convergent and divergent validity, and criterion validity) and is therefore evaluated in terms of each individual component. Aspects of criterion and construct validity are measured using validity coefficients such as Pearson-product moment correlation, Spearman's rank order correlation, Kendall's rank order correlation or the phi coefficient. Construct validity can also be analysed using factor analysis. For example, factor analysis can be used to determine that scales measuring similar constructs demonstrate an association and scales measuring different constructs do not demonstrate an association (Stokes, 2011).

Test reliability affects test validity. Tests with poor reliability also have poor validity because

unreliable tests fail to produce consistent scores. It is possible however for a test to have excellent reliability but poor validity. Even when a test yields stable and precise values across trials or between days, it may not validly measure a specific outcome (Heyward, 2010).

2.2.4 Principles of data analysis

Preliminary data analysis involves descriptive statistics and assessing data distributions for normality. The basic features of the data in a study are described using descriptive statistics which provide simple summaries about the sample and the measures. Descriptive statistics for categorical variables state the frequency of the observation within the data set and the relative percentage of that frequency within the dataset (Carter, 2011). Continuous variables are described by a measure of central tendency (mean, median, or mode) and a measure of variation about the mean (standard deviation or inter-quartile range). Graphically, categorical variables are depicted using pie charts and bar charts, while continuous data are represented using histograms or boxplots.

Data normality is an underlying assumption in parametric testing and is illustrated by a normal curve which is symmetrical about the mean. An assessment of the normality of data is a prerequisite for many statistical tests. Normality can be determined through the visual interpretation of descriptive data including normality Q-Q plots and histograms. Normality can also be assessed using numerical methods such as the Shapiro-Wilk test. The Shapiro-Wilk test assesses if data is normally distributed for each independent variable and is recommended in relatively small sample sizes (<50 participants). The statistical result of the test indicates whether the data is normally ($p > 0.05$) or not normally distributed ($p < 0.05$). If data is found to be non-normally distributed, log transformations can be applied to achieve log-normality or non parametric tests can be used. Normally distributed data is described as mean (standard deviation) and non-normally distributed data is described as median (inter-quartile range).

A statistical significance test asks if an observed result differs from some hypothesised value by more than would be expected from purely chance variation. With each statistical test, it is necessary to specify the hypothesis to be tested and the alternative that will be decided upon if this is rejected. The hypothesis to be tested is called the null hypothesis and is labelled H0, the alternative hypothesis is labelled H1. H0 is assumed to be true unless the measurement data clearly demonstrate otherwise. If H0 is rejected, the result is declared to be 'statistically significant' i.e. that a systematic difference from the hypothesised value exists. However statistical significance does not necessarily equate to a clinically meaningful difference and this

must be also considered with each statistical test result. A test statistic is considered to be exceptional if it has only a small chance of occurring if the null hypothesis is true (Mullins, 2003). The probability chosen to define an exceptional outcome is called the 'significance level' of the test and is labelled alpha (α). Alpha is most frequently defined as 0.05. Whether the result of a test is deemed statistically significant is commonly reported using p-values. The p-value is the probability of obtaining a more extreme result than the one observed in a repeat of the study, when that null hypothesis is true. When a test has a significance value of $\alpha = 0.05$, a p-value less than 0.05 means that the null hypothesis should be rejected and the result is deemed to be statistically significant. If the p-value is greater than 0.05, the null hypothesis is generally accepted. The p-value provides a measure of the strength of the evidence against the null hypothesis and therefore is a useful and meaningful statistical result to report. When a result is declared to be statistically significant it is useful to put error bounds around the mean difference observed. These error bounds allow for chance variation and provide an interval of numbers containing the most plausible values for the population parameter. The probability that this procedure produces an interval that contains the actual true parameter value is known as the confidence level and is generally chosen to be 0.9, 0.95 or 0.99.

To assess difference in continuous variables between groups a number of statistical tests can be used including independent-samples t-test, paired samples t-test and analysis of variance (ANOVA) (Bland, 2000). Non-parametric equivalents of these tests include the Mann Whitney U test, the Wilcoxon signed-rank test and the Freidman test. Independent samples t-tests are used when sets of data are obtained from two separate groups and there is no special relationship between the individual values from the two groups. In a paired sample t-test, two separate measurements are taken on the same group and different time points. ANOVA is used to compare measures taken from two or more groups at two or more time points. A number of assumptions underlie each statistical test and these must be considered before the test is run. Assumptions relate to the study design, the measurements taken and the characteristics of the data collected. For example, the statistical model underlying an independent samples t-test requires that there is one dependent variable, one independent variable, the data values are independent of each other, are approximately normally distributed for each group of the independent variable and demonstrate homogeneity of variance. The statistical model underlying ANOVA is identical to that of an independent samples t test; the only difference is that the number of groups involved is typically greater than two. Homogeneity of variance within ANOVA is known as the assumption of sphericity. In this thesis, the primary statistical tests used were independent t-tests and ANOVA.

Use of multiple statistical tests simultaneously can lead to much higher type 1 error rates. Methods for dealing with multiple testing involve adjusting α in some way, so that the probability of observing at least one significant result due to chance remains below the desired significance level. The simplest and most conservative approach is the Bonferroni correction, which sets the significance cut-off at α/n. For example, with 20 tests and α = 0.05, the null hypothesis would only be rejected if the p-value was less than 0.0025.

2.3 Measurement of physical functioning

Physical functioning can be objectively assessed using measures of exercise capacity, strength, and physical activity. The following section will discuss these three measures which are used in Study 1 and Study 3 in this thesis. Subsequent sections will discuss the measurement of body composition and quality of life which were also assessed in Study 1.

2.3.1 Exercise capacity

Physical fitness is defined as 'a set of attributes that people have or achieve that relates to the ability to perform physical activity' (Caspersen et al., 1985). The components of physical fitness can be categorised into two groups: health-related physical fitness and skill-related physical fitness. The health related components of physical fitness encompass cardiorespiratory endurance, muscular strength, muscular endurance, body composition and flexibility. The focus of the following section will be on cardiorespiratory endurance or exercise capacity. The measurement of muscular strength and body composition are discussed in Section 2.3.2 and Section 2.4 respectively.

Exercise capacity is related to the ability to perform large muscle, dynamic, moderate-to-vigorous intensity exercise for prolonged periods of time. Performance of exercise at this level of physical exertion depends on the integrated physiologic and functional state of the respiratory, cardiovascular and musculoskeletal systems (Pescatello, 2013). Poor exercise capacity or fitness levels are associated with an increased risk of premature death from all causes and specifically from cardiovascular disease (Blair et al., 1989). Higher fitness levels are associated with higher levels of habitual physical activity which in turn are associated with many health benefits, as outlined in Section 2.3.3. Therefore exercise capacity is an important outcome to assess in any clinical population.

Exercise capacity is highly important across the cancer continuum. A recent study was the first to demonstrate that higher levels of cardiorespiratory fitness are associated with a reduced risk of lung and colorectal cancer in men (Lakoski et al., 2015). Furthermore, this study found that higher fitness was associated with a significant reduction in risk of death from cancer or cardiovascular disease following a cancer diagnosis. Higher fitness levels are also associated with improved outcomes after surgery. Both a lower anaerobic threshold and a lower distance achieved on the incremental shuttle walk test have been associated with an increased rate of post-operative morbidity and mortality following oesophagogastric cancer surgery (Moyes et al., 2013, Murray et al., 2007).

2.3.1.1 Measurement of exercise capacity

Cardiorespiratory endurance is related to 'the ability of the circulatory and respiratory systems to supply fuel during sustained physical activity and eliminate products after supplying fuel' (Caspersen et al., 1985). The objective assessment of cardiorespiratory endurance is an important recognised outcome in various clinical and research settings. Formal exercise testing is widely used and gives comprehensive information to aid diagnosis, prognosis and decision making (American Thoracic Society/American College of Chest Physicians, 2003). Cardiorespiratory endurance or functional aerobic capacity can be measured in the laboratory or in the field depending on the equipment available, the patient population, and the experience of the tester.

The gold standard criterion for assessing aerobic capacity is by measuring maximal oxygen consumption (VO_{2max}) or the rate of oxygen utilisation of the muscles during aerobic exercise (Shephard et al., 1968). VO_{2max} is measured using a cardiopulmonary exercise test (CPET) where respiratory gas analysis is performed during graded exercise to exhaustion. Disadvantages of maximal exercise testing are that it may be unpleasant for participants; it requires experienced personnel, specialised equipment and medical supervision; and is expensive. Consequently maximal exercise tests are not always feasible and submaximal exercise tests are often used as an alternative. The major categories of submaximal tests are predictive and performance tests. Predictive tests are submaximal tests that predict maximal aerobic capacity on the basis of workload achieved at a predetermined sub-maximal heart rate or rating of perceived exertion (Jones et al., 2008a). Performance tests involve measuring the responses to standardised physical activities that are typically encountered in everyday life (Noonan and Dean, 2000). Research has shown moderate to high correlations between

submaximal and maximal exercise capacity and therefore submaximal testing is a useful substitute to maximal exercise testing (May et al., 2010, Cahalin et al., 1996, Riley et al., 1992, Win et al., 2006). In clinical cohorts, submaximal exercise testing is used more commonly than maximal testing, as it is easily administrated, less likely to cause adverse events and does not require medical supervision.

Field walking tests are commonly used predictive submaximal tests where the distance covered during the tests correlate with measures of peak oxygen consumption or VO_{2max}. Field walking tests have been shown to be strong, independent predictors of morbidity and mortality for various disorders (Celli et al., 2004, Lederer et al., 2006, Cahalin et al., 1996). In this thesis, field tests were used to measure exercise capacity. For the reasons outlined above, field tests were deemed the most feasible, safe and appropriate for this clinical population. Two field tests were used in this thesis, the incremental shuttle walk test in Study 1 and the six minute walk test in Study 3. Both tests are described below in Section 2.3.1.2 and Section 2.3.1.4.

2.3.1.2 The Incremental Shuttle Walk Test

The Incremental Shuttle Walk Test (ISWT) is an externally paced, incremental walking test, where the distance achieved is an indication of an individual's fitness level (Singh et al., 1992). The ISWT was originally developed for patients with chronic obstructive pulmonary disease and is considered a valid and reliable test to assess maximal exercise capacity in this population (Parreira et al., 2014). The ISWT has also been used to assess exercise capacity in conditions such as cardiac disease, peripheral artery disease, obesity, pulmonary hypertension, intermittent claudication, bronchiectasis and in people with critical illness. The ISWT has been validated in patients with lung cancer and in surgical populations where the distance covered correlates well with peak oxygen consumption to provide an indication of aerobic fitness (Win et al., 2006, Struthers et al., 2008). It has been shown to be a sensitive indicator of operative risk in oesophageal cancer patients undergoing surgery (Murray et al., 2007). Benefits of this test are that it is standardised, incremental and externally paced which minimises the effect of patient motivation and the influence of the tester. Predictive equations for the distance in the ISWT are available for healthy adults (Probst et al., 2012, Jurgensen et al., 2011). In 2013, age-specific normal values were established for a healthy British population aged 40-90 years (Harrison et al., 2013). Predicted maximal exercise capacity (VO_2 max) can be calculated from the following equation; VO_2 max = 4.19 + 0.025 (distance in metres) (Singh et al., 1994).

2.3.1.3 The ISWT measurement procedure

The ISWT was performed using methods established by Singh and colleagues (1992). Resting heart rate and blood pressure were measured and recorded prior to commencing the test. The formula 220-age was used to calculate the participants predicted maximal heart rate and subsequently 85% of this was calculated. Each participant was fitted with a polar heart rate monitor and this was worn for the duration of the test (Timex Personal Trainer). Standardised instructions were given on a CD. These instructions were repeated verbally to ensure they were understood and each participant knew what was expected during the test. Participants walked between two cones in time to a set of auditory beeps played on the CD. The participant kept pace with the auditory signal such that he/she completed a turn as each beep sounded. The two cones were placed 9 meters apart making the shuttle distance 10 metres long. Every minute the audio signal sounds at increasingly shorter intervals. There are 12 levels of speed beginning at 0.5m/s and ending at 2.37m/s. One beep indicates the length of one shuttle and three beeps indicates an increase in speed. No encouragement was provided during the test, however the following standard prompts were used; each time the there was a triple beep: "increase your speed now..." and if the participant was more than 0.5m away from the cone when the beep sounds: "You're not going fast enough; try to make up the speed this time". It was determined that the participant could no longer keep up with the beeps when they were more than a half metre from the cone when the beep sounded and they could not increase their pace sufficiently by the next beep. The end point of the test was reached when the participants reached 85% of his/her predicted maximal heart rate, was too breathless to continue, could no longer keep up with the beeps or chose to stop for any other reason. The number of shuttles (laps between the cones) was recorded. Each shuttle represents a distance of ten metres. The primary outcome was the distance covered calculated from the completed number of shuttles.

2.3.1.4 The Six Minute Walk Test

The Six Minute Walk Test (6MWT) is a performance-based measure of functional exercise capacity which measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The 6MWT was developed by Balke in 1963 as a means to evaluate functional capacity (Balke, 1963). Different variations of the timed walk have been tested, and the six minute timed walk was recommended given its reproducibility and ease of administration compared to timed tests of longer duration (Butland et al., 1982). The 6MWT was originally developed for patients

with pulmonary or cardiac disease; however the test has since been used as a performance-based measure of functional exercise capacity in other populations including healthy older adults, people undergoing knee or hip arthroplasty and in populations with various chronic diseases including heart failure, COPD, stroke and rheumatic conditions. In recent decades the 6MWT has been increasingly used in cancer research (Ligibel et al., 2012, Riesenberg and Lubbe, 2010, Temel et al., 2009). The distance walked in the 6MWT has been proposed as a prognostic factor for survival in patients with advanced lung cancer (Jones et al., 2012). Recently the 6MWT was found to be a valid and reliable measure of exercise capacity in a general cancer population and the use of this test was recommended for cancer patients (Schmidt et al., 2013).

2.3.1.5 The 6MWT measurement procedure

The 6MWT was performed according to the American Thoracic Society Guidelines (2002). Resting heart rate, blood pressure and oxygen saturation were measured and recorded prior to commencing the test. The participant was familiarised with the Modified Borg Dyspnoea Scale (Appendix IV). Each participant was fitted with a polar heart rate monitor and this was worn for the duration of the test. The test was performed indoors along a long, flat, straight, enclosed corridor. The walking course was 30 metres in length and the length of the corridor was marked every 3 metres. The turnaround points were marked with a cone.

The following instruction was given to each participant: *"The object of this test is to walk as far as possible for 6 minutes. 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 am going to show you. Please watch the way I turn without hesitation."* How to turn without hesitation was then demonstrated. *"Are you ready to do that? I am going 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."* The number of times the patient returned to the starting point on the course was recorded during the test. At the end of each minute the patient's heart rate from the polar heart rate monitor was recorded and the patient was asked to rate themselves on the BORG rate of perceived exertion scale. During the test the following standardised encouragement

were given in an even tone of voice;

Time remaining	Instruction to patient
5 minutes	*You are doing well. You have 5 minutes to go*
4 minutes	*Keep up the good work. You have 4 minutes to go*
3 minutes	*You are doing well. You are halfway done*
2 minutes	*Keep up the good work. You have only 2 minutes left*
1 minutes	*You are doing well. You have only 1 minute to go*
15 seconds	*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.* *Stop.*

If the participant stopped walking during the test and needed a rest the time was not stopped. The following instruction was given; *"You can lean against the wall if you would like; then continue walking whenever you feel able."* At the end of the test the total number of laps completed was counted and this was added to the additional distance covered (the number of metres in the final partial lap) to calculate the total distance walked. The primary outcome was the total distance covered in the six minutes. Predictive equations for the distance in the 6MWT are available for healthy adults (Casanova et al., 2011).

2.3.1.6 Safety considerations

Safety considerations which were common to both field tests are detailed in this section. Exclusion criteria for exercise testing included those with a neurological or musculoskeletal condition limiting independent mobility, those who were deemed medically unsuitable to complete an exercise test or those with known absolute contraindications to exercise testing and exercise training as per the American College of Sports Medicine guidelines (Pescatello, 2013). For cancer survivors, details related to their past medical history were documented in their medical records and in the database maintained in St. James's Hospital. Any further queries regarding participants past medical history was directed to the medical team. Control participants were asked to verbally report whether they had any respiratory, cardiac or metabolic disease or other relevant medical conditions.

Each participant filled out a Physical Activity Readiness Questionnaire (Appendix V) which was developed by the Canadian Society for Exercise Physiology to identify adults who may be at risk with commencing or increasing exercise (Adams, 1999). The PAR-Q collects information regarding the presence of a heart condition, chest pain, dizziness, bone or joint pain, use of anti-hypertensives or diuretics or any other known contraindications to exercise. Further details were required if the participant responded "yes" to any questions. Clinical reasoning was used to determine if the participant was suitable to complete the test. For example if the participant was taking antihypertensive medications, the test was completed provided resting blood pressure measurements taken on the morning of testing were within normal ranges. Before the exercise test, resting heart rate and blood pressure measurements were taken using an automatic blood pressure monitor (Omron 705IT). If resting blood pressure was consistently higher than 144/94 on the day of testing, the fitness test was not completed and the participant was advised to inform their G.P at their next appointment.

Termination criteria for the fitness tests were established and the test was to be immediately stopped if any following occurred:

- Any chest pain that was suspicious of angina
- Intolerable dyspnoea
- Evolving light headedness or dizziness
- Leg pain or fatigue to limit further exercise
- Evolving mental confusion or lack of coordination
- Diaphoresis
- Pale or ashen appearance
- Any other clinically warranted reason

After testing it was ensured that each participants reported feeling well and their heart rate had returned to resting values before the leaving the centre. The standard operating procedure for safety during exercise testing is included as Appendix VI.

2.3.2 Muscle strength

Muscular strength is defined as the ability of a muscle group to develop maximal contractile force against a resistance in a single contraction (Heyward, 2010). Strength is an important component of health related physical fitness and can be quantified through isometric, isotonic

and isokinetic measurements. Isometric contractions generate force without changing the length of the muscle. In contrast, isotonic contractions maintain constant tension in the muscle as the muscle changes length and therefore this is associated with the movement of a body part. Isotonic contractions can be either concentric or eccentric. In isokinetic muscle contraction, the muscle contracts maximally throughout its full range of movement. The defining characteristic of isokinetic muscle contractions is that they result in movements of a constant speed. The velocity of the contraction is controlled mechanically. Strength testing is useful for a number of reasons. It can be used to predict performance, to establish baseline measures before a training programme, to monitor progress during training, to identify muscle imbalance and as a measure of the overall effectiveness of resistance training or a rehabilitation programme. Minimal levels of muscle strength are needed to perform activities of daily living, to maintain functional independence throughout the ageing process and to partake in active leisure-time pursuits without undue stress or fatigue. Adequate levels of muscular strength decrease the chance of developing osteoporotic fractures, low back problems and musculoskeletal injuries. The measurement of muscle strength is an important outcome in a cancer population. Cachexia and sarcopenia are particularly prevalent in an oesophageal cancer population and these conditions are characterised by a loss of skeletal muscle mass. A loss of muscle mass can result in decreased muscle strength and consequently reduced functional capacity (Doherty, 2003, Evans and Campbell, 1993, Donohoe et al., 2011b).

2.3.2.1 Measurement of muscle strength

Isokinetic muscle testing is considered the gold standard measurement for muscle strength and therefore is frequently used as a reference standard to compare to other instruments of muscle strength. Isokinetic dynamometers are computerised machines capable of providing multiple elements of measuring muscle strength including peak force, endurance, power, angle of maximal force, and occurrence and they are capable of generating strength curves (Li et al., 2006). However disadvantages of isokinetic dynamometry are that it is expensive, bulky, time consuming, and requires training and skill to use. Therefore a more practical means of muscle strength measurement is required for repeated clinical testing in a variety of locations. Hand held dynamometry is a simple non-invasive measure which provides a quantified measurement of muscle strength. This method of strength testing is widely used across research and clinical settings as it is easy to use, relatively inexpensive and portable. Hand held dynamometry has demonstrated moderate to good reliability and validity when compared to

isokinetic testing and therefore is recommended as the practical standard for muscle strength assessment (Stark et al., 2011). For these reasons, hand held dynamometry was used as the measure of muscle strength in the studies included in this thesis.

2.3.2.2 Hand grip strength

Hand grip strength (HGS) is widely used as a means of predicting health outcomes, functional decline and loss of independence (Bohannon, 2001, Norman et al., 2011). Low HGS has been consistently associated with a greater likelihood of premature mortality, the development of disability and an increased risk of complications or prolonged length of stay after hospitalisation or surgery (Leong et al., 2015, Bohannon, 2008). HGS correlates well with overall upper and lower limb strength and is therefore a good surrogate of generalised muscle strength (Bohannon, 2012, Norman et al., 2010, Samson et al., 2000). In patients with advanced cancer, HGS has been shown to be independently associated with important biological, functional and quality of life characteristics (Kilgour et al., 2013). Furthermore HGS has been shown to be a significant predictor of increased post-operative complications and mortality after oesophagectomy (Chen et al., 2011).

In the studies included in this thesis, HGS was measured using a Jamar digital handgrip dynamometer (Figure 2.1). The Jamar dynamometer has been shown to be a valid and reliable measure of hand grip strength in a number of populations (Abizanda et al., 2012, Harkonen et al., 1993, Mathiowetz et al., 1984). More recently, hand held dynamometry has been validated in patients with advanced lung and gastrointestinal cancer (Trutschnigg et al., 2008). The Jamar hand dynamometer is the most widely cited instrument in the literature and is generally accepted as the gold standard by which other dynamometers are evaluated (Mathiowetz, 2002). The clinical utility of the Jamar dynamometer is enhanced by the wide availability of normative data which has been established in a number of populations including; healthy Caucasian adults (Gunther et al., 2008), British men and women (Spruit et al., 2013), healthy Swiss adults (Werle et al., 2009), American adults with or without chronic diseases (Yorke et al., 2015) and in an Irish adult population (Kenny et al., 2013). This normative data enables comparisons to be made between specific study cohorts and the general population.

2.3.2.3 HGS measurement procedure

The Jamar dynamometer is a small portable device which weighs approximately 600g. The

readout displays isometric grip force from 0-90 kg. The unit's display can be set to display pounds or kilograms. The Jamar is a variable hand span dynamometer with five handle positions. The second handle position is the most reliable and consistently used position in both clinical and research settings (Roberts et al., 2011). It has been shown that measurements taken at a single standard handle position are sufficiently accurate to assess grip strength for all participants and a single handle position reduces fatigue and increases the comparability of results between participants (Trampisch et al., 2012). Accordingly the dynamometer was maintained in the second handle position for all measurements included in this thesis.

Participants completed the HGS protocol as per the protocol recommended by the American Society of Hand Therapists (Fess, 1992). According to this protocol each participant was seated in a chair with both feet touching the ground. The shoulder was adducted and neutrally rotated with the elbow flexed at a 90° angle. The forearm was in a neutral position with the wrist in slight extension (0°-30°). The participant squeezed the dynamometer as hard as possible using one brief maximal contraction and no extraneous body movement. Three trials were administered for each hand, allowing a 1 minute rest between trials. The best score was used as a measure of the participant's static strength.

Figure 2.1 Jamar HGS dynamometer

2.3.3 Physical activity levels

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that requires energy expenditure (Caspersen et al., 1985). This includes activities undertaken while working, playing, carrying out household activities, travelling, and engaging in recreational

pursuits. Exercise is a subcategory of physical activity that is planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness. PA is the most variable component of an individual's total daily energy expenditure (EE), which in addition to voluntary PA is comprised of basal metabolic rate (BMR) and thermogenesis (Dishman et al., 2001). BMR is the amount of energy expended while at rest in a neutrally temperate environment, in the post-absorptive state. In many people BMR represents approximately 60-70% of total EE. The main determinants of BMR are age, gender, body weight, and body composition. Thermogenesis is the amount of energy utilised for digestion, absorption and transportation of nutrients. This accounts for about 10% of total energy intake associated with a mixed western diet.

Regular moderate and/or vigorous intensity physical activity is associated with significant health benefits including weight control, bone, muscle and joint health and psychological wellbeing. Furthermore regular physical activity reduces the risk of chronic diseases, such as coronary disease, type II diabetes, hypertension, stroke, cancer, osteoporosis and depression. Physical activity is highly relevant across the cancer continuum. It is well established that physical activity plays a role in the prevention of many cancers and is effective in decreasing treatment side effects, speeding recovery after a cancer diagnosis, and enhancing survival (Schmitz et al., 2010).

In 2011 the American College of Sports Medicine (ACSM) released an updated statement on physical activity guidelines to promote and maintain health and reduce the risk of chronic disease. Guidelines on physical activity encompass all dimensions of activity i.e. intensity, frequency, duration and mode. They recommend that adults engage in 30-60 minutes of moderate intensity exercise on ≥ five days a week or 20-60 minutes a day of vigorous exercise on ≥ three days a week or a combination of both (Garber et al., 2011). Exercise may be performed in one (continuous) session per day or in multiple sessions of 10 minutes to accumulate the desired duration and volume of exercise per day. For maximum health benefits it is recommended that moderate and vigorous intensity activity is built up in bouts of at least 10 minutes. In 2010, an ACSM roundtable consensus statement on exercise guidelines for cancer survivors was published (Schmitz et al., 2010). This provides recommendations to health care professionals regarding the implementation of physical activity programs for cancer survivors both during and after cancer treatment. The physical activity levels recommended for cancer survivors are identical to the general population with the addition of specific precautions which must be considered with individual cancer populations.

2.3.3.1 Measurement of physical activity

Physical activity is a complex set of behaviours, with possible measurements made of its duration, frequency, intensity, type or setting (Bauman et al., 2006). The high degree of variability in daily PA within and among people in free living populations makes the accurate assessment of PA very difficult. There are a large number of techniques for the assessment of PA, which include behavioural observation, questionnaires, and physiological markers such as heart rate, calorimetry, and motion sensors (Westerterp, 2009).

Calorimetry, in particular the doubly labelled water method, is the most precise measure of EE and is considered the gold standard for the validation of field methods of assessing PA (Melanson and Freedson, 1996). Doubly-labelled water is an isotope based technique of measuring total EE and BMR to calculate activity related EE (Westerterp, 2009). However, doubly-labelled water is a complex and costly technique and therefore is primarily used in small study populations only (Plasqui and Westerterp, 2007). Indirect calorimetry, which provides a measure of respiratory gas exchange (oxygen consumption) during exercise, can also be used to estimate EE as a result of PA (Rowlands et al., 2004).

Behavioural observation is one of the earliest methods to assess PA. An advantage of this measure over other measures of PA is that it also provides contextual information. Disadvantages are that the method is time consuming, the presence of the observer might interfere with the activity levels of the subject and the classification of observed activities, especially activity intensity, are subjective (Westerterp, 2009). Self reports are the most widely used measure of PA, particularly in epidemiological studies. The methodology is cheap and allows application in large populations. An activity diary can be very accurate about type, frequency and duration when maintained accurately and contemporaneously. A diary however, may have the effect of motivating people to be more active than usual during the time period being studied. A recall questionnaire avoids the problem of interference with usual activity but its accuracy varies according to the length of time being recalled and the complexity or regularity of habits. Questionnaires are most useful as a method of ranking activity in large scale epidemiological studies. Examples of commonly used PA questionnaires include the Minnesota Leisure Time Physical Activity Questionnaire, the Harvard Alumni/Paffenbarger Physical Activity Survey, the International Physical Activity Questionnaire and the Global Physical Activity Questionnaire. Despite their large scale application, the reliability and validity of these self report measures are low and they show poor correlations with doubly labelled water (Maddison et al., 2007, Rush et al., 2008). There is a tendency for people to either significantly under or over estimate their levels of PA (Maddison et al., 2007,

Celis-Morales et al., 2012, Mahabir et al., 2006).

Heart rate (HR) monitoring was one of the first objective methods for the assessment of PA. Heart rate monitors provide surrogate measures of EE and intensity and can also indicate time, which permits a measure of the frequency, duration and rate at which physical activities are carried out. However HR monitoring is an indirect measure and limitations of this method include the non-linearity of HR during sedentary and light activities and the fact that the rise in HR with activity depends on the aerobic fitness level of the individual. Furthermore stimuli other than exercise and activity such as caffeine or nicotine can also stimulate the heart to beat faster and this can lead to an overestimation of activity intensity.

Other objective measures of PA include motion sensors, which measure activity in one or more plane of movement. The simplest type of motion sensor is the pedometer, which counts the steps that a person takes, and is particularly useful for capturing walking behaviour. However, a limitation of the pedometer is that it does not record the intensity of the activity being undertaken. Accelerometers are more advanced motion sensors which provide a measure of both frequency and intensity of movement. Accelerometers are usually placed as close as possible to the body's centre of gravity or on the hip in the mid axillary line and can measure acceleration in one (uniaxial), two (biaxial) or three (triaxial) planes. Some disadvantages of accelerometers are that they can be expensive and are not suitable for aquatic activities or activities where there is minimal movement of the body's centre of gravity, such as cycling or rowing (Dishman et al., 2001).

The choice of PA measurement tool depends primarily on the research question, the accuracy required, feasibility and participant burden (Broderick et al., 2014c). Accelerometers are growing in popularity as the tool of choice to measure habitual PA in daily life (Westerterp, 2009). Accelerometers are objective, feasible and with minimal wearer burden can measure some or all of the following: EE, the number and length of activity bouts, breaks in sedentary time, adherence to activity guidelines and postural transitions. Therefore accelerometers have been recommended as one of the best measures of PA in cancer based studies (Broderick et al., 2014c).

Considering the advantages and disadvantages of each measure of PA as discussed in this section, accelerometers were chosen as the most appropriate method of measuring habitual PA levels for the studies in this thesis. Two acceleromerers were used in this thesis, the RT3 accelerometer in Study 1 and the ActiGraph accelerometer in Study 3. Following the commencement of Study 1, the accelerometry monitoring system available in the department

upgraded from the older RT3 to the Actigraph GT3X. The RT3 was used to completion of Study 1 and then PA monitoring changed to the Actigraph GT3X system. The RT3 and ActiGraph are described below in Section 2.3.3.2 and Section 2.3.3.3 respectively.

2.3.3.2 RT3 accelerometer

The RT3 accelerometer (Stayhealthy Inc, Monrovia, CA) assesses activity in three planes [vertical, anteroposterior and mediolateral]. The RT3 measures 7.1 x 5.6 x 2.8 cm, weighs 65.2 grams (Figure 2.2) and is generally placed at the hip. It can record up to 21 days in 1 minute epochs and provides activity counts and a measure of EE. The RT3 meter generates data every minute and is set to report on a composite three-dimensional signal called the vector magnitude. The vector magnitude indicates the intensity of PA. The RT3 accelerometer has been shown to be a valid (Rowlands et al., 2004) and reliable (Powell and Rowlands, 2004) measure of PA levels in healthy populations. Furthermore the RT3 has been validated in a range of other populations including children (Hussey et al., 2009), functionally impaired older adults (Sumukadas et al., 2008), overweight and obese women and adults with COPD (Van Remoortel et al., 2012) and neurological dysfunction (Hale et al., 2008).

Figure 2.2 RT3 accelerometer

2.3.3.3 ActiGraph accelerometer

The ActiGraph accelerometer (ActiGraph, Pensacola, FL) measures activity in three planes (vertical, anteroposterior and mediolateral). The ActiGraph wGT3X-BT measures 4.6 x 3.3 x 1.5 cm and weighs 19 grams (Figure 2.3). It has a battery life of up to 25 days with data storage of up to 120 days or 2GB. It can be worn on the wrist, waist, ankle or thigh. It provides measures of raw acceleration (G's), activity counts, EE, MET rates, steps taken, PA intensity, activity bouts, sedentary bouts and body position. Similarly to the RT3, the ActiGraph generates data every minute and is set to report on a composite three-dimensional signal called the vector magnitude. The ActiGraph accelerometer has been shown to be a valid (Kelly et al., 2013) and reliable (Santos-Lozano et al., 2012) measure of PA levels in healthy populations.

Figure 2.3 ActiGraph accelerometer

2.3.3.4 Physical activity measurement procedure

The basic measurement procedure was the same for both accelerometers. Each participant was provided with an accelerometer to wear during waking hours for seven days. Participants were asked not to change their activities over the monitoring period. It was explained that the aim was to get an idea of their 'normal' activity patterns. The RT3 monitor was worn clipped on to the band of trousers, a belt or a skirt. The ActiGraph monitor was provided to the participant with a belt which was worn around the hips. Participants were asked to place the monitor at their right hip. Participants were provided with instructions on monitor use and were asked to record the times they put on and took off the monitor each morning and night (Appendix VII). In addition participants were asked to record any other times during the day that they removed the activity monitor and when it was put back on. Reasons to remove the activity monitor included; going for a shower/bath, going for a swim or going for a sleep in bed

during the day. Each participant in Study 1 also filled out an activity diary detailing any specific exercise or PA undertaken over the monitoring period. A stamped addressed envelope was provided for participants to return the monitor and diaries to the study investigator after seven days.

2.3.3.5 Physical activity data analysis

Data from the RT3 accelerometer was downloaded via a docking station to a computer where it was converted to a Microsoft Excel file. All data analysis was completed in Microsoft Excel. Activity intensity was defined from previously validated cut points (Rowlands et al., 2004). Light intensity activity was defined as 100-984 counts per minute, moderate intensity activity was defined as 984-2340 counts per minute and vigorous intensity activity was defined as >2340 counts per minute. Sedentary behaviour was defined as ≤100 counts per minute (Healy et al., 2011). Periods of ≥60 minutes of consecutive zeros were deemed non-wear time and were removed during analysis. The ActiGraph accelerometer was connected via USB cable to a computer where it was uploaded to the ActiLife programme. All data analysis was completed using the ActiLife software. The data, collected at the pre-selected sample rate of 30Hz, was analysed in 60 second epochs. Wear time validity of the data was determined according to a set algorithm where ≥60 minutes of consecutive zeros were classified as non-wear time (Troiano et al., 2007). Activity intensity was defined using previously validated cut-points (Freedson et al., 1998). Sedentary activity was defined as 0-99 counts per minute, light intensity activity was defined as 100-759 counts per minute, moderate intensity activity was defined as 1952-5724 counts per minute and vigorous intensity activity was defined as 5725-9498 counts per minute.

For both the RT3 and the ActiGraph, the activity diary was analysed in conjunction with the accelerometer output and non-wearing time (bed, bath and shower time) was deleted. Missed days were identified and deleted. Days where the monitor had been worn for less than 10 hours were not included in the analysis (Troiano et al., 2007). The average time (number of minutes) per day spent sedentary and engaged in each intensity of activity was calculated (total minutes spent in activity intensity in the week ÷ number of days monitor was worn). Sedentary time, expressed as a percentage of overall wear time was also calculated. A secondary analysis of the data was conducted to assess for time spent in bouts of moderate and vigorous intensity activity. This was done to assess for adherence to physical activity guidelines (30 minutes moderate-to-vigorous intensity activity at least 5 days per week) which

stipulate that activity should be accumulated in bouts of at least 10 minutes duration (Garber et al., 2011, Schmitz et al., 2010). Both moderate and vigorous intensity minutes were treated equally within each bout. For the RT3 accelerometer, analysis was performed using the conditional formatting option function in Microsoft Excel. The file was examined manually for bouts of moderate-to-vigorous intensity activity lasting ≥ 10 minutes. Within each bout, one minute of light activity was permitted provided there was at least 5 minutes of moderate-to-vigorous activity both before and after it. For the ActiGraph accelerometer, the ActiLife software identified bouts of ≥ 10 minutes duration of moderate to vigorous activity as per the cutpoints established by Freedson et al., (1998). A 'drop out' or non-compliant time of 2 minutes was permitted per bout.

2.4 Body composition

Body composition is the body's relative amount of fat to fat-free mass. Measurements of body composition describe the percentages of fat, bone, water and muscle in human bodies. Several aspects of body composition, in particular the amount and distribution of body fat and the amount and composition of lean mass are important health outcomes (Wells and Fewtrell, 2006). The measurement of body composition is particularly important in a cancer population as many body composition features have been associated with cancer incidence, aetiology, and therapeutic outcomes (Parsons et al., 2012).

2.4.1 Measurement of body composition

In the clinical setting, anthropometric methods such as body weight, body mass index (BMI), circumferential measurements and skinfold thickness are commonly used. Bioelectrical impedance analysis (BIA) is also widely used clinically and has advantages over BMI in that it provides estimates of fat free mass and percentage body fat. Laboratory methods which can be used to measure body composition include dual-energy X- ray absorptiometry (DEXA), CT imaging analysis and magnetic resonance imaging (MRI). CT and MRI are considered very precise imaging systems that can separate fat from other soft tissues of the body, making these methods gold standards for estimating muscle mass in research (Cruz-Jentoft et al., 2010). In this thesis, body composition was measured primarily via anthropometric measures and BIA. These techniques are described in Section 2.4.2 and Section 2.4.4. In Study 1, body

composition was also retrospectively analysed in greater detail through the gathering of longitudinal body weight data and the assessment of the presence of sarcopenia during treatment using available abdominal CT-scans. The analysis of the CT scans to identify sarcopenia is described in Section 2.4.6.

2.4.2 Anthropometry

Anthropometry refers to the measurement of the size and proportion of the body using measures of body weight, height, circumferences and length. These measures are cheap and feasible to perform and are widely used as measures of body composition (van der Kooy and Seidell, 1993). BMI assesses body weight relative to height. It's a useful, indirect measure of body composition because it correlates with body fat in some people. It is a more accurate guide than body weight alone because it considers height as well as weight. However a limitation of BMI is that it does not distinguish between fat mass and muscle mass and therefore may misclassify well trained people with dense muscle mass but very little body fat as overweight or obese. Accordingly circumferential measures, skinfold thickness or more direct methods of measuring body fat are recommended for use in combination with BMI measures to identify those at increased risk for chronic disease. The measurement of waist circumference is a simple way to determine where fat is located in the body and is a very useful measure of the presence of abdominal obesity. Abdominal obesity is strongly associated with an increased risk of type II diabetes, cardiovascular disease and death, even after controlling for BMI (Ohlson et al., 1985, Larsson et al., 1984).

2.4.3 Anthropometry measurement procedures

Body weight

Body weight was measured, to the nearest 0.1kg on the digital scales of the Tanita MC 180 Multi-Frequency Body Composition Analyzer (described in Section 2.4.4). Participants were measured in one layer of light clothing. The machine deducts a predetermined weight, equivalent to one layer of light clothing, from the participants recorded weight.

Standing height

Standing height was measured using a portable SECA stadiometer. Participants were asked to stand, without shoes, on the footplate, with their back against the stadiometer, legs together,

arms down by their sides and mid-axillary line in parallel to the stadiometer. The head was positioned in the Frankfurt horizontal plane, the standard plane used for the correct orientation of the head, established by a line passing through the tragion (front of ear) and the lowest point of the eye socket. The headboard was lowered until it touched the crown of the head, compressing the hair. Measurements were taken to the nearest 0.1cm.

Body mass index

BMI was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). BMI is used to classify persons who are underweight (<18.5 $kg.m^{-2}$), normal weight (18.5-24.9 $kg.m^{-2}$), overweight (25-29.9 $kg.m^{-2}$) or obese (Class I: 30-4.5 $kg.m^{-2}$; Class II 35-39. $kg.m^{-2}$; Class III: ≥40) (WHO, 2000).

Waist circumference

Waist circumference was measured using a non-stretch flexible tape placed directly on the skin at the midpoint between the superior border of the iliac crest and the lowest rib, following normal expiration (WHO, 2011). The tape was checked to ensure it was positioned perpendicular to the long axis of the body and parallel to the floor. Measurements were taken in duplicate, to the nearest millimetre, and averaged for data entry. The waist circumference cut off points for an increased risk of metabolic complications are >94 cm in men and >80 cm in women. The cut off points for a substantially increased risk of metabolic complications are >102 cm in men and >88 cm in women.

2.4.4 Bioelectrical impedance analysis

BIA is a relatively simple, quick, portable and non invasive measure of body composition that is used in a wide variety of clinical and research settings (Jaffrin, 2009). A low, safe electrical signal (50Khz) is sent through the body via metal footpads and handgrips (where applicable) which are housed in a single stand-alone unit. BIA can be measured using a four-electrode method or an eight-electrode method. The four-electrode method of BIA works using four electrodes found in the footplate of the analyser. The results are based on the leg to leg measurement and equations are used to estimate the body fat content for the remainder of the body. This method provides complete body readings only. The eight-electrode method of BIA works using eight electrodes, four of which are found in the footplate of the analyser and four of which are found in the handgrips. As the electrical signal travels in more than one direction and flows through a greater section of the body this method allows for segmental

analysis of body composition and provides a more in-depth measurement than the four electrode method (Pietrobelli et al., 2004). Impedance is measured in Ohms and can be defined as the strength and speed of an electrical signal travelling through the body. BIA is based on the fact that lean tissue, such as muscle and blood, contain high levels of water and electrolytes and therefore acts as a conductor of an electrical signal. Fat tissue is comparatively anhydrous and acts as a resistor to the flow of an electrical signal (Wagner and Heyward, 1999). Increasing levels of fat mass result in higher impedance value and correspond to higher levels of body fat. The only direct measurements that the BIA makes are weight and impedance; all other values such as body fat percentage, fat free mass, total body water, etc., are calculated using an equation based on these and other values such as height, age, gender and body type.

Body composition was measured using the Tanita MC 180 Multi-Frequency Body Composition Analyzer in Study 1. This is an eight-electrode BIA system which has been validated as a measure of body composition and has shown moderate to high correlations with the criterion method DEXA (Jebb et al., 2000, Pietrobelli et al., 2004, Volgyi et al., 2008). However, as BIA provides an estimation of body composition, this method has some limitations. BIA has been shown to underestimate percentage body fat when compared to DEXA (Neovius et al., 2006, Leahy et al., 2012).

2.4.5 BIA measurement procedure

The level gauge on the Tanita MC 180 Multi-Frequency Body Composition Analyzer was checked to ensure the machine was level with the floor. The feet of the machine were adjusted accordingly (Multi-Frequency Body Composition Analyzer MC-180 Instruction Manual). Participants stood on the machine in bare feet and held the handgrips loosely down by their sides, ensuring correct placement on the electrodes. The following information was inputted: gender, standard body type, age and height. To complete the measure (<20 second duration), participants stood upright, ensuring that the thighs were not touching and that arms were straight down by their sides. The following details were recorded: weight (kg), BMI (kg/m^2), body fat (kg), body fat (%), muscle mass (kg), fat free mass (kg), bone mass (kg), total body water (%) and BMR.

2.4.6 Sarcopenia

Sarcopenia is a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength. It is associated with a risk of adverse outcomes such as physical disability, poor quality of life and death (Cawthon et al., 2007, Rolland et al., 2008). There are many factors which can contribute to the development of sarcopenia. Primarily, sarcopenia is a geriatric symptom which occurs with advancing age, however other causes can include: early life development influences, suboptimal diet, bed rest or sedentary lifestyle, chronic diseases and certain drug treatments (Cruz-Jentoft et al., 2010). Sarcopenia can be a feature of other syndromes such as cancer cachexia. Cachexia is a complex metabolic syndrome associated with inflammation, insulin resistance, anorexia and increased breakdown of muscle proteins. Therefore most cachectic individuals are also sarcopenic, but most sarcopenic individuals are not considered cachectic (Cruz-Jentoft et al., 2010). Malnutrition and sarcopenia are adverse risk factors for patients undergoing neoadjuvant therapy and surgery (Awad and Lobo, 2011, Bower and Martin, 2009) and therefore their measurement is important to consider and include when investigating cancer cohorts. As discussed in Chapter 1, oesophageal cancer in particular, is a tumour which is associated with a relatively high frequency of malnutrition, sarcopenia and cachexia.

The presence of sarcopenia is often identified through the measurement of muscle mass, with a muscle mass of more than two standard deviations below that typical of healthy adults a suggested definition (Baumgartner et al., 1998). There are a wide variety of methods available to measure muscle mass including MRI, DEXA, BIA and CT. CT and MRI are considered the gold standard techniques (Cruz-Jentoft et al., 2010), however their use is often limited due to expense, lack of expertise and lack of access. In this centre (SJH), patients undergoing treatment for oesophageal cancer have CT scans before and after neoadjuvant treatment, before surgery and at various other time points as required. These CT scans are taken for diagnostic purposes, however they are available electronically as part of the patient's medical records. Therefore, with ethical permission, it was possible to access these scans in order to determine the presence of sarcopenia during treatment for participants who participated in Study 1. The use of diagnostic scans for this purpose has previously been recommended in the literature (Prado et al., 2008).

2.4.7 Sarcopenia measurement procedure

Muscle cross sectional area analysis was carried out at the 3rd lumbar vertebra (L3) level using Hounsfield unit (HU) thresholds (-29 to +150) on a Siemens Leonardo workstation. The directly ascertained unit was area (cm^2) of total L3 skeletal muscle. Cross sectional areas for muscle were normalised for stature (cm^2/m^2) as previously described (Baumgartner et al., 1998). Participants were deemed to be sarcopenic if their L3 skeletal muscle index fell below the established cut points of 52.4 cm^2/m^2 for men or 38.5 cm^2/m^2 for women (Prado et al., 2008). Estimates of whole body stores were generated using the following regression equations which show a close correlation between muscle areas in CT images at the third lumbar vertebrae and whole body compartments of fat-free mass: Total body fat-free mass (FFM) (kg) = 0.3 × [skeletal muscle at L3 (cm2)] + 6.06 (r = 0.94) (Mourtzakis et al., 2008).

2.5 Health related quality of life

As stated in Chapter 1 (Section 1.2), HRQOL is generally defined as the functional effect of a medical condition and/or its consequent therapy upon a patient and relates to physical, mental, emotional, and social functioning. HRQOL is widely recognised as an outcome of importance which complements more direct measures of population health such as life expectancy and morbidity and mortality rates. Measuring HRQOL can help determine the burden of disease and can provide valuable insights into the relationships between HRQOL and risk factors, outcomes and prognosis. Furthermore analysis of HRQOL data can identify subgroups with relatively poor perceived health and help to guide interventions to improve their situations and avert more serious consequences.

As discussed in Chapter 1, there have been major advances and improved outcomes in the treatment of oesophageal cancer in recent decades. With this improved survivorship, studies into quality of life, both physical and psychological, are increasingly relevant to patient cohorts who have received complex and attritional therapies. Patient reported outcomes, such as HRQOL questionnaires, complement objective data to provide a broader and more comprehensive understanding of the patient experience. Subjective reports of HRQOL were assessed in Study 1 in this thesis.

2.5.1 Measurement of HRQOL

HRQOL is generally measured through interview or questionnaires. The gold standard measurement is for patients to self-report their HRQOL using a patient reported outcome measure (PROM). PROMs are any report of status that comes directly from the patient, without interpretation of the patient's response by a clinician or any other person; examples include indexes, scales or questionnaires. If a patient is too ill or too young to complete a patient reported outcome measure proxy data may be required on the patient's HRQOL. There are numerous questionnaires available to evaluate HRQOL which are tailored to specific conditions and populations. These measurements can be used to quantify changes in HRQOL over time or to compare the HRQOL of patients with different conditions or who receive different treatments.

Within a cancer population, the EORTC QLQ-C30 is one of the most widely used tools for evaluating HRQOL. This questionnaire was specifically developed to assess the HRQOL of patients with cancer. It has been translated and validated into 81 languages has been used in more than 3,000 studies worldwide. It consists of a core HRQOL questionnaire (QLQ-C30) which is supplemented by disease specific modules specific to individual cancers, for example the OES-18 for patients with oesophageal cancer. The results of the systematic review in Chapter 1 demonstrated that the EORTC QLQ-C30 is the most commonly used instrument to measure HRQOL in an oesophageal cancer population. Accordingly for ease of comparability, this instrument was chosen to evaluate HRQOL in this thesis.

2.5.2 EORTC QLQ-C30

The EORTC QLQ-C30 (version 3.0) with the oesophageal site-specific module EORTC QLQ-OES18 was used (Appendix VIII). The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QOL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QOL represents a high QOL, but a high score for a symptom scale/item represents a high level of symptomatology or problems. The oesphageal module has four symptom scales (dysphagia, eating problems, reflux and pain) and six single items (trouble with swallowing saliva, choking, dry mouth and taste, coughing and speech problems).

This questionnaire has been shown to be a valid and reliable measure of HRQOL in patients with oesophageal cancer (Aaronson et al., 1993, Blazeby et al., 2003).

2.5.3 EORTC QLQ-C30 data analysis

Scoring of the EORTC QLQ-C30 was completed in accordance with the scoring manual (Fayers et al., 2001). The numerical responses from the questionnaires were entered into a Microsoft Excel spreadsheet. A raw score for each scale was calculated to estimate the average of items that contribute to the scale. A linear transformation was then used to standardise the raw score so that the scores ranged from 0 to 100. The scoring procedure is outlined in Appendix IX.

Chapter 3 Qualitative Methods

3.1 Introduction

This chapter will describe study designs, sampling methods, procedures and data analysis related to the qualitative studies included in this thesis. These methods and procedures are common to Study 2 and Study 4 and subsequent chapters will refer back to the relevant sections when discussing individual study methods.

3.2 Qualitative research

Qualitative research is primarily exploratory research. It is used to gain an understanding of underlying opinions, reasons, and motivations. It provides insights into the problem or helps to develop ideas or hypotheses for potential quantitative research. Qualitative data are usually in the form of words rather than numbers and are a source of well grounded, rich descriptions and explanations of processes in identifiable local contexts (Miles and Huberman, 1994).

Qualitative research in its most basic form involves the analysis of any unstructured data. Common data collection techniques include; observation, interview or the review of documents. Qualitative research can be conducted using a number of methodologies including ethnography, phenomenology, grounded theory or qualitative descriptive. Qualitative data are examined descriptively to notice similarities and differences in the data: categories, patterns and themes are then described and sometimes interpreted to provide a rich description of the experience as-lived (Magilvy and Thomas, 2009).

Ethnography, phenomenology and grounded theory are based on specific methodological frameworks that emerged from specific disciplinary traditions (Lambert and Lambert, 2012). These methodologies describe the data and also tend to explain the phenomena. By comparison, qualitative descriptive studies are the least “theoretical” of all of the qualitative methodologies. Qualitative descriptive studies are a rich, straight description of an experience or event. With qualitative descriptive there is no pre-selection of study variables, no manipulation of variables and no prior commitment to any one theoretical view of a target phenomenon. Qualitative descriptive research stays ‘close to the data’ with the end result

being a comprehensive description of informants experiences in a language similar to the informants own language (Neergaard et al., 2009). Qualitative descriptive is the design of choice when a straight forward description of the phenomenon without an in-depth level of interpretation is desired (Lambert and Lambert, 2012).

As the goal of the qualitative research in this thesis was not to generate any theory, but, rather, to identify and describe the experiences and opinions of survivors of oesophageal cancer in relation to their treatment and recovery, a qualitative descriptive approach was chosen as the most appropriate.

3.3 Study designs

Many approaches to qualitative research can be taken with the two main forms being interview and observation. Observation of participants occurs in the context of a natural scene and observational data is used for the purpose of description. A skilled observer is trained in the process of monitoring both verbal and nonverbal cues, and in the use of concrete, unambiguous and descriptive language. Several observation strategies can be used including; watching unobserved from the outside, maintaining a passive presence, engaging in limited interaction or acting as a full participant in the situation. Interviews can be carried out as the primary research strategy or in conjunction with observation, document analysis or other techniques. Interviews can take the form of informal or conversational, semi-structured, standardised open ended, or focus groups. Interviews can be carried out face to face or using other forms of communication such as the telephone, MSN messenger and email (Opdenakker, 2006). The advantage of interviews over other methods is that the interviewer has an opportunity to probe or ask follow up questions and, while they are time consuming and resource intensive for the researcher, they are generally easier for the respondent, particularly when opinions or impressions are being sought.

In this thesis semi-structured individual interviews were chosen as the method of data collection. Semi-structured interviews are common in qualitative descriptive research (Sandelowski, 2000) and have previously been used in an oesophageal cancer population (Andreassen et al., 2006, Mills and Sullivan, 2000, Verschuur et al., 2006). A semi-structured interview is usually organised around an interview guide or schedule. This guide contains topics, themes, or areas to be covered during the course of the interview, rather than a

sequenced script of standardised questions. The aim is to ensure flexibility in how and what sequence questions are asked, and in whether and how particular areas might be followed up and developed with different interviewees. Questions are designed to be simple, open-ended and flexible and are directed towards discovering the who, what, where and how of events and experiences (Sandelowski, 2000). This allows participants to tell their own story in their own way and prevents a structure being put on answers.

Given the wide geographical dispersion and varying occupational statuses of potential participants, individual interviews, as opposed to focus groups, were deemed the most feasible research method in this population. Furthermore, it has been suggested that group composition and dynamics in a clinical population such as this one could result in less than candid accounts of negative experiences or reluctance to describe accounts which are at odds with other patients experiences (McCorry et al., 2009). Focus groups can also limit the depth of the data collected as the time and space for the detail of each individual's experience is limited. A further disadvantage of focus groups is that the more reserved participants may be intimidated in a group situation and not have the confidence to fully participate, resulting in the discussion being dominated by more outspoken participants.

In this thesis, both face to face and telephone interviews took place in order to ease participant burden and maximise recruitment potential. The major difference between face to face and telephone interviews is the absence of visual and environmental cues with telephone interviews. This may result in loss of important non-verbal data such as facial expression or body language. However intonation, hesitations and sighs can be recorded and noted during telephone interviews and these can be useful to compensate for the absence of nonverbal responses. Loss of contextual data including the environment or the physical features of the participants can also occur with telephone interviews. However such data does not always enhance the understanding or interpretation of words and therefore the loss of contextual data may not necessarily undermine the quality of the study findings (Novick, 2008). Telephone interviews may also result in a loss or distortion of verbal data as compared to face to face interviews. It may be more difficult to build up a rapport between the interviewer and the participant over the telephone. This may result in fewer opportunities for probing and in-depth discussion. However it has been reported that as telephone interviews allow the participant to remain in familiar comfortable surroundings, he/she may be more relaxed on the telephone and willing to talk freely (Novick, 2008). Therefore, despite the common perception that face-to-face interviews are superior to telephone interviews, a review by Novick (2008) revealed there is very little formal evidence regarding the merits and

shortcoming of one as compared to the other. Consequently this review concluded that until further well-designed studies have been carried out to compare interview modalities, there is no reason to favour a particular mode for qualitative interviews (Novick, 2008).

3.4 Sampling

A key characteristic of qualitative samples is that they are relatively small in size. This enables in-depth exploration of the phenomena under investigation. Qualitative samples tend to be purposive, rather than random. This is because the research question tends to be quite specific (e.g views of a certain group about a particular subject known to them specifically) and therefore random sampling would not answer the question. Furthermore with the small number of cases involved, random sampling could lead to a very biased sample (Miles and Huberman, 1994). With purposive sampling, participants are selected based on their knowledge and experience of the central topic of the study. The goal is to obtain cases deemed rich in information for the purpose of saturating the data. There a number of purposive sampling strategies that can be used in qualitative research. Examples include homogenous groups, extreme or deviant cases, typical cases, stakeholder sampling, intensity sampling, maximum variation sampling and criterion sampling (Miles and Huberman, 1994, Palys, 2008). Any sampling technique can be used in qualitative descriptive studies, however maximum variation sampling is often recommended as useful method to get a broad insight into a subject (Sandelowski, 2000, Neergaard et al., 2009).

In this thesis two types of purposive sampling were used: criterion sampling and maximum variation sampling. Criterion sampling involves selecting information rich cases that meet some predetermined criterion of importance. Maximum variation sampling includes informants who cover a spectrum of positions and perspectives in relation to the phenomenon being studied (Palys, 2008). Specific details of sampling for both Study 2 and Study 4 are detailed in Chapter 5 and Chapter 7 respectively.

3.5 Sample size

The sample size for qualitative studies is generally determined by ‘data saturation’. Saturation

is defined as the point in data collection when no new or relevant information or perspectives are emerging from the data. Hence, this is the point at which no more data needs to be collected (Given, 2008). A method of continuous data analysis was used to identify data saturation (Pope et al., 2000). In this thesis, recruitment for Study 2 and Study 4 ceased once 'saturation' was reached.

3.6 Procedural aspect of interviews

In this thesis, interviews took place in the Trinity Centre for Health Sciences, the Clinical Research Facility in St. James's Hospital or over the phone. The interviews took place at a time and place that was most convenient for the participant. All interviews were carried out by the main investigator (JG). The main focus of the interviews was on the accounts of the survivors of oesophageal cancer but participants were given the option of attending with a close friend or family member if they wished. Contributions from family members who attended the interviews were transcribed, analysed and included in the study results because relatives are often involved in the treatment and recovery process and therefore provide useful and relevant additional information.

A flexible interview schedule was used to guide the interviews and ensure all the main topics were discussed. During face to face interviews, relevant non-verbal communication was noted as field notes. Throughout the interview, respondent validation, or member checking was carried out, if deemed necessary, to clarify particular points the participants made. Following each interview overall impressions were memoed by the researcher (JG). In addition, where relevant, significant quotes, major ideas presented and potential revisions to the schedule were noted. All interviews were recorded using a digital voice recorder (Philips Voice Tracer digital recorder 3400).

3.7 Data analysis

3.7.1 Data preparation

All recorded data was listened to once and then transcribed verbatim by the researcher (JG). Documented memos and field notes, where available, were read as the recording was replayed, ensuring non-verbal information was captured and added to the data. Accurate

transcription was ensured by listening to the recordings again while re-reading the transcripts. Any typographical errors or omissions were corrected, enhancing rigor and credibility (Milne and Oberle, 2005). To ensure confidentiality each participant was assigned a study code on completion of the interview. All names and any other details that could possibly identify participants were removed from the transcripts.

The transcription of interviews can provide valuable learning and improve the research skills of the study investigator. Firstly, the transcription of interviews is an excellent way to become familiar with the data. The typing up of the recordings familiarises the interviewer with the information again, allows embedding of the information and a fresh perspective after the recording has taken place. Furthermore, the close attention required to transcribe data can facilitate the close reading and interpretive skills needed to analyse the data. Transcription can be recognised as an interpretive act where meanings are created rather than simply being considered the mechanical act of putting spoken sounds on paper (Braun and Clarke, 2006). A far more thorough understanding of the data is developed having transcribed it and therefore time spent in transcription is not wasted as it informs the early stages of analysis. If the data was transcribed by a third party the investigator would need to spend time familiarising himself/herself with the data and checking the transcripts against the original audio recordings for accuracy. After the transcription stage, the investigator (JG) felt familiar with the content of the data and was able to identify overt patterns and repeating issues in one or more interviews. These patterns were noted and were referred back to when coding the data. This highlights the value of transcription to the overall qualitative research process.

In addition, the transcription process gave the investigator (JG) the opportunity to listen to the interviews as the study was progressing. This enabled the investigator to reflect on interviewer style and identify any potential interviewer bias. Through the process of listening to the recordings of the interviews, the investigator was able to assess whether the questions asked were always open ended and whether the participants were given appropriate time to think and answer. This is important as participants must be allowed to follow their own thoughts during data collection to ensure participant driven data and data driven analysis. The transcription of the interviews provided an opportunity for the investigator to identify where she may have influenced the results, for example the interviewer may have subconsciously given clues with her tone of voice which may subtly influence the participant towards the interviewers own opinions, prejudices or values. The opportunity to continually reflect on the conduct, style and flow of each interview gave the researcher the opportunity to revise and improve her interview style and decrease any interviewer bias. Consequently the study

investigator had the opportunity to become a more competent and experienced qualitative researcher.

The learning which occurred as a result of the transcription and analysis of Study 2 led to improvements in interview technique by the investigator (JG) in Study 4. For example, having had the opportunity to reflect on interviewer style and technique throughout Study 2, the investigator was aware of the importance of allowing time for the participant to form an answer. This is important as participants must be allowed to follow their own thoughts during data collection to ensure participant driven data and data driven analysis. Asking questions during a conversational lapse could change the flow of the conversation. Therefore the investigator learned to develop a level of comfort with silences and pauses in conversation. Furthermore the investigator was cognizant of the importance of continually reflecting on any potential interviewer bias throughout data collection in Study 4. It is important to recognise the participant as the expert of their own experiences and remain open to what they believe. Ongoing reflection and note taking was required to ensure interviewer assumptions did not have any effect on what was learned.

3.7.2 Qualitative data analysis

Thematic content analysis, as described by Braun and Clark (2006), was used for analysis of the qualitative studies in this thesis. Thematic analysis is a method for identifying, analysing and reporting patterns or themes within data. Patterns are identified through a rigorous process of data familiarisation, data coding and theme development and revision. This form of analysis was chosen as it is not closely aligned to any pre-existing theoretical framework. It can be a realist method, which reports experiences, meanings and the reality of participants (Braun and Clarke, 2006). An inductive approach was chosen, in which the themes are strongly linked to the data (Braun and Clarke, 2006, Pope et al., 2000). Themes were identified at the semantic level. This involves the identification of themes within their explicit or surface meanings and where analysis does not look beyond what the participant has said. No attempt is made to interpret or theorise broader meanings or implications (Braun and Clarke, 2006). An inductive semantic approach to thematic analysis is therefore the ideal analysis for a qualitative descriptive study.

Table 3.1 Phases of thematic analysis (Braun & Clark, 2006)

Phases of thematic analysis	
1. Familiarisation with the data	Transcribing interview data, reading and re-reading data, noting down initial ideas.
2. Generating initial codes	Systematic coding of the data across the entire data-set, collating data relevant to each code.
3. Searching for themes	Collating codes into potential themes, gathering all data relevant to each potential theme.
4. Reviewing themes	Checking the themes work in relation to the coded extracts (Stage 1) and the entire data-set (Stage 2).
5. Defining and naming themes	Generating clear definitions and names for each theme. Ongoing analysis to refine the specifics of each theme.
6. Producing the report	The final opportunity for analysis. Selection of extracts, final analysis of extracts, relating back to the research question and literature. Producing a scholarly report.

The process of data analysis involved six phases as detailed in Table 3.1. The first phase occurred during data collection and data preparation. During these processes familiarisation with the data occurred through the transcription of the interviews and repeated active reading of the transcripts searching for meaning and patterns. Notes on initial ideas for themes and codes were produced during this process, which informed the early stages of analysis (Braun and Clarke, 2006). In the second phase, initial codes were generated. A code is a tag, most often a word or short phrase that symbolically assigns a summative, salient, essence-capturing, and/or evocative attribute for a portion of language-based data and can range from a single word to a full sentence to an entire page of text (Saldaña, 2012). Coding is an interpretive rendering of the data and entails (1) compiling a list of codes (codebook) corresponding to themes observed in the text and (2) judging for each segment of text whether a specific code is present (Hruschka, 2004). Coding breaks down the data, line by line, segment by segment, incident by incident. Coding can be inductive or deductive. Deductive or a priori codes are identified from sources outside the data such as the research question, previous literature in the area of interest or questions and topics from the interview schedule. Inductive or grounded codes emerge from the data and are developed by the researcher by directly examining the data. In this thesis, both inductive and deductive coding was used, as previously

described in the literature (Fereday and Muir-Cochrane, 2006). Codes can be further labelled as in vivo (in the language of the participants) or in vitro (constructed by the researchers). Coding can be performed either manually or using computer assisted qualitative data analysis software (CAQDAS). In this thesis coding was carried out using CAQDAS with the programme NVivo 10 for Windows (QSR International Pty Ltd, Victoria, Australia).

The initial codes in phase two were generated based on the objectives of the study and from familiarisation with the data. Initially the transcripts were read in their entirety in order to get a sense of the whole. On the second reading, line-by-line analysis was used to identify additional codes and sub-categories of code within the preliminary codes. The first version of the codebook was devised based on this basic content analysis. The codebook outlines each code and sub-code with explanations for each. This was done to enable other researchers to independently analyse the data. On the third reading, codes were assigned to the data and this was completed systematically throughout the entire data-set. The suitability of the coding system and the first version of the codebook was checked by a senior researcher (EG) familiar with the study population, who checked approximately 20% of the coded data. Due to the large amount of data, a subset of 20% was chosen based on the literature (Hruschka, 2004). Code suitability, potential themes and definitions were discussed and clarifications proposed.

Phase three re-focused the analysis at the broader level of themes, rather than codes. A theme captures something important about the data in relation to the research question and represents some level of patterned response or meaning within the data set (Braun and Clarke, 2006). During phase three, the long list of codes generated in phase two were sorted into potential themes. The relationships between codes and themes and between different levels of themes (i.e. primary themes and sub themes) were considered at this stage. Sub-themes are essentially themes within a theme that give structure to large or complex themes (Braun and Clarke, 2006). When all the codes were sorted into potential themes, all the relevant coded extracts were collated within the identified themes. The codebook was then revised and modified. Codes and sub-codes were expanded if the codes did not adequately cover the theme, or discarded if they were unwarranted. A second and final version of the codebook was then produced (Appendix X) and the data re-coded with this new codebook. Examples of the coding system are illustrated in Table 3.2.

Table 3.2 Examples of the coding system

Raw Data	Coded text unit	Code	Sub-theme	Theme
The physios were over there, they had me walking around obviously and up and down stairs and I was grand. My strength for that was grand. The first day I had the operation I could walk.. there was no problem. It was just later on.. getting the full fitness back.. no. I didn't know. I still don't feel I'm back to full fitness either yea.	It was just later on.. getting the full fitness back.. no. I didn't know. I still don't feel I'm back to full fitness either yea.	Decreased fitness	Physical changes	Living with and beyond oesophageal cancer
But actually it's good that I do it because if I didn't do that I'd probably be doing nothing at all. So I dunno what I should be doing in terms of knowing particular guidelines but I know that in general I should.	So I dunno what I should be doing in terms of knowing particular guidelines	Guidelines-no knowledge	Exercise knowledge & understanding	Physical activity and exercise in oesophageal cancer survivorship
I'm keeping it up, as I say I get the odd day maybe, weather permitting that you couldn't get out but eh.. I kind of...make it, kind of... try to get into a routine and make it a habit that no matter what way you're feeling you get up and go out and do it.. I like to keep myself active so..	I kind of... make it, kind of... try to get into a routine and make it a habit that no matter what way you're feeling you get up and go out and do it.	Exercise facilitator-habit	Facilitators to exercise	Physical activity and exercise during treatment for oesophageal cancer

After phase three a set of candidate themes and subthemes had been devised. Phase four involved a refinement of these themes. Refinement of themes occurred in two stages. Firstly, all the collated extracts for each theme were read to assess whether they formed a coherent pattern. Secondly, the validity of individual themes was considered in relation to the entire data set. Therefore the entire data set was re-read in order to (1) ascertain whether the themes were suitable and (2) re-code any additional or missed data within the finalised themes. Throughout this phase, adjustments were made to coded data extracts and themes when they did not 'fit'. For example data extracts were moved from one theme to another, new themes were created, or themes were re-worked or discarded. In the fifth phase, the finalised themes and sub-themes were refined, defined and named. The final analysis or phase six occurred during the production of the results and the discussion of the findings.

3.7.3 Inter-rater and intra-rater reliability

An investigation of inter-rater and intra-rater reliability of the coding systems used in this thesis was completed. Inter-rater reliability assesses the degree to which codings of text by multiple coders are similar (Hruschka, 2004). Intra-rater reliability assesses the agreement in the coding of text by one coder at two different time points. To investigate the inter-rater reliability in both Study 2 and Study 4, a subset (20%) of the interview transcripts were coded by two independent coders: the main investigator (JG) and an independent coder (EG). The figure of 20% was chosen for the subset in accordance with coding practices in the literature (Hruschka, 2004). The independent coder (EG), was provided with an un-coded copy of 20% of the transcripts and asked to code it using the final codebook. All agreements and disagreements were counted to establish inter-rater reliability. Any disagreements between the initial coder (JG) and the independent coder were discussed and resolved. The same 20% portion of the data was coded by the original researcher (JG) with a time interval of one month between initial and subsequent coding. The results were compared to establish the intra-rater reliability. The formula presented in Table 3.3 was used to calculate the reliability of the coding and is expressed as a percentage agreement (Miles and Huberman, 1994).

Table 3.3 Formula used to calculate reliability of the coding system

$$\frac{\text{Number of agreements} \times 100}{\text{Total number of agreement + disagreements}}$$

Chapter 4 Study 1: Physical functioning after curative treatment for oesophageal cancer

4.1 Introduction

Due to the increasing incidence and survival rates associated with oesophageal cancer there is now a growing population of people living longer as survivors of this disease. The results of the systematic review in Chapter 1 demonstrated the significant negative impact curative treatment for oesophageal cancer can have on both subjectively and objectively measured physical functioning. The review also highlighted the paucity of objective measures of physical functioning in this cohort. While some recent studies included in the review have investigated the immediate effect of treatment on outcomes such as strength and fitness there is no data available on the long term physical functioning of survivors of oesophageal cancer in the months and years after curative treatment. Therefore it is unclear whether the reduction in physical functioning frequently observed during treatment is maintained into longer term survivorship in this cohort.

Reduced strength, fitness and physical activity levels have been identified in long term survivors of breast, colorectal and lung cancer (Broderick et al., 2014b, Sanchez-Jimenez et al., 2014, Jones et al., 2008b) and rehabilitation programmes are increasingly being put in place to address these deficits. The complexity of the management of oesophageal cancer puts survivors of this disease at potentially greater risk of suboptimal physical functioning into survivorship. Furthermore, as discussed in Chapter 1, oesophageal cancer is a disease which is particularly associated with weight loss and sarcopenia. Significant losses of muscle mass during treatment and recovery may have persistent effects on functional performance in this group. Poor physical functioning is associated with decreased overall HRQOL and an increased risk of disability and therefore this is an outcome which warrants investigation in this clinical population. Due to the large discrepancies often identified between subjective perception of health and objective measurement of health outcomes, objective measures of physical performance are required to inform rehabilitation strategies in the newly emerging cohort of oesophageal cancer survivors.

4.2 Study aims and objectives

The primary aim of this study was to provide a cross sectional description of the physical functioning and HRQOL of survivors of oesophageal cancer in the survivorship phase. The secondary aim of this study was to compare the physical functioning and HRQOL of survivors of oesophageal cancer to age and gender matched control participants with no history of cancer.

The specific objectives were:

- To determine body composition, exercise capacity, physical activity levels, muscle strength and HRQOL of oesophageal cancer survivors at least 6 months post oesophagectomy.
- To quantify the changes in body composition experienced by this cohort from diagnosis up to three years post oesophagectomy.
- To compare the physical functioning and HRQOL of oesophageal cancer survivors with age and gender matched control participants with no history of cancer.

4.3 Methods and measures

4.3.1 Study design

A cross sectional study design was used to describe the physical functioning and HRQOL of curatively treated survivors of oesophageal cancer. A retrospective medical record review was used to quantify changes in body composition experienced by this cohort throughout the cancer continuum. A case-control design was used to compare survivors of oesophageal cancer with a group of age and gender matched participants with no history of cancer.

The inclusion criteria for the oesophageal cancer survivors were: (1) >18 years of age and (2) at least six months post oesophagectomy with curative intent. Accordingly all participants were in the survivorship time period, as described in the PEACE framework (Courneya and Friedenreich, 2007). According to this framework, at six months post treatment, a person is considered to have completed short term recovery and is attempting to resume normal activities (Courneya and Friedenreich, 2001). Exclusion criteria included: (1) evidence of active or recurrent disease (2) a neurological or musculoskeletal condition limiting independent mobility or (3) contraindications to exercise testing as per the American College of Sports

Medicine guidelines (Pescatello, 2013). Exclusion criteria for the control group were the same as for the survivor group in addition to having no previous cancer diagnosis.

4.3.2 Sampling and recruitment

Cancer survivors eligible to participate were identified from an institutional database maintained prospectively at the National Oesophageal and Gastric Centre at St James's Hospital (SJH), Dublin. A list of patients who had undergone oesophagectomy with a curative intent between January 2010 and December 2012 was obtained. Before contacting each participant it was ascertained that they were currently free of disease and eligible to participate. This was done through contact with the medical team, the oesophageal cancer database manager and/or medical chart review. Oesophageal cancer survivors who were deemed eligible were posted an information package inviting them to take part in the study. The package included a cover letter, a participant information leaflet (PIL) (Appendix XI) which detailed the aims and requirements of the study, an expression of interest form and a stamped addressed envelope. Participants indicated their interest in taking part by returning a letter or phoning the lead investigator. An appointment was then made for the participant to come in for the study assessment. Recruitment and testing for the cancer cohort took place between October 2012 and May 2014.

An age (±5 years) and gender matched control participant was recruited for a subset of the survivors of oesophageal cancer who completed the study protocol. Control participants were recruited through advertising on the following; Trinity College Dublin and St. James's Hospital web notice boards, posters displayed on college and hospital notice boards and through word of mouth. Participants indicated their interest in taking part by phoning or emailing the lead investigator. Recruitment and testing for the control participants took place between April 2014 and April 2015.

4.3.3 Sample size calculation

A sample size calculation was carried out for the case-control analysis section of this study. Worldwide the incidence rates of oesophageal cancer are more than double in men than in women (male: female ratio 2.4: 1). This incidence is reflected in St. James's Hospital where almost 68% of patients treated for oesophageal cancer are male. Due to the male predominance in this disease, the sample size for this study was powered by male specific

values for hand grip strength. The required sample size was calculated based on a minimal detectable change of 5.2kg in hand grip strength (Puthoff and Saskowski, 2013). With an alpha level of 0.05 and a standard deviation of 6.4kg (Werle et al., 2009), it was estimated that 25 male participants in each group were required for this study to obtain 80% power.

4.3.4 Ethical approval

Ethical approval was granted by the SJH/AMNCH research ethics committee and all participants provided written, informed consent (Appendix XI & Appendix XII).

4.3.5 Measurement and testing protocol

Each participant attended the exercise laboratory in the Trinity Centre for Health Sciences at St. James's Hospital for one appointment during which all the assessments outlined below were completed:

- **Hand grip strength** was measured using a Jamar dynamometer according to the procedures outlined in Section 2.3.2.3.
- **Exercise capacity** was measuring using the ISWT as outlined in Section 2.3.1.3.
- Habitual **physical activity levels** over 5-7 days were measured using the RT3 triaxial accelerometer as outlined in Section 2.3.3.4.
- **HRQOL** was measured using the EORTC QLQ-C30 questionnaire with the oesophageal site specific module OES18 as described in Section 2.5.2.
- **Standing height** was measured according to the procedures outlined in Section 2.4.3.
- **Waist circumference** was measured according to the procedures outlined in Section 2.4.3.
- Current **body composition** including body weight was measured using BIA according to the procedures outlined in Section 2.4.5.

4.3.6 Retrospective body composition analysis

In addition to measuring the current body composition of this cohort, a retrospective review of each participant's medical records was conducted to establish the changes in body composition experienced by this group during and after treatment.

4.3.6.1 Body weight

A medical chart review was conducted to quantify the changes in body weight experienced by this cohort from diagnosis to the present. Where available, each patient's body weight was recorded for the following approximate time points:

- Pre-neoadjuvant treatment (multimodal group only)
- Pre-operatively
- 1 month post-operatively
- 3 months post-operatively
- 6 months post-operatively
- 1 year post-operatively
- 2 years post-operatively
- 3 years post-operatively

BMI was also calculated for each of these time points. As this was a retrospective chart review, body weight for each participant was not available at all time points nor were body weight measurements for each participant taken at the exact time points listed. For body weight measured in the first year, measurements taken within four weeks of each time point were included. For body weight collected at one, two and three years, measurements taken within six months of each time point were included.

4.3.6.2 Sarcopenia

Where available, diagnostic abdominal CT scans were used to determine the presence of sarcopenia during treatment as per the procedure outlined in Section 2.4.7. For participants who had undergone multimodal treatment consisting of neoadjuvant therapy and surgery, the presence of sarcopenia was measured pre and post neoadjuvant therapy. For the participants who underwent surgery only, the presence of sarcopenia was measured pre-operatively.

4.3.7 Data analysis

Data analysis was performed using SPSS (version 20) (IBM, Armonk, New York, USA). Data normality was assessed using normality plots and the Shapiro-Wilk test ($p>0.05$). Means and standard deviations (SD) are presented for each continuous variable with a normal distribution. Medians and interquartile ranges are presented for each continuous variable with

a skewed distribution. Differences between cases and controls were assessed using independent t-tests and Mann Whitney U tests. To reduce the risk of type 1 error in the case-control analysis, corrections were made for multiple comparisons using the Bonferroni correction and significance was set at $p \leq 0.001$ (two sided).

4.4 Results

4.4.1 Cross sectional study

4.4.1.1 Participant characteristics

Ninety-six survivors of oesophageal cancer were screened for eligibility (as per Section 4.3.1); of these 19 were deemed ineligible to contact. Reasons for exclusion included: the patient had since deceased, had a recurrence of disease, was currently undergoing treatment for another medical condition, had been lost to service follow up, was living abroad or was otherwise deemed unsuitable to contact. Seventy-seven patients were deemed eligible for the study and were invited to take part. Of these, 44 did not participate for the following reasons: 28 did not respond, four refused and 12 patients made contact to express interest or to receive further information about the study, however they did not attend for assessment and were lost to follow up. Reasons for this included other medical concerns, cancelled hospital appointments, no further interest in the study or non attendance for study appointment and no response to follow up phone calls. Four participants refused to participate in the study. The reasons for refusal were: one person felt physically unable to complete the study assessments, one did not want to speak about the surgery and felt that wearing the RT3 accelerometer and maintaining the exercise diary would be difficult and two people returned a letter stating they were not interested in participation but did not give a specific reason for this. The flow diagram of the recruitment of the cancer cohort is detailed in Figure 4.1.

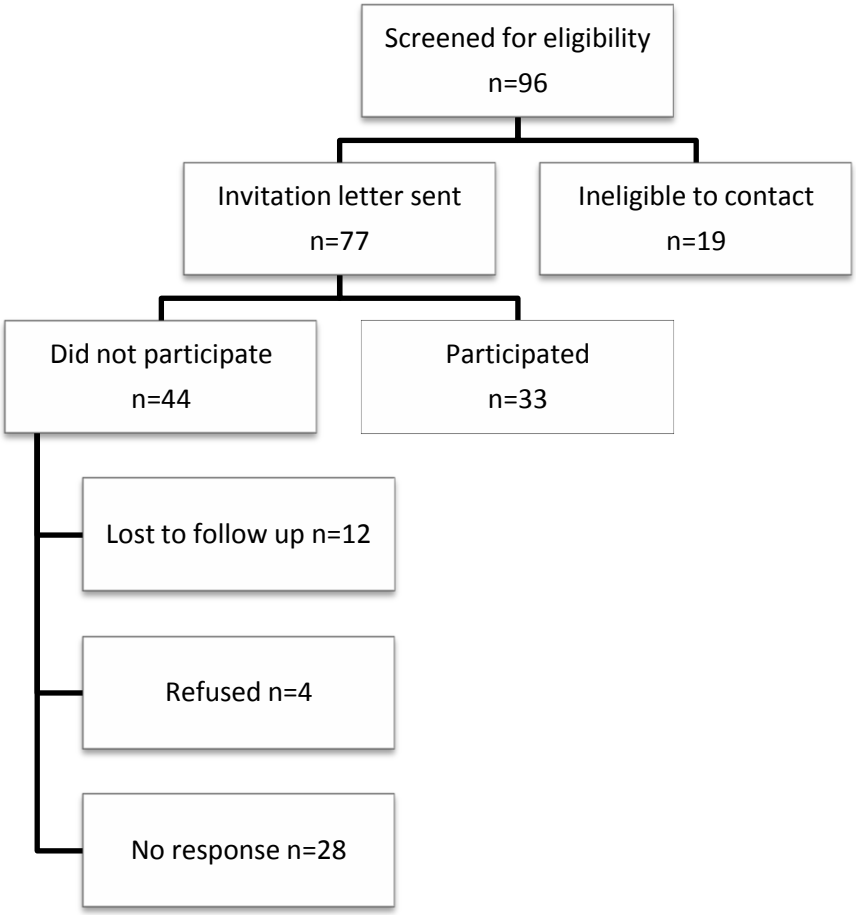

Figure 4.1 Recruitment of cancer cohort for cross sectional study

In total, 33 survivors of oesophageal cancer (five female) with a mean (SD) age of 64.67 (7.42) years completed the study protocol. All participants were Caucasian. The mean (SD) time since surgery was 23.61 (6.50) months. Participant demographics are detailed in Table 4.1. The predominant subtype of oesophageal cancer was adenocarcinoma (67%) and the most common surgery performed was en-bloc radical 2-stage oesophagectomy (64%). Eighteen participants (55%) underwent multimodal treatment consisting of neo-adjuvant or adjuvant chemotherapy and/or radiotherapy in addition to surgery. Fifteen participants (45%) were treated with surgery only. Thirteen participants (39%) had a cardiac co-morbidity, the most common being hypertension, and four participants had a metabolic co-morbidity, the most common being diabetes. Sixty-one per cent of this cohort had experienced post-operative complications.

Table 4.1 Participant demographics and disease related information

Demographics (n=33)	
Age (years)*	64.67 (7.42)
Range	51-78
Gender *n (%)*	
Male	28 (85)
Female	5 (15)
Time since surgery (months) *	23.61 (6.50)
Range	11-40
Hand dominance *n (%)*	
Right	29 (88)
Left	4 (12)
Employment status *n (%)*	
Working	9 (27)
Not working/retired	24 (73)
Co-morbidities *n (%)*	
Cardiac	13 (39)
Respiratory	1 (3)
Metabolic	4 (12)
Previous Cancer	1(3)
Cancer Type n (%)	
Adenocarcinoma	22 (67)
Squamous Cell Carcinoma	9 (27)
High Grade Dysplasia	2 (6)
Surgery Type *n (%)*	
2-stage oesophagectomy	21 (64)
3-stage oesophagectomy	4 (12)
Transhiatal oesophagectomy	7 (21)
Oesophago-gastrectomy	1 (3)
Treatment Type *n (%)*	
Multimodal	18 (55)
Surgery only	15 (45)
Post-operative Complications *n (%)*	
Yes	20 (61)
No	13 (39)

*mean (standard deviation)

4.4.1.2 Data normality

The following data were non normally distributed ($p<0.05$): average time spent in vigorous intensity activity per day, average time spent in bouts of moderate-vigorous activity per day, fat mass (kg) in men and the EORTC QLQ-C30 questionnaire scores. Accordingly these data are described as median (inter-quartile range).

4.4.1.3 Physical performance outcomes

The results for hand grip strength and ISWT distance for men and women are detailed in Table 4.2. The average distance achieved on the ISWT by men and women was 548 (147.98) metres and 452.00 (120.91) metres respectively, which both fall short of the distance which would be expected for healthy adults aged 60-69 to achieve (699 metres).

Table 4.2 HGS and ISWT results in cancer cohort

	Men (n=27)	**Women (n=5)**
Dominant hand grip strength (kg)	39.08 (10.89)	25.54 (5.88)
Non-dominant hand grip strength (kg)	36.84 (9.92)	25.18 (5.84)
ISWT distance (metres)	548.95 (147.98)[a]	452.00 (120.91)

Data are displayed as mean (standard deviation). [a]n=19 Abbreviations: *kg* kilogram

Results for objectively measured habitual physical activity levels are detailed in Table 4.3. Participants wore the RT3 accelerometer for an average (SD) of 6.68 (0.65) days (range 5-7 days). This cohort spent 57.51% of their day sedentary, with an average of 30.38 (21.08) minutes per day engaged in moderate intensity activity. However when the data was analysed for time spent in bouts (≥10minutes) of activity, it revealed that this cohort spent a median of 7.86 (26.28) minutes per day engaged in bouts of moderate-to-vigorous intensity activity and accordingly this group were not meeting the PA guidelines recommended for cancer survivors.

Table 4.3 Objectively measured physical activity levels in cancer cohort

	Cancer Cohort n=31
Sedentary behavior (min.day^{-1})	477.41 (102.93)
Sedentary behaviour (%)	57.51 (11.23)
Light activity (min.day^{-1})	314.05 (81.19)
Moderate activity (min.day^{-1})	30.38 (21.08)
Vigorous activity (min.day^{-1}) †	1.23 (4.00)
Mod-to-vig activity (≥10 minute bouts) (min.day^{-1})†	7.86 (26.28)

Data are displayed as mean (standard deviation) unless indicated otherwise.
† Variable not normally distributed, data presented as median (interquartile range).

4.4.1.4 Health related quality of life results

HRQOL data as measured by the EORTC QLQ-C30 and the EORTC QLQ-OES18 questionnaires are shown in Table 4.4. The median global QOL score was 83.33 reflecting a good overall HRQOL in this group. The domains of role, cognitive and social functioning in particular scored very highly with a median score of 100. Within the symptom scales, the predominant symptom reported was fatigue with a median score of 22.22. The results of the EORTC QLQ-OES18 demonstrate minimal reporting of any persistent oesophageal specific symptoms in this cohort. Mean (SD) scores are also reported for informative purposes and to enable comparisons with the literature.

Table 4.4 HRQOL results in cancer cohort

EORTC QLQ-C30 (n=33)	**Mean (SD)**	**Median (IQR)**
Global health status/QOL	77.78 (18.24)	83.33 (25.00)
Functional Scales †		
Physical functioning	91.11 (9.08)	93.33 (13.00)
Role functioning	92.93 (13.20)	100.00 (17.00)
Emotional functioning	85.61 (15.06)	91.67 (25.00)
Cognitive functioning	87.37 (17.69)	100.00 (17.00)
Social functioning	95.45 (10.43)	100.00 (0.00)
Symptom Scales/items ‡		
Fatigue	22.56 (17.67)	22.22 (28.00)
Nausea and vomiting	5.56 (10.75)	0.00 (8.00)
Pain	6.57 (11.74)	0.00 (17.00)
Dyspnoea	8.08 (16.73)	0.00 (0.00)
Insomnia	10.10 (17.65)	0.00 (33.00)
Appetite loss	9.09 (20.87)	0.00 (0.00)
Constipation	4.04 (13.84)	0.00 (0.00)
Diarrhoea	10.10 (15.55)	0.00 (33.00)
Financial difficulties	3.03 (9.73)	0.00 (0.00)
EORTC QLQ OES-18 (n=33) ‡		
Dysphagia	1.11 (10.96)	1.00 (0.00)
Eating	17.17 (19.76)	8.33 (29.00)
Reflux	13.64 (15.28)	16.67 (17.00)
Pain	5.39 (10.44)	0.00 (11.00)
Trouble swallowing saliva	5.05 (18.86)	0.00 (0.00)
Choked when swallowing	9.09 (22.47)	0.00 (0.00)
Dry Mouth	11.11 (23.07)	0.00 (17.00)
Trouble with taste	4.04 (11.04)	0.00 (0.00)
Trouble with coughing	12.12 (18.29)	0.00 (33.00)
Trouble talking	2.02 (8.08)	0.00 (0.00)

Abbreviations: *SD* standard deviation, *IQR* interquartile range.†Scores range from 0 to 100; Higher scores represent higher levels of functioning or QOL. ‡Scores range from 0 to 100; Higher scores represent higher levels of symptoms or problems.

4.4.1.5 Anthropometric and body composition analysis results

Current body composition measurements

The results for the current body composition measurements for this cohort are detailed in Table 4.5. This group had an average BMI of 24.72 kg/m^2 for men and 23.82 kg/m^2 for women, which both fall within the normal healthy range of 18.5-24.9 kg/m^2. The average waist circumference for men was 89.87 (11.90)cm which is below the cut off point of 94cm (above 94cm indicates an increased risk of metabolic complications in men). For women, the average waist circumference was 82.20 (11.19)cm, slightly higher than the cutoff point of 80cm (above 80cm indicates an increased risk of metabolic complications in women).

Table 4.5 Anthropometric and body composition measurements in cancer cohort

	Men (n=28)	**Women (n=5)**
Weight (kg)	75.16 (13.67)	63.09 (11.92)
Height (cm)	174.30 (5.74)	162.70 (3.19)
BMI (kg/m²)	24.72 (4.25)	23.82 (4.29)
Body Fat (kg)†	15.25 (11.12)†	20.83 (7.05)
Body Fat (%)	19.73 (7.04)	32.30 (5.66)
Muscle Mass (kg)	56.54 (6.15)	40.09 (4.97)
Fat Free Mass (kg)†	59.52 (6.45)	42.25 (5.24)
Bone Mass (kg)	2.98 (0.30)	2.16 (0.23)
Total Body Water (%)	55.40 (5.27)	47.68 (3.78)
BMR	1707.36 (206.03)	1262.20 (164.42)
Waist Circumference (cm)	89.87 (11.90)	82.20 (11.19)

Data are displayed as mean (standard deviation) unless indicated otherwise.
† Variable not normally distributed, data presented as median (interquartile range).
Abbreviations: *kg* kilogram, *cm* centimetre, *m* metre, BMR basal metabolic rate.

Retrospective body composition analysis

The changes in body weight and BMI experienced by this cohort from pre-treatment up to three years post-operatively are listed in Table 4.6. The male participants experienced a decrease in body weight and BMI from pre to post treatment and body weight had not returned to pre-treatment values by three years post-operatively.

Table 4.6 Changes in body weight and BMI throughout treatment and recovery in cancer cohort

	Pre-neoadjuvant treatment	Pre-op	1 month post-op	3 months post-op	6 months post-op	1 year post-op	2 years post-op	3 years post-op
Men	**(n=17)**	**(n=26)**	**(n=26)**	**(n=26)**	**(n=23)**	**(n=22)**	**(n=22)**	**(n=10)**
Body Weight (kg)	81.48 (14.48)	81.32 (14.00)	78.90 (13.46)	75.98 (12.51)	75.32 (12.26)	76.28 (14.20)	75.41 (15.41)	73.32 (13.50)
BMI (kg/m²)	26.83 (5.14)	26.76 (4.20)	25.95 (3.89)	25.00 (3.65)	24.96 (3.79)	24.95 (4.42)	24.66 (5.03)	24.11 (3.94)
Women		**(n=3)**	**(n=5)**	**(n=4)**	**(n=5)**	**(n=5)**	**(n=3)**	**(n=3)**
Body Weight (kg)		61.50 (10.75)	64.14 (16.82)	64.17 (15.99)	60.84 (14.98)	60.56 (11.55)	56.9 (9.09)	67.3 (12.52)
BMI (kg/m²)		23.01 (4.35)	24.20 (6.12)	23.94 (5.96)	22.94 (5.34)	22.86 (3.99)	22.01 (3.61)	25.81 (3.91)

Data are displayed as mean (standard deviation). Abbreviations: *kg* kilogram, *m* metre, *pre-op* pre-operatively, *post-op* post-operatively.

Sarcopenia

For patients who were treated with surgery only, 12 pre-operative CT scans were available to review. In the multimodal group, pre and post neoadjuvant treatment scans were available for 17 participants. Results for fat free mass and lumbar skeletal muscle index for both the surgery only and multimodal groups are detailed in Table 4.7 and Table 4.8. In the multimodal group, the number of patients classified as sarcopenic increased from four (23%) before commencing neoadjuvant therapy to eight (47%) following completion of neoadjuvant treatment, with a mean (SD) reduction of 2.41 (5.04) kg of estimated total body fat free mass. In the surgery only group, three (25%) patients were classified as sarcopenic pre surgery.

Table 4.7 Sarcopenia measurements for surgery only group

Surgery Only Group	**Men (n=9)**	**Women (n=3)**
Fat free mass (cm^2)	183.26 (29.91)	120.77 (14.08)
Estimated total body fat free mass (kg)	61.04 (8.97)	42.29 (4.22)
Lumbar skeletal muscle index (cm^2/m^2)	61.11 (10.38)	45.49 (4.10)
Number (%) classified as sarcopenic	3 (33)	0 (0)

Data are displayed as mean (standard deviation). Abbreviations: *cm* centimetre, *kg* kilogram, *m* metre.

Table 4.8 Sarcopenia measurements for multimodal group

Multimodal Group	**Pre-neoadjuvant therapy**	**Post-neoadjuvant therapy**
Men (n=16)		
Fat free mass (cm^2)	177.98 (21.34)	169.96 (17.94)
Estimated total body fat free mass (kg)	59.45 (6.40)	57.05 (5.38)
Lumbar skeletal muscle index (cm^2/m^2)	57.75 (6.85)	55.12 (5.51)
Women (n=1)		
Fat free mass (cm^2)	104.16	96.17
Estimated total body fat free mass (kg)	37.31	34.91
Lumbar skeletal muscle index (cm^2/m^2)	40.18	37.10
Total Multimodal Group (n=17)		
Number (%) classified as sarcopenic	4 (23)	8 (47)

Data are displayed as mean (standard deviation). Abbreviations: *cm* centimetre, *kg* kilogram, *m* metre.

4.4.2 Case-control analysis

4.4.2.1 Participant characteristics

Twenty five male survivors of oesophageal cancer and twenty five age (±5 years) matched male control participants were included in the case-control analysis. The cancer cohort was selected from the participants included in the cross sectional study and were matched with non cancer control participants. Forty-seven potential control participants expressed an interest in participating in the study. Of these eleven did not take part for various reasons and following further eligibility screening a further 11 were not suitably matched and were not included in the study analysis. Demographic characteristics and disease related information for the cancer cohort and control participants are listed in Table 4.9.

Table 4.9 Demographic characteristics and disease related information for cancer cohort and control participants

	Cancer Cohort (n=25)	**Controls (n=25)**
Age (years)*	63.20 (6.28)	60.40 (5.88)
Range	54-75	52-72
Time since surgery (months)*	21.64 (5.79)	
Hand dominance *n (%)*		
Right	22 (88)	21 (84)
Left	3 (12)	4 (16)
Employment status *n (%)*		
Working	7 (28)	14 (56)
Not working/retired	18 (72)	11 (44)
Cancer Type n (%)		
Adenocarcinoma	20 (80)	
Squamous Cell Carcinoma	4 (16)	
High Grade Dysplasia	1 (4)	
Surgery Type *n (%)*		
2-stage oesophagectomy	20 (80)	
3-stage oesophagectomy	1 (4)	
Transhiatal oesophagectomy	3 (12)	
Oesophago-gastrectomy	1 (4%)	
Treatment Type *n (%)*		
Multimodal	17 (68)	
Surgery only	8 (32)	

*Values are mean (standard deviation)

4.4.2.2 Data normality and homogeneity of variance

The following data were non normally distributed ($p<0.05$): fat mass (kg), average time spent in vigorous intensity activity per day, average time spent in bouts of moderate-vigorous

activity per day and the EORTC-QLQ-C30 questionnaire scores. Accordingly non parametric tests were used to assess differences between groups for these variables. For all normally distributed variables there was homogeneity of variances, as assessed by Levene's test for equality of variances ($p>0.05$).

4.4.2.3 Physical performance outcomes

Hand grip strength, ISWT distance and physical activity levels are detailed in Table 4.10. Mean HGS for both dominant and non dominant hands were the same for both groups ($p=0.081$ and $p=0.053$, respectively). The control group achieved an average (SD) of 773.48 (114) metres in the ISWT indicating significantly higher fitness levels than the cancer cohort who achieved an average (SD) of 558.33 (146) metres ($p<0.001$) (Figure 4.2). Participants wore the RT3 accelerometer for an average (SD) of 6.76 (0.54) days (range 5-7 days). The mean number of objectively measured minutes per day spent sedentary and engaged in light intensity activity along with sedentary behaviour expressed as a percentage of overall wear time revealed that time spent engaged in sedentary behaviour was high and similar in both groups. The control participants spent significantly more time engaged in moderate ($p<0.001$) and vigorous intensity ($p<0.001$) activity than the cancer cohort (Figure 4.3 and Figure 4.4). The control participants also spent significantly more time in bouts (≥10 minutes) of moderate-vigorous activity than the cancer cohort ($p=0.001$) (Figure 4.5). Accordingly the control group were, on average, meeting the physical activity guidelines recommended for health benefits, whereas the cancer cohort were not.

Table 4.10 Physical performance outcomes in oesophageal cancer and control groups

	Cancer Cohort	Controls	Mean Difference (95% C.I)	P value
Hand Grip Strength [a]				
Dominant hand grip strength (kg)	40.59 (10.96)	45.61 (8.61)	-5.02 (-10.66, 0.63)	.081
Non-dominant hand grip strength (kg)	37.70 (8.73)	42.34 (7.63)	-4.63 (-9.34, 0.07)	.053
Fitness [b]				
ISWT distance (metres)	558.33 (146.34)	773.48 (114.00)	-215.14 (-297.32, -132.97)	<.001*
Physical Activity Levels [c]				
Sedentary behavior (min.day^{-1})	484.27 (105.77)	476.76 (79.03)	7.51 (-46.00, 61.02)	.779
Sedentary behavior (% of total wear time)	58.56 (11.71)	54.25 (8.77)	4.31(-1.61, 10.24)	.150
Light activity (min.day^{-1})	300.51 (79.63)	320.65 (89.03)	-20.14 (-68.75, 28.47)	.409
Moderate activity (min.day^{-1})	33.17 (21.89)	65.77 (30.45)	-32.60 (-47.90, -17.30)	<.001*
Vigorous activity (min.day^{-1}) ‡	1.36 (5.01)	11.28 (21.82)		<.001†
Mod-to-vig activity (≥10 minute bouts) (min.day^{-1})‡	10.5 (25.31)	41.16 (47.07)		.001†

Data are displayed as mean (standard deviation) unless indicated otherwise. ‡ Variable not normally distributed, data presented as median (interquartile range). *Significant difference between cases and controls (independent t test). †Significant difference between cases and controls (Mann Whitney U-test). [a]n=49, [b]n=41, [c]n=49 Abbreviations: *kg* kilogram, *ISWT* incremental shuttle walk test, *min* minutes, *mod* moderate, *vig* vigorous, *C.I* confidence interval.

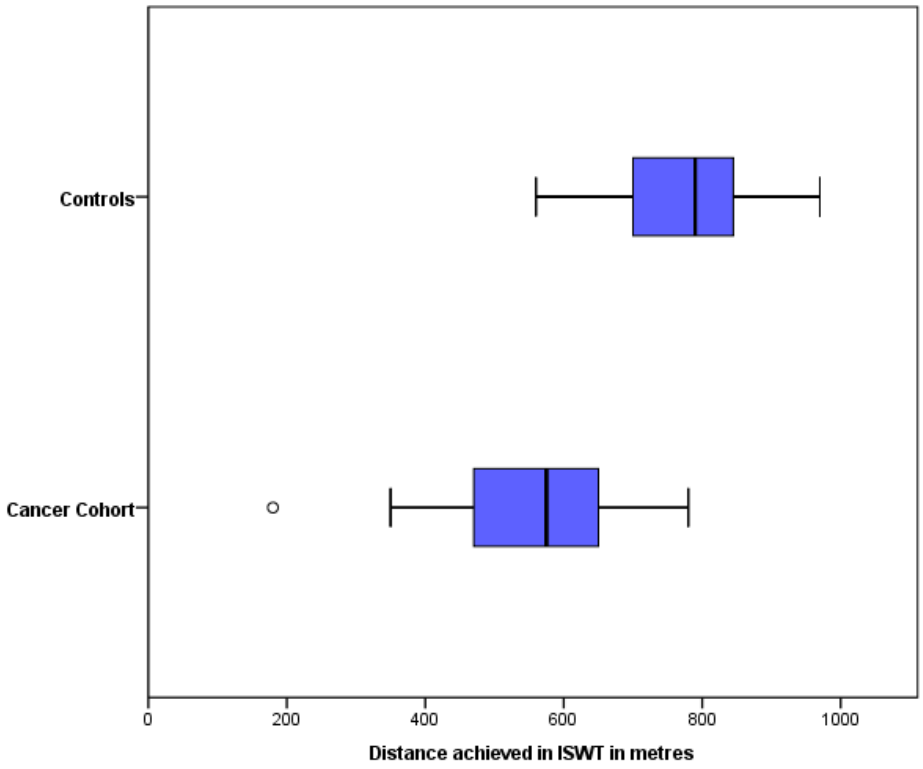

Figure 4.2 Distance achieved in the ISWT for cancer cohort and controls (represented as median and interquartile range)

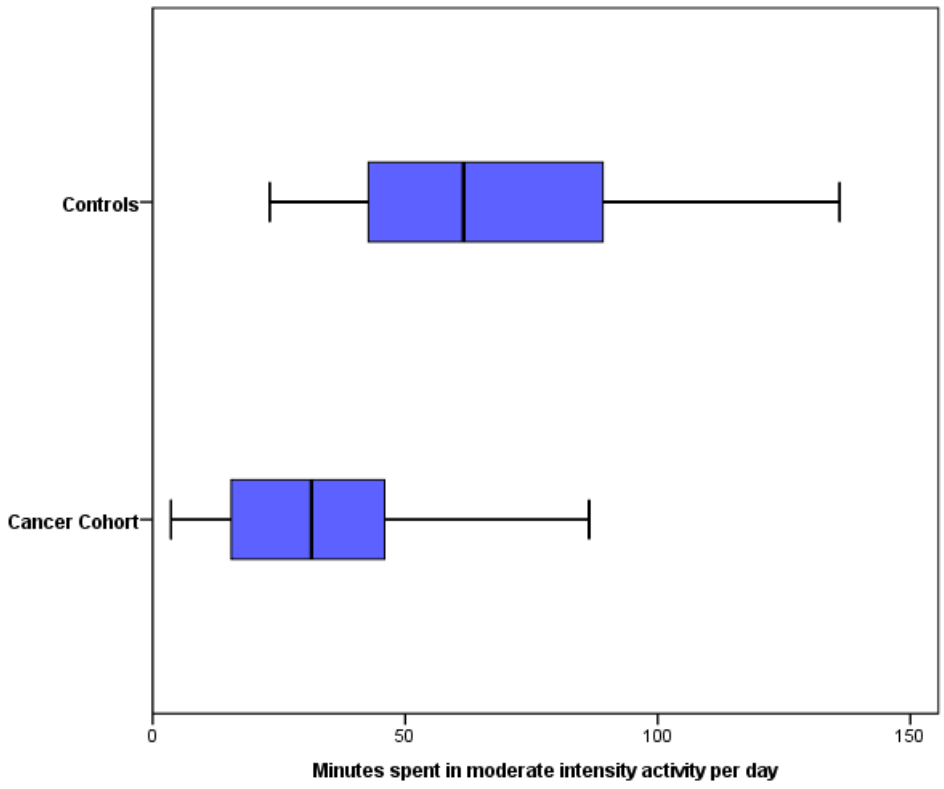

Figure 4.3 Time per day spent in moderate intensity activity for cancer cohort and controls (represented as median and interquartile range)

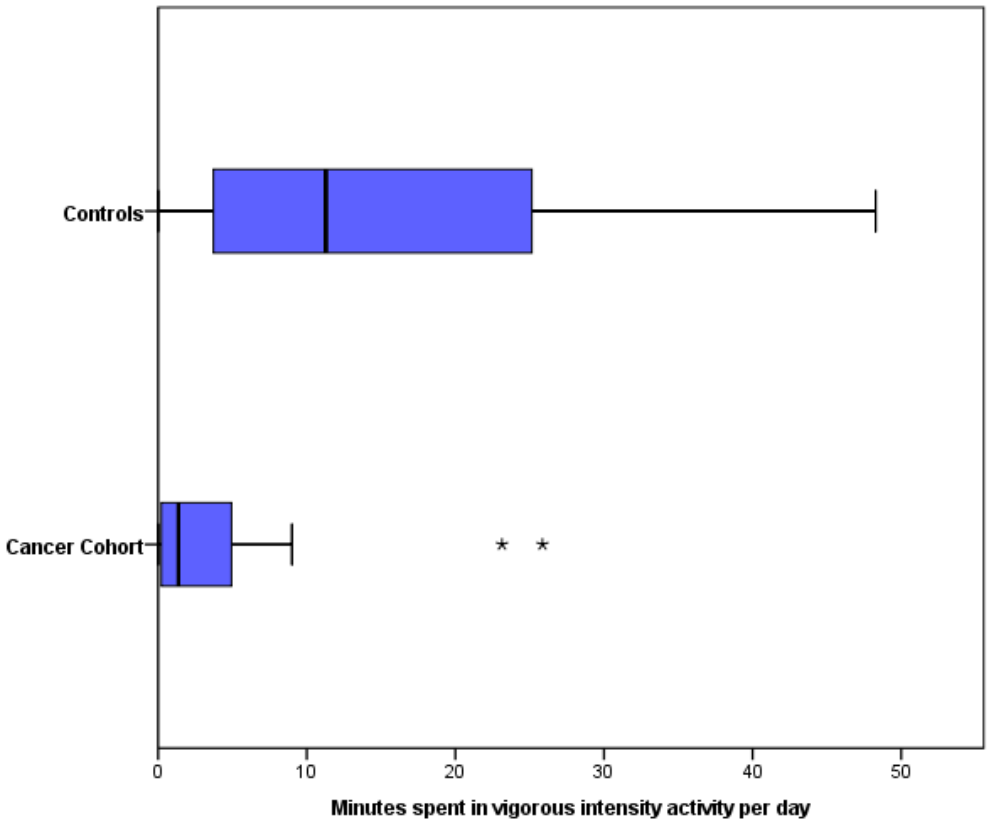

Figure 4.4 Time per day spent in vigorous intensity activity for cancer cohort and controls (represented as median and interquartile range)

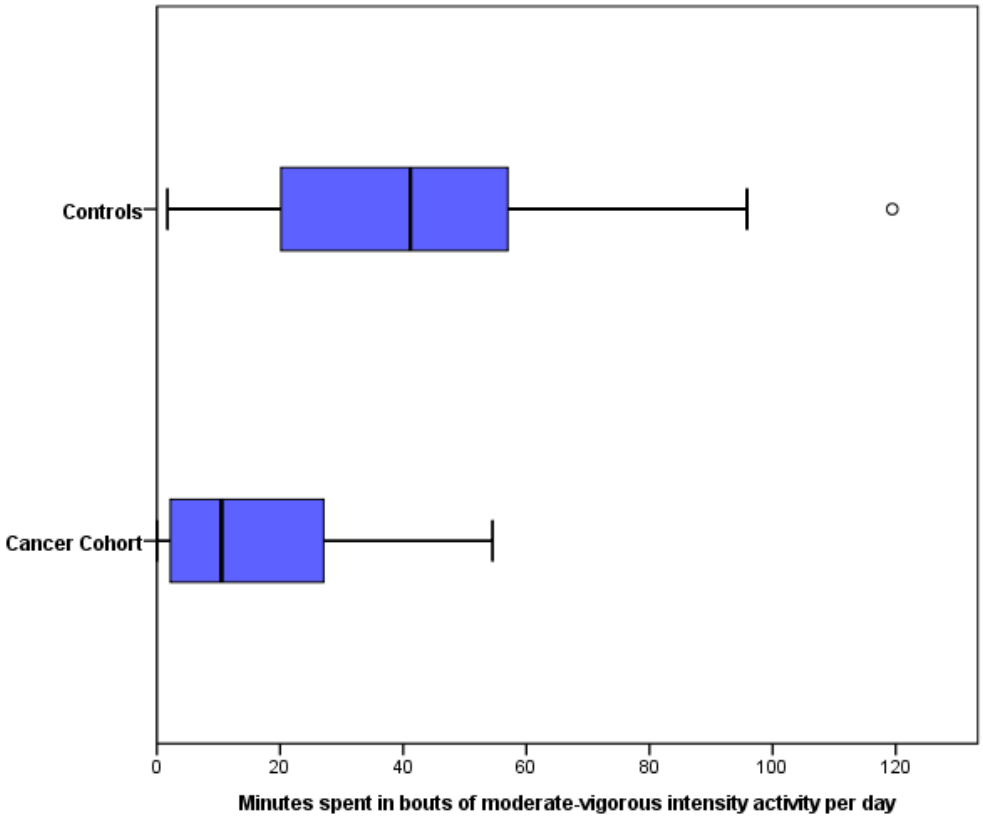

Figure 4.5 Time per day spent in bouts of moderate-vigorous intensity activity for cancer cohort and controls (represented as median and interquartile range)

4.4.2.4 Health related quality of life results

HRQOL data as measured by the EORTC-QLQ questionnaire are shown in Table 4.11. Global health status and QOL scored similarly in both groups (p=0.246), however physical (p<0.001) and role functioning (p=0.001) domains differed significantly between groups. There were also significant differences between the groups for the fatigue (p<0.001) and diarrhoea (p=0.001) symptom scales.

Table 4.11 HRQOL results in oesophageal cancer and control groups

	Cancer Cohort (n=25)	**Controls (n=25)**	**P value**
Global health status/QOL	75.67 (18.15)	82.00 (11.20)	.245
Functional Scales †			
Physical functioning	90.67 (9.81)	99.73 (1.33)	<.001*
Role functioning	90.67 (14.50)	100.00 (0.00)	.001*
Emotional functioning	85.00 (16.49)	89.33 (14.34)	.305
Cognitive functioning	90.00 (15.96)	94.00 (14.34)	.210
Social functioning	96.00 (9.95)	100.00 (0.00)	.039
Symptom Scales/items ‡			
Fatigue	20.44 (17.18)	4.00 (9.56)	<.001*
Nausea and vomiting	4.67 (10.23)	0.00 (0.00)	.020
Pain	7.33 (12.80)	3.33 (8.33)	.260
Dyspnoea	9.33 (18.05)	1.33 (6.67)	.042
Insomnia	10.67 (18.56)	8.00 (17.43)	.531
Appetite loss	10.67 (23.01)	0.00 (0.00)	.020
Constipation	4.00 (14.66)	0.00 (0.00)	.153
Diarrhoea	12.00 (16.33)	0.00 (0.00)	.001*
Financial difficulties	4.00 (11.05)	0.00 (0.00)	.077

Data are displayed as mean (standard deviation). *Significant difference between cases and controls (Mann Whitney U-test); means are given for informative purposes. †Scores range from 0 to 100; Higher scores represent higher levels of functioning or QOL. ‡Scores range from 0 to 100; Higher scores represent higher levels of symptoms or problems. Abbreviations: *QOL* quality of life

4.4.2.5 Anthropometric & body composition analysis

Results for body composition analysis including body weight, BMI, waist circumference and muscle mass were similar in both groups (Table 4.12).

Table 4.12 Anthropometric and body composition analysis results in oesophageal cancer and control groups

	Cancer Cohort (n=25)	Controls (n=25)	Mean Difference (95% C.I.)	P value
Weight (kg)	74.87 (13.55)	80.26 (9.86)	-5.38 (-12.13, 1.36)	.115
Height (cm)	174.68 (5.60)	175.99 (5.89)	-1.31 (-4.58, 1.96)	.423
BMI (kg/m²)	24.54 (4.33)	25.93 (3.01)	-1.39 (-3.51, 0.73)	.193
Body Fat (kg) ‡	15.15 (11.35)	17.85 (7.82)		.322
Body Fat (%)	19.36 (7.19)	19.87 (5.15)	-0.51 (-4.06, 3.05)	.775
Muscle Mass (kg)	56.57 (6.02)	60.73 (5.01)	-4.16 (-7.31, -1.01)	.011
Fat Free Mass (kg)‡	59.20 (10.38)	63.25 (6.72)		.035
Waist Circumference (cm)	89.25 (11.92)	90.80 (7.75)	-1.55 (-7.30, 4.20)	.590

Data are displayed as mean (standard deviation) unless indicated otherwise. ‡Variable not normally distributed, data presented as median (interquartile range). Abbreviations: *kg* kilogram, *cm* centimetre, *m* metre, *C.I.* confidence interval.

4.5 Discussion

While extensive subjective reporting of HRQOL attests to impaired physical functioning as a common consequence of treatment for oesophageal cancer, there is a lack of clinically meaningful published objective data to inform rehabilitation strategies in this complex cohort, particularly in the early years after completion of curative treatment. This study sought to assess the magnitude of the reported deficit in physical functioning through objective measurement and comparison with an age and sex matched control group and recorded a highly significant compromise in fitness and physical activity levels.

The results of the cross sectional study revealed suboptimal physical functioning in survivors of oesophageal cancer, in particular in relation to fitness and physical activity levels which were less than normative values and recommended guidelines. The cancer cohort were comparable to the control group in terms of time spent sedentary and engaged in light intensity activity, however they spent significantly less time engaged in moderate and vigorous intensity activity. As discussed in Section 2.3.3, these higher activity intensities are the foundations of the physical activity guidelines recommended for health benefits in cancer survivors. It has been well documented that survivors across a broad range of cancer types are inactive after diagnosis and into survivorship (Lynch et al., 2010a, Lynch et al., 2011, Loprinzi et al., 2013), however they may be no more inactive than the age matched general population (Broderick et

al., 2014b, Neil et al., 2014). The significantly lower physical activity levels observed in the cancer cohort as compared to controls in this study highlights the greater impact of more complex cancers on physical functioning.

This cancer cohort exhibited a relatively high overall HRQOL and minimal limitations in terms of cognitive and social functioning. When compared with controls however, the physical functioning domain was significantly lower for the cancer cohort. This result is consistent with previous literature which has demonstrated reduced physical functioning scores into longer term survivorship after oesophageal cancer (Scarpa et al., 2013, Hauser et al., 2014, Egberts et al., 2007). These findings also compliment the objective measurement of impaired physical functioning in this study. The mean difference between the cancer cohort and the controls was 9.06 points for physical functioning and 9.33 points for role functioning, just approaching the a difference of 10 points which is deemed clinically relevant (Osoba et al., 1998). Of note, overall health status and HRQOL were the same for both groups, suggesting that while these cancer survivors may be compromised in terms of their physical functioning this does not appear to affect their overall perception of their health and HRQOL. It has previously been shown that emotional functioning in oesophageal cancer survivors improves after curative treatment and into survivorship. This has been attributed to the fact that patients may feel depressed at diagnosis but over time become more confident and happier that they have been successfully treated (Lagergren et al., 2007). High global HRQOL scores may mask the underlying compromise in physical functioning in this cohort and lead to under-recognition by both healthcare professionals and survivors of oesophageal cancer of this issue.

In this study, current body composition measurements were relatively healthy in the cancer group and comparable to controls. This differs from other cancer cohorts such as breast cancer survivors who often present as overweight or obese in the months and years after treatment (Vance et al., 2011). While obesity is a risk factor for developing oesophageal cancer, these healthy body weight and BMI measurements may be due to the weight loss experienced during and after treatment. This weight loss was demonstrated in this group by the retrospective investigation into changes in body weight across the cancer continuum. Previous research has shown that during the first six months after surgery, nearly two-thirds of survivors of oesophageal cancer lost at least 10% of their preoperative BMI and 20% lost at least 20% (Martin et al., 2007). Furthermore, weight loss can be protracted after oesophagectomy and can continue up to three years post-operatively (Martin and Lagergren, 2009). This cohort exhibited a decrease in body weight and BMI at one, three and six months post-operatively with body weight continuing to be decreased up to three years post surgery.

In addition this group experienced loss of fat free mass during their treatment and over 30% of the total study cohort (n=11) were classified as sarcopenic prior to surgery. For the patients who underwent neo-adjuvant therapy the number of patients who were sarcopenic doubled from before to after this treatment. Sarcopenia is associated with reduced strength, physical performance and exercise capacity (Prado et al., 2008, Collins et al., 2014) and the evidence of sarcopenia during treatment in this group is a factor to consider in the context of the reduced physical functioning observed. While current strength measures were similar for both groups, the history of sarcopenia and weight loss suggests that survivors of oesophageal cancer may benefit from resistance training to build up muscle mass and strength.

4.5.1 Limitations

This study has a number of limitations which warrant discussion. The cross sectional nature of the study only allows an investigation into the differences between groups and therefore a cause-effect relationship cannot be determined between a cancer diagnosis and treatment and the reduced physical functioning observed. Due to the use of a field walking test, fitness levels were measured indirectly. This test however is clinically meaningful and is easily reproducible in a variety of settings and was deemed the most appropriate test for this study for the reasons outlined in Chapter 2.

Due to the use of a field walking test, fitness levels were measured indirectly. This test however is clinically meaningful and is easily reproducible in a variety of settings and was deemed the most appropriate test for this study for the reasons outlined in Chapter 2. Primarily the ISWT was chosen for this study as it is incremental and externally paced. This reduces the influence of participant motivation which may be different between cases and controls. There was however some limitations observed with the use of the ISWT in this clinical population. Some of the older and more deconditioned participants reported that keeping in synchrony with the beeps and turning at the cone every 10 metres was difficult at times. Therefore, when considering the appropriate field test for a clinical, older and potentially deconditioned population, such as cancer patients, it may be more appropriate to use an alternative field walking test such as the 6MWT. With the 6MWT, participants can pace the test themselves, do not need to keep in synchrony with external pacing and only need to turn around the cone every 30 metres. Therefore this test may be more feasible, acceptable and comfortable for these populations.

A further limitation of this study was that the participants in the case and control groups were matched by age and gender only. Matching the case and control groups by additional criteria such as educational attainment, deprivation index or ethnic group may have increased the comparability of the groups. By matching by age and gender only, the participants in the case and control groups in this study may have come from different socio-economic or educational backgrounds and this may have had an influence on their fitness and physical activity levels. Socio-economic status and educational attainment can be important determinants of health behaviour because they can influence people's attitudes, experiences, access to exercise facilities and exposure to several health risk factors. Those of a higher socio-economic status or educational attainment may be more likely to participate in research and be included in the control group. In contrast, lower socio-economic status is a risk factor for developing cancer, and therefore the cancer survivor group or cases may have included a higher percentage of those with a lower socio-economic status. Accordingly socio-economic status and educational attainment could potentially have been confounding factors in the results obtained in this study.

Finally, there is an unavoidable self selection bias associated with the inclusion of voluntary control participants and accordingly this group may have had a higher interest and engagement in exercise and activity than other members of the general population.

4.6 Conclusion

This study provides a comprehensive overview of the physical functioning and rehabilitative needs of oesophageal cancer survivors, information which has not been available previously, and with a case-control comparison cohort, and provides data that suggest that a comprehensive multidisciplinary rehabilitation programme consisting of resistance training, aerobic exercise and an increase in habitual physical activity levels may be a promising intervention to improve physical performance and HRQOL in survivorship.

Chapter 5 Study 2: Patient perspectives on functional recovery and physical activity following oesophagectomy

5.1 Introduction

The results of Study 1 demonstrated suboptimal physical functioning in survivors of oesophageal cancer with significant compromise observed in fitness and physical activity levels. In addition, informal discussion with this cohort revealed a number of ongoing concerns and issues which were potential barriers to participation in physical activity and optimal functional recovery. Areas highlighted included concerns regarding weight loss associated with increased physical activity, a lack of knowledge regarding recommended physical activity levels and a reluctance to exercise at a moderate or high intensity. This preliminary qualitative fieldwork with this group highlighted the need for a more formal approach to investigate these concerns. Qualitative information in this cohort complements the quantitative data already gathered to provide a more in-depth and contextualised understanding of the patient experience and patient needs.

This study aimed to further explore the potential reasons for the suboptimal physical functioning observed; whether it was prevalent throughout the lifetime of this group or whether it was as a result of the complex and demanding treatment which they received. This study also aimed to address participants' perception of their own physical functioning and the importance they placed on it. Finally, as it has been suggested that rehabilitation may be a promising intervention to improve physical performance and HRQOL in this group, this study was an opportunity to examine patient preferences for interventional programmes of this nature.

5.2 Study aims and objectives

The overall aim of this study was to describe the experiences of treatment and recovery for survivors of oesophageal cancer, in particular in relation to the impact of treatment on exercise and physical activity levels into survivorship. The specific objectives of the study were:

- To describe the effect of a cancer diagnosis and its treatment on participants' general

health and physical activity levels.

- To explore participants' knowledge of physical activity guidelines and perceptions about their own level of physical activity.
- To identify potential barriers and facilitators to recommended physical activity levels and exercise.
- To obtain participants' views on the development of rehabilitation programmes for patients with oesophageal cancer.

5.3 Methods and measures

5.3.1 Study design

As discussed in Chapter 3 (Section 3.2 & Section 3.3), a qualitative descriptive study design was used in this study and individual semi structured interviews with open ended questions were carried out.

5.3.2 Sampling and recruitment

As described in Section 3.4, combination purposive sampling consisting of criterion and maximum variation sampling was used in this study. Eligible participants were disease free survivors of curative treatment including surgery for oesophageal cancer. Maximum variation sampling was used with regards to years post surgery (one - five years), age (50's, 60's and 70's), treatment type (multimodal and surgery only) and surgery type (transthoracic and transhiatal). As the aim of this study was to get a broad overview of the experience of oesophageal cancer recovery and survivorship, participants were only included if they were at least one year post completion of treatment. Recovery after oesophageal cancer surgery can be prolonged and therefore completing interviews closer to treatment may have resulted in the focus being on more acute and specific problems and concerns.

The sampling criteria were set out, as described above, and all participants who completed Study 1 were considered for inclusion. Therefore all participants who took part in Study 2 also participated in Study 1. This enabled some triangulation of the data gathered from both studies. Eligibility was confirmed for each participant prior to invitation to participate by ensuring that they were currently disease free. This was done through contact with the medical team, the oesophageal cancer database manager and/or medical chart review. Eligible

participants were contacted by telephone to inform them that the study was being undertaken and to ascertain whether they would be willing to receive more detailed information by post about what participation involved. If agreeable, participants were sent a letter and participant information leaflet detailing the aims and requirements of the study (Appendix XIII). Participants were contacted again by telephone one week later to establish their interest in participation. When the potential participants agreed to take part, they were given the option of completing the interview in person or over the phone and asked to nominate the day and time that best suited them. Participants were contacted in groups of three to four and invited to take part.

5.3.3 Interview schedule

The development of the interview schedule involved (1) reviewing the initial fieldwork with participants in Study 1, (2) examining the literature on qualitative descriptive research in general and in an oesophageal cancer population and (3) referring to the study objectives listed in section 5.2. As discussed in section 3.3, questions were designed to be simple, open-ended and flexible. Additional questions designed to probe for more depth were included in the schedule, to be used if deemed necessary. The interview schedule is contained in Appendix XIV.

5.3.4 Ethical approval

Ethical approval was granted by the SJH/AMNCH research ethics committee and all participants provided written, informed consent (Appendix XIII & Appendix XII).

5.3.5 Data analysis

Data analysis of the interview transcripts was carried out as described in Section 3.7.

5.4 Results

5.4.1 Participant selection and identification of saturation

Twenty five potential participants were selected from the oesophageal cancer database and assessed for eligibility. Of these, three were unsuitable to contact due to cancer recurrence

(n=2) or hospitalisation with another medical condition (n=1). Twenty two potential participants were contacted and invited to take part in the study and of these, 16 completed an interview. Six patients did not participate; three were not interested and three were unable due to other medical conditions at time of invitation to the study. The flow diagram of the study recruitment is detailed below (Figure 5.1). Recruitment took place between March 2014 and March 2015. As described in Section 3.5, recruitment was ongoing until data saturation was reached. It was clear from the analysis of the 14th - 16th interviews that no new information, perspectives or themes were emerging from the data and therefore recruitment was stopped at 16 participants.

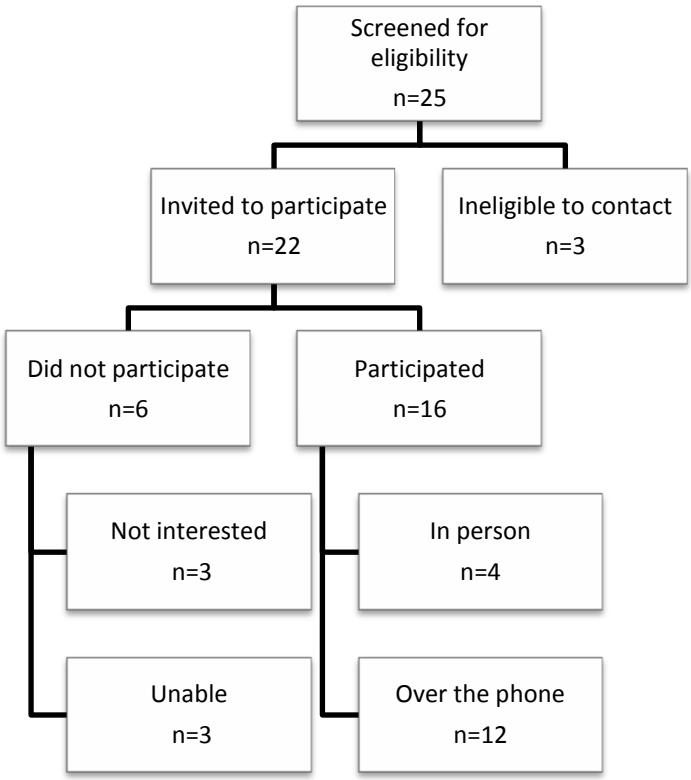

Figure 5.1 Recruitment of study participants

5.4.2 Participant characteristics

Sixteen participants (14 men) with an average age of 63 years completed an individual semi-structured interview with the lead investigator (JG). Participant characteristics and interview details are presented in Table 5.1. Four face-to-face interviews took place and 12 interviews were carried out over the phone. Two participants completed a face-to-face interview with

their spouse. All other interviews were completed independently. The average time since surgery was 36 months with a range of 13-54 months. Nine participants had completed multimodal treatment, while seven were treated with surgery only. Forty-four per cent of participants experienced post-operative complications according to records maintained in the SJH institutional database. The average interview duration was 18 minutes with a range from 12 - 26 minutes. Over 50,000 words of original content was transcribed.

Table 5.1 Participant characteristics and interview details

Participant ID	Gender	Age	Treatment Type	Surgery Type	Post-operative complications	Time since surgery (months)	Interview Type	People present	Interview Duration (minutes)
QP01	Male	62	Multimodal	Transthoracic	No	18	Face-to-face	Participant only	12
QP02	Male	72	Multimodal	Transthoracic	No	13	Face-to-face	Participant & wife	16
QP03	Male	59	Multimodal	Transthoracic	No	36	Face-to-face	Participant only	12
QP04	Female	67	Surgery only	Transthoracic	No	38	Telephone	Participant only	19
QP05	Male	55	Surgery only	Transthoracic	Yes	33	Telephone	Participant only	17
QP06	Male	62	Surgery only	Transthoracic	Yes	51	Telephone	Participant only	24
QP07	Male	64	Surgery only	Transhiatal	Yes	20	Telephone	Participant only	17
QP08	Male	56	Surgery only	Transhiatal	No	46	Telephone	Participant only	13
QP09	Male	69	Multimodal	Transthoracic	No	37	Face-to-face	Participant & wife	15
QP10	Male	62	Multimodal	Transthoracic	No	37	Telephone	Participant only	13
QP11	Male	66	Multimodal	Transthoracic	No	32	Telephone	Participant only	15
QP12	Male	63	Multimodal	Transthoracic	Yes	43	Telephone	Participant only	18
QP13	Female	70	Multimodal	Transthoracic	Yes	47	Telephone	Participant only	26
QP14	Male	59	Multimodal	Transthoracic	No	33	Telephone	Participant only	24
QP15	Male	71	Surgery only	Transhiatal	Yes	38	Telephone	Participant only	22
QP16	Male	57	Surgery only	Transthoracic	Yes	54	Telephone	Participant only	26

5.4.3 Inter-rater and intra-rater reliability

Section 3.7.3 outlines the method used to examine the reliability of the coding and the formula used to calculate the inter-rater and intra-rater reliability. The results are presented in Table 5.2 and Table 5.3. Most discrepancies were errors of omission, where one or the other coder overlooked text that could be coded. All disagreements that were not an error of omission were resolved through discussion.

$$\frac{\text{Number of agreements} \times 100}{\text{Total number of agreement + disagreements}}$$

$$= \frac{204 \times 100}{204 + 78}$$

$$= 72\%$$

Table 5.2 Inter-rater reliability of the coding system (Miles & Huberman, 1994)

$$\frac{\text{Number of agreements} \times 100}{\text{Total number of agreement + disagreements}}$$

$$= \frac{246 \times 100}{246 + 266}$$

$$= 94\%$$

Table 5.3 Intra-rater reliability of the coding system (Miles & Huberman, 1994)

It is common to expect that inter-rater reliability be ≥70%, while intra-reliability would be expected to be ≥80% (Miles and Huberman, 1994). The results obtained demonstrate the reliability, both inter-rater and intra-rater, of the coding system.

5.4.4 Themes and sub-themes

Three primary themes and a number of sub themes were identified from the analysis of the interview transcripts. These themes and sub-themes are presented in Table 5.4

Table 5.4 Themes and sub-themes generated through interview analysis

Themes	1. Living with and beyond oesophageal cancer	2. Physical activity and exercise in oesophageal cancer survivorship	3. The role of rehabilitation in oesophageal cancer survivorship
Sub-themes	• Recovery • Physical changes • Lifestyle changes • Emotional journey	• Current activity levels • Barriers to exercise • Facilitators to exercise • Exercise knowledge & understanding	• Interest in rehabilitation • Benefits of rehabilitation • Structure of rehabilitation

5.4.4.1 Theme 1: Living with and beyond oesophageal cancer

The first theme identified in the data was 'living with and beyond oesophageal cancer'. This theme describes the impact oesophageal cancer had on participants' lives. Within this theme, four subthemes emerged which dealt particularly with overall recovery, physical changes, lifestyle changes and the emotional journey associated with a diagnosis of and treatment for oesophageal cancer.

Recovery

This cohort of disease free survivors, ranging from one to five years post surgery, discussed the concept of feeling 'back to normal' after treatment for oesophageal cancer with varied responses. Some participants did describe feeling back to normal at the time of interview. Others felt that they had not returned to normal, while some described the feeling of a 'new normal'.

"Oh yea I'm very much back to normal yea." [QP14]

"It's a different normal" [QP13]

"Well I certainly wouldn't be back to normal now. But pretty good." [QP11]

"Far from back to normal." [QP02]

Participants described a prolonged recovery period with frequent reports of it taking at least one to three years to feel back to normal.

"I'd say three years after my surgery I started to feel that like. It was a long aul haul you know." [QP06]

"It takes a good bit of time to get back to normal, or near enough anyway, there's a lot of time that is involved you know... I'd say you're talking the guts of two years." [QP10]

"Well I would put it down to two years now." [QP13]

"I'd say I was about a year and a half or that before I kind of more or less got going like what I am." [QP16]

The first few weeks and months after discharge from hospital were described as particularly difficult with participants feeling unwell, fatigued, drained, having difficulty with eating and being generally unable to participate in many activities of daily living.

"For a long time I sat in the corner here in the chair and I wasn't able to eat or do activities." [QP13]

For some, this prolonged recovery was unexpected and they had not realised how sick they would be. Factors that participants felt had helped in their recovery were discussed and included an early diagnosis, not receiving chemotherapy or radiotherapy and having no complications post discharge. Others spoke of the importance of spousal support in their recovery, while some felt recovery would be harder on a younger or an older person. A

number of participants spoke about the role of the inpatient physiotherapy in terms of expediting their physical recovery and helping them to mobilise in the initial postoperative days.

> *"The good physios that were there in the hospital... but you know they have to force you out, if they don't you just take the easy way out and don't get the exercise and I think that's the same for any operation in any hospital visit that, you know, they are not leaving you sitting in the bed, which is good." [QP15]*

Physical changes

A primary focus of this research was on the physical sequelae of oesophageal cancer treatment. Participants described changes in their physical functioning that they were aware of since their diagnosis and treatment. This included noticeable decreases in stamina, strength and fitness levels. Some participants felt they had not regained the strength and fitness levels which they would have had pre-diagnosis.

> *"I still don't feel I'm back to full fitness either." [QP03]*
>
> *"Well my fitness isn't very.. I'm not feeling very strong if you know what I mean. I don't have the same strength at all." [QP07]*
>
> *"There's a lap here around I used to always walk it before I had my surgery or anything was wrong with me, it's a 6 mile walk, I used to do it most days...But I wouldn't do it now.. I'd go down to the end of the road for a handy walk there, probably about 2 miles." [QP10]*
>
> *"It is just a feeling that I am limited in stamina terms." [QP01]*
>
> *"I certainly get tired where I wouldn't before." [QP13]*
>
> *"Yes definitely slowed down.. like before I could go do something all day but now if I got about 2 or 3 hours out of something I'd be doing well I'd feel." [QP16]*
>
> *"Ah I wouldn't have the same strength in the arm or anything like that." [QP16]*

"I'd say I probably lost about 30% of my strength." [QP02]

"Stairs are really hard going so I feel sorry for people who live in 2 storey houses and have to go upstairs." [QP13]

In addition to these more general losses in physical functioning, a number of participants referred to specific physical changes or treatment side effects which they had either experienced over the course of treatment or were still lingering into survivorship. These included side effects commonly associated with cancer treatments such as pain at surgical incision sites, musculoskeletal or sensory issues and radiation pneumonitis. Side effects perhaps more specifically associated with oesophageal cancer were also described and included voice changes, reflux and feeling particularly drained after eating or bowel movements. Table 5.5 contains quotes which illustrate these specific side effects.

Table 5.5 Specific physical changes or treatment side effects

Pain	"Maybe say in the garden... If you done a lot of say heavy shovelling or something like that your side would get sore, there where I had the surgery." [QP10]
Musculoskeletal or sensory problems	"My right shoulder socket for about three months after, the pain was unbelievable. It's because, I believe you're in surgery for four to six to eight hours, and your right arm is up in the air in that position" [QP14] "After the chemotherapy I had a numbness in my left leg for at least three or four months." [QP14]
Voice Changes	"I find since the operation that when...I over-exert it's not that I'd be tired but my voice goes...and the hearing would be weird.. Or when I get cold, going to a night game now, a football game at night... and the voice goes." [QP03] "I go hoarse as you hear... that happens me, I could be talking and then I just go hoarse... but the voice comes back so I don't know if it's related or not." [QP13]
Reflux	"I used to do yoga...and I done that for two years but I discovered I was getting my old problem with acid back anytime I lay down on the floor. I had to be upright most of the time... I couldn't lie down flat 'cos I used to get this acid coming back so I had to stop the yoga." [QP06] "At night time when you'd be lying, I can't sleep on my left side because the food will repeat on ya." [QP10]

	"But I wake up naturally with the...indigestion and the stomach and that.. And I find now I'm able to bend over a bit longer now.. At first when I'd bend over, I couldn't bend over.. say doing a bit of weeding or something out in the garden, pulling up the weeds, if I done two or three, but at least now I could bend over for a little bit longer anyway and I'm not as bad..If I stay down it would start coming up on me, if you know what I mean.. Before it used to come up on me as soon as you bend over at all.. but I still sleep in the bed with a couple of pillows, I still keep on under my shoulder blades and keep up that way anyway." [QP16]
Other	"One thing that has happened to me since the surgery and the treatment... my nose runs an awful lot, I'm forever blowing my nose! (laughs) and if I go out for a walk I have to bring a packet of tissues with me." [QP14] "I was coughing for a couple of months after the surgery as well but [the surgeon] told me that's just irritation from the radiation therapy." [QP14] "For perhaps a half an hour after a heavy meal or sometimes for 20 minutes or half an hour after moving bowels I can feel quite drained and tired and I just need to rest for those periods." [QP01]

As would be expected in an oesophageal cancer population, a number of participants reported experiencing noticeable changes in their body composition during their treatment and recovery. The loss of a significant amount of weight e.g. 12-15 kilos, at some point during the cancer continuum was frequently reported. However at the time of interview, the majority reported that their weight had stabilised, often at a lower weight than pre-diagnosis.

"Well I certainly have dropped about 15 kilos from what was my max." [QP01]

"I would have lost maybe two stone or the best part of it since the operation and I haven't put any weight on." [QP07]

"Well I'm grand now. I'm staying around the 12 stone mark, a little beyond it, it's grand." [QP10]

"I think I'm roughly the same weight now for the last two years or so." [QP14]

Weight loss was associated with both positive and negative connotations. It was described as being a source of worry over the course of treatment and particularly in the early recovery

phase and for some remained a concern at the time of interview. On the other hand, some saw their weight loss as a positive and were happier with their current weight than what it had been pre-diagnosis. As a result, participants reported now being at a healthier and more appropriate weight for their height, being able to exercise more easily and having less back pain and joint pain.

> *"The eating now is improving but I'm not putting on the fecking weight." [QP02]*
>
> *"Before I had the surgery and all that I probably was a couple of stone heavier and I feel a lot better that I lost that." [QP10]*
>
> *"I think I went from about 13 stone to about nine and a half. I'm back now to about 11 stone or something. Which I think is plenty for my height you know." [QP11]*
>
> *"It's gone back up... to my right weight because I think I was too heavy originally anyway." [QP11]*
>
> *"I'm four stone less than I... my stomach isn't as big as it was... which is no harm... So in terms of exercise you know... there are pluses and minuses... one of the pluses is that because I lost four stone my knee doesn't hurt as much as it used to now when I go walk because I'm carrying less weight." [QP15]*
>
> *"And the back used to give me an awful lot of problems before but thanks be to God, touch wood, the back hasn't come to get me now for a while... I had an operation and all done on the back before but I suppose with all the weight and all on, there's a heavy strain on it that way... So if I have the weight off it seems to be better on the back that way." [QP16]*

Lifestyle changes

In addition to specific physical changes, participants also described changes to their lifestyle which had occurred since completing their cancer treatment. While participants reported that they had no particular restrictions or limitations with regards to completing any activities, a slightly more 'restrictive' lifestyle was described which involved a general slowing down and more planning and pacing of activities.

"The lifestyle would be slightly more restrictive." [QP05]

"I'll think about travel in terms of minimising... any excessive hardship... I don't feel that I'm unduly constrained, it's just that I'll plan it a bit more so that there isn't anything really hugely physical involved in transferring from one thing to another." [QP01]

"No no I try everything and I do as best I can. But it takes me longer to do the same things if you know what I'm saying." [QP07]

"I can really do most things at a slower pace." [QP13]

"Yes definitely slowed down." [QP16]

Participants described needing to take a rest or a nap every afternoon due to continued feelings of fatigue.

"I try and take a rest every afternoon and I find if I don't then I'm very tired by 8 o'clock at night." [QP04]

"I come home and just for example today now, I was absolutely shattered, my body just feels like.. I don't know how to describe it...it's like a heavy feeling of fatigue and it's just...you don't feel unwell or anything but you feel certainly the need to lie down for say an hour and a half, it's like a battery or something and that's ongoing and there's no let up on that side of it." [QP05]

"Now I take a rest every afternoon for an hour and I'm still doing that. I'd rest from 2 to 3 most days." [QP06]

"I just have, I reckon I get about an hour of fatigue during the middle of the day, a tiredness...Each day varies, some days I don't have to, and sometimes I do lie down, I wouldn't actually go asleep but I'd just put my head now for half an hour it's a great help and I can get back up then." [QP14]

Significant occupational changes which had occurred since cancer treatment included needing an apprentice, changing from full time to part time or retiring.

"Since I've had the op, I've had a lad with me, an apprentice like, a young lad... and he has the strength where I'm afraid to over exert the upper body just in case... and they know that in there so they have him with me for that reason." [QP03]

"In relation to work and I spoke to [the surgeon] about this...he was happy enough for me to continue in the part time... and for me that's plenty because I'm finding..my job involves standing, I'm not sitting at all... standing all day so...I would find I finish work at 3 in the afternoon, I come home and just for example today now, I was absolutely shattered." [QP05]

"I just do a few days [working] now, I don't think I'd like the whole week of it now you know...like 6 days of the week now I wouldn't like it back but 2 or 3 days I find grand." [QP11]

"I could have went back to work as well but it's just... this touch of fatigueness.. my chief medical officer... he was borderline over it and he said maybe it's best that you don't." [QP14]

The major changes to the gastrointestinal system which occur with oesophagectomy lead to changes in eating and dietary habits for survivors of oesophageal cancer. While this was not the focus of this study, food and eating changes were mentioned frequently and were described as a significant lifestyle change for participants. Many participants described struggling with a poor appetite and having problems as a result of overeating, particularly in the early stages of recovery. At the time of interview however, most described their eating habits as stable or almost returned to normal as a result of finding alternative eating habits which were more suitable e.g. eating smaller amounts more frequently and avoiding certain foods. Of note and particularly relevant to the focus of this study was the description of needing to rest after eating or not being able to exercise for an hour or more after eating.

"It's only he'd eat less and more often... that'd be the biggest difference. It wouldn't be a problem now, it's just different." [QP09Wife]

"The only thing is the eating like, eating small amounts... smaller amounts... and organising to do it, have the eating done let's say an hour or an hour and a half before I go cycling or do anything like that. That's really the only change." [QP08]

"I still have the odd bit of tiredness... well the only time that I have tiredness now is when I eat... say after eating my dinner, say maybe about 10 minutes after eating I'd feel like lying down and resting." [QP10]

Emotional journey

While the interviews were focused on the physical rather than the emotional recovery after oesophageal cancer treatment, participants did discuss their emotional journey. Some described feelings of anxiety and depression, particularly in the initial time period after completing treatment.

"I'd say I did suffer a bit from depression... Because there were a lot of bad days now. Even though the operation went great. But there were terrible days. The 6 months immediately after the operation, terrible... The cold and everything. And trying to eat. And trying to manage." [QP02]

However the prevailing outlook at time of interview was a positive one. Participants felt lucky, were very happy with their progress and reported doing very well. Some said they had almost forgotten they had had cancer at all.

"I really feel I've done awfully well... I really feel very fortunate." [QP04]

"Yea well as I say I seem to have been lucky.. since then now things have gone very well anyway, health wise anyway." [QP12]

"Ah sure when I had the diagnosis sure I kinda went downhill thinking about it even and eh as it is now sure jeez I'm in great form... Yea I'm feeling good I have to say, you know I've never been as happy now to be honest with ya, especially when you get all the news that I had. Because I was a bit down for a long time and I was struggling to get better. I persevered anyway." [QP06]

"Oh I'm grand now, not a bother at all now.. it's grand." [QP09]

"Sometimes I do think back and say did that really happen you know." [QP14]

"Well the time does pass and you tend to forget about it." [QP15]

5.4.4.2 Theme 2: Physical activity and exercise in oesophageal cancer survivorship

The second theme to emerge from the data was 'physical activity and exercise in oesophageal cancer survivorship'. The major subthemes were: participants' current levels of activity, any barriers or facilitators to increased exercise and optimal activity levels and participants' knowledge and understanding about exercise and activity.

Current activity levels

At the time of interview most participants described themselves as an 'active person' and the majority reported having no particular limitations or restrictions in terms of exercise and activity. Some described their current exercise habits e.g. walking for two or three miles or for 30 – 40 minutes on some or all days of the week. Walking was the most common type of exercise reported. Some reported that their activity levels were the same as pre-diagnosis, while others reported that they had changed. Mostly this change was a reduction in activity levels but one participant did report an increase compared to pre-diagnosis. For those who did report an activity limitation, it was mainly in relation to not feeling able to exercise at a high intensity e.g. they would 'walk but not run' or a there was a reduction in the amount they could lift as a result of reduced strength.

"I'm very conscious since I've stopped working that I don't sit around all day you know. I'm up and I'm doing stuff." [QP14]

"I can do most of the things I want to do." [QP01]

"Generally I would argue that I can do as much now as I did before it." [QP15]

"Exercise and walking and that... is still the same you know." [QP12]

"And I did a lot of walking and played a bit of golf. Not to the same standards." [QP02]

"I can't run but I definitely can walk." [QP06]

"I might go for a walk alright but... it wouldn't be a fast walk or anything it would just be a steady walk... an easy walk." [QP07]

"I won't jog it, I just walk fast." [QP15]

Barriers to exercise

While some participants reported having no barriers to exercise and optimal activity levels others did describe some barriers which they were currently experiencing. While some of the barriers reported were specifically related to having had cancer, others were not and could be considered common barriers to exercise in any population. Barriers which related to having a history of cancer included participants having a fear or reluctance to 'push themselves' or to exercise at a moderate or high intensity. This fear generally resulted from a lack of knowledge about the safety of exercise after cancer treatment and what activities would or would not be recommended. Other cancer specific barriers were reduced food intake and concern regarding weight loss. Participants perceived the reduced food intake as a lack of 'fuel' and thus a reason for their reduced energy and activity levels. Similarly, some participants described a reluctance to exercise in case it created a negative energy balance and resulted in further weight loss which they did not want. Physical side effects such as irregular bowel movements restricted one participant's ability to exercise freely, away from a toilet. Finally, the reduced fitness and stamina levels reported into survivorship were highlighted as a barrier to exercise. More general barriers to exercise included: ageing, a lack of interest, 'laziness' and the weather. Quotes to illustrate each of these barriers are detailed in Table 5.6.

Table 5.6 General and disease specific barriers to exercise

Fear or reluctance to 'push themselves'	*"Are you supposed to [exercise] or not you know what I mean? I don't because I would be half afraid." [QP03]* *"You know sometimes I want to push myself and do a bit more but then I'll say no." [QP05]* *"I mean I was half afraid for a good while after I came back, well my wife was worse than me... you know 'don't lift that, don't bring in the turf from the garage'... you know what you can and cannot do... until somebody explained to me.. I think it was [the surgeon] you know, if you feel you can do it, do it." [QP15]*
Reduced food intake	*"I don't have the same strength at all but I put that down to that I'm not taking in enough of fuel as they say, you know 'cos I'm not eating near as much as I used to." [QP07]* *"When you're only eating half, it's kinda like a car on half fuel you won't go as far as you used to! (laughs) that the way that I look at it." [QP16]*
Weight loss	*"I thought I was doing a little too much maybe, starting off. And I restricted myself, I sort of cut down on my activity. I had to cut down because I was losing weight. The little bit of weight that I was trying to get on sure I was walking too far you know." [QP06]* *JG: "Do you think that increased activity and exercise would benefit you?" "Well I don't know if it would or not like you know because I'm not carrying any weight or anything... you know I'm only just, I'm less weight than I was like.. I'd be lighter now and I wouldn't want to lose any more I don't think." [QP07]*
Physical side effects	*"When I was walking a bit you were afraid to go anywhere, walking up and down the road, I knew I had neighbours that would let me in to go to the toilet but you wouldn't want to be calling to anyone.. you know what I mean, you had them kind of discomforts when you were going anywhere." [QP16]*

Reduced stamina	*"Secondly, the belief that actually my stamina levels wouldn't allow me to do as much as I would have done previously." [QP01]* *"If I do too much one day then the next day I'm just plonked. I really just take the day off." [QP04}* *"I don't have the energy I don't think for doing much exercise.. I don't have the energy I find is the biggest thing. After you do a bit of work during the day you're tired in the evening." [QP07]*
Ageing	*"Yes you do get out of the exercise and just as you get a bit older." [QP04]* *"I'm as strong as I'm going to be at my age now, you know I mean I'm not working so I don't have to.. when I was working it was all lifting, everything was heavy lifting where I was.. but now that's all done so it's only natural that I probably slow down that little bit and but a bit of weight on, it doesn't do me any harm you know." [QP06]* *"I don't think I'd ever be...well I'm not young I'm 66 now.. I'd never be in the nick I was in but I'm as good as I can get myself I'd say." [QP11]* *"Well you see it's hard to segregate out what's arising from the operation or from ageing because I'm heading for 73 now...But I often have aches and pains and I say now is that just a result of ageing." [QP15]*
Lack of interest	*"I just...I find it very hard just to walk for no reason." [QP04]*
'Laziness'	*"Well I think the two things that would hold me back are one, laziness which I think I have to a degree." [QP01]*
Weather	*"The weather is huge though...the rain this winter was just appalling, you couldn't get outside the door. And if you went out you came home with a cold." [QP02Wife]* *"Because the weather is so volatile...sometimes you can't go out for a walk." [QP15]* *"You know if the weather is good I would do a fair bit of walking especially in the summer time you know. I would definitely...in the winter time maybe not." [QP12]*

Facilitators to exercise

Facilitators to returning to exercise and activity after oesophageal cancer treatment were described. Participants spoke about the importance of having a positive attitude and a determination to get back to exercise. A feeling of restlessness was described where participants would have been frustrated if they had not returned to normal activity and exercise. Wanting to 'get out of the armchair', 'get moving', and 'get back to normal' were all mentioned as important motivations to exercise. Having been active throughout their lives was also important as participants wanted to return to their pre diagnosis exercise levels. Goal setting such as walking longer distances or returning to a specific hobby such as boxing or handball were also mentioned as exercise incentives. The importance of building activity up slowly was discussed as participants felt that this was the best way to safely and feasibly return to habitual exercise levels. The establishment of normal eating habits was also considered a very important facilitator to returning to exercise. Participants felt that once they were eating better, they felt better in general and increased energy and activity levels resulted. When eating was a problem, exercise was not a priority. Quotes to illustrate facilitators to the return to exercise are detailed in Table 5.7.

Table 5.7 Facilitators to the return to exercise and physical activity after treatment for oesophageal cancer

Attitude	*"[the surgeon] asked me well why do you think you got better quicker and I said well good treatment, positive attitude and getting up and doing things." [QP01]* *"But then he'd be determined to do it, he'd have a great attitude to keep out and about." [QP09Wife]*
'Get moving'/get back to normal	*"I was lazy as well when I went home for the first few weeks until I sorta shook myself up and said right you can't be sitting in the arm chair for the rest of your life." [QP12]* *"Actually just getting out, not lying down or not sitting down was a positive thing for me to do in terms of recovery... Although I don't do a huge amount I think I'd probably be quite restless and maybe even depressed if I wasn't going and doing things." [QP01]* *"I would get very frustrated if I can't get out and about. The winter now I find.. I even thought of maybe joining a gym in the winter.. If you get wet days you really do get... I mean I'm ready for the loony bin!" [QP04]*

Active throughout life	*"I've always been one for exercise anyway before I was diagnosed." [QP05]* *"I'm happy to be doing that because when I wasn't able to [exercise], I missed it terribly. I missed the time in the gym and I was very conscious of getting back to that and getting back into my routine." [QP05]* *"You see I always walked you know and it was hard to.. I was mad to get back doing it." [QP10}*
Goal setting	*"For myself I can tell ya, my aim was to get down and walk down in the forest, about 7 miles from home here." [QP06]* *"I'd like now if I could maybe do another bit you know, extend the bit that I'm doing sometimes... maybe later on now when the summer comes this year I might go and get on another half mile or something like that you know." [QP10]*
Build up slowly	*"Well its 3 years since he had his operation now and he has built up now over the couple of years." [QP09Wife]* *"I'd go out and I'd walk 50 yards or 100 yards and gradually, day by day, made it a little bit longer..now it was slow walking but I operate on the principle as often as I feel like." [QP15]*
Eating properly	*"Once I started eating properly.. I was getting out for the walks then and all that kind of thing". [QP11]* *"So generally it's the food and that I think is one of the main things...once that's working everything else kind of follows on then after that...you feel better in general so you feel like doing more." [QP16]*

Other facilitators to exercise in general reported were: making exercise a habit, the use of exercise equipment, good weather, walking the dogs, parking far away and having somewhere to go. Quotes to illustrate general facilitators to exercise and activity are detailed in Table 5.8.

Table 5.8 General facilitators to exercise and physical activity

Habit	*"It was my first day back [to work] and my first day back I went to the gym the first day and I've been pretty much consistency, 4 days you know, every week." [QP05]* *"Habit is the biggest thing. I remember when I was in Dublin and coming home in the evening I would always have the stuff in the boot and as I came to the corner...you know where the gym was 'will I, won't I.. will I, won't I' and I'd make excuses to pass it by but yet when you go in and do it you always feel better of it." [QP15]*
Exercise equipment	*"I just got myself one of those treadmills as well...because the weather is so volatile.. sometimes you can't go out for a walk." [QP15]* *"I have one of the air walkers here in the house.. and occasionally I'd get up on that and give about 10 minutes on.. you know the yoke you step on and your two arms are on it.. I'd use that an odd time." [QP16]*
Weather	*"You know if the weather is good I would do a fair bit of walking especially in the summer time you know." [QP12]* *"Now that the spring weather is starting to come in you can get out and do a bit of gardening as well." [QP14]*
Other	*"I don't exercise as a matter of course.. walking the dogs I sorta do as much for the dogs as for myself. More so for the dogs than myself! (laughs) But actually it's good that I do it because if I didn't do that I'd probably be doing nothing at all." [QP01]* *"It's so much easier to just take the car. But I try and park away so that I do have to walk to wherever I'm going." [QP04]* *"Well we're lucky around here the [park] is just around the corner and the shopping outlet is just up the other way so there's always somewhere worth going to, you can get a cup of tea or coffee when you get there and go again." [QP13]*

Exercise knowledge and understanding

Participants' knowledge and understanding with regards to exercise and activity were explored. They were asked if they remembered any specific advice given to them by healthcare professionals regarding exercise and activity throughout their treatment and

recovery. A number of participants, now a few years post completion of treatment, stated that they could not remember the advice they were given, while others vaguely recalled some advice such as being told to walk or to exercise or to return to normal.

> *"I don't recall any specific advice. I think there probably were some words of advice but to be honest I don't recall them." [QP01]*
>
> *"I suppose I was told to walk and you know try and live as normal a life as possible." [QP13]*
>
> *"Well no I don't remember any advice.. I can't say that they told me.. I'm sure they did tell me but I just can't remember." [QP07]*
>
> *"Yea maybe I got a leaflet or something about it now." [QP08]*
>
> *"Just to try and get back to normal living as soon as possible." [QP04]*
>
> *"Well they recommended a good bit of walking." [QP02]*
>
> *"Going home, it was to continue to exercise but not excessively." [QP01]*
>
> *"I think the physiotherapists on the ward.. I think they just recommended slowly but surely." [QP14]*

Overall participants emphasised having enough information regarding their diagnosis and treatment throughout the cancer continuum. Some participants however, stated that they were not given any specific advice about exercise and activity and felt that more information of this nature would have been beneficial.

> *"You don't know if you're supposed to sorta do exercise. You get no follow on sort of chart from anyone... Like they don't say walk for an hour every day.. or get back to full running..or whatever.... no nothing.. You're left to yourself and you're saying should I or shouldn't I.. and you're half wary... Still to this day don't know whether I should or not." [QP03]*

"Probably yea a little bit more [advice] in that end of it.. a bit more on the activity and exercise but from the context of the support, what you're going to go through.. that was hugely positive and very inclusive, you were kept up to speed with everything but certainly on the other side of it yes." [QP05]

"Well, like I said, I done my own thing and maybe it I had of gotten a little bit of help from a physio more than anybody I could have maybe been a bit better at doing other things you know whatever they were, but I didn't get any help or I wasn't told about anything really, I didn't know." [QP06]

"No I wasn't really given any advice about exercise... If I hadn't had the infection I suppose the physiotherapist would have kept watching me and she would have probably have kept me doing exercise.. I could go walking down the corridor and that kind of thing.. and maybe have told me to.. when I was going home to do it, but she lost track of me. So I had no real.. I didn't have an exercise programme coming home with me or anything like that." [QP12]

"I mean we got plenty of it from the dieticians and stuff right but very little in terms of what exercise you should be...taking." [QP15]

Thirteen of the sixteen participants had never heard of physical activity guidelines and did not know what they were. Some participants had a vague awareness of activity guidelines and referred to their understanding of them during the interview, as illustrated in the quotes below.

"While I would be busy and doing things and maybe gardening and whatever but actually I do not walk 20 minutes, seven times a week now. I definitely don't." [QP04]

"They say if you do it three times a week, about 40 minutes, a good fast walk that's as good as you need.. anything beyond it might be too much you know and that's what I'm keeping at." [QP15]

"Some people say like walk a mile or two a day but very few people are doing it." [QP16]

Mostly, participants recognised that exercise is beneficial; some benefits described included feeling better after exercise and improved fitness and strength levels.

> *"I found that the more I did the better I felt, interestingly... I would know that in general yes exercise is good and that I should do it." [QP01]*
>
> *"I definitely would feel now I need to be more walking. I think I would be best if I was doing more kind of exercise." [QP04]*
>
> *"I certainly feel a whole lot better than I did say 12 months ago. I would say I'm better... but that [exercise] has helped...It's completely beneficial, you can feel the benefit." [QP05]*
>
> *"I suppose I should do a bit of [exercise] really... to keep my muscles.. a bit of weight lifting or something like that I should be doing because I'd know I haven't the strength or.. I'm losing that you know.. muscle.. what's the right way to put it I don't know.. you know what I'm trying to say" [QP07]*
>
> *JG: "Do you think then that exercise and activity would be beneficial?" Oh yea you'd have to.. I even noticed after my surgery now, you know the.. your breathing would be a bit bad because they collapse your lung...I noticed I used to do short walks.. and it got you going.. you know I wouldn't be breathing as heavy now walking." [QP10]*

Some participants however, queried the benefits of exercise, in particular in relation to weight loss. Exercise was viewed primarily as a means to lose weight or maintain a healthy weight; when this was not necessary, the need for exercise was queried. Other reasons included not seeing any particular benefits to exercise in general or not ever having a great interest in exercise.

> *JG: Do you think that increased activity and exercise would benefit you?" "Well I don't know if it would or not like you know because I'm not carrying any weight or anything.. you know I'm only just, I'm less weight than I was like.. I'd be lighter now and I wouldn't want to lose any more I don't think." [QP07]*

"I don't see a lot of benefit in [exercise] now. Health wise." [QP02]

JG: "If you were to do any more [exercise] would it be beneficial to you?" Em.. I don't know. I was never a great exercise person. I garden, I cleaned, I walk, I played golf. But em doing exercises.. em you know.. I was never an exercise person or Pilates or any of that you know. So that was never me." [QP13]

5.4.4.3 Theme 3: The role of rehabilitation in oesophageal cancer survivorship

The final theme which emerged from the data in this study was 'the role of rehabilitation in oesophageal cancer survivorship'. The major subthemes were: interest in rehabilitation, the potential benefits of rehabilitation and the structure of rehabilitation.

Interest in rehabilitation

The vast majority of participants stated that they would have had an interest in rehabilitation and felt that it would be of benefit in an oesophageal cancer population.

"Rehab is badly needed. There's no doubt in the world about it." [QP02]

"It would have been fantastic." [QP02Wife]

"Well I didn't know of anything like that then.. but it would have benefitted me... Some kind of a programme would have been a big help." [QP06]

Benefits of rehabilitation

While some participants recognised the potential physical benefits of rehabilitation, the benefit of increased information was more frequently reported. Participants felt that increased education with regards to their physical recovery would be hugely valuable, particularly in relation to what side effects to expect, the type and quantity of exercise recommended during recovery and guidance with regards to activities that should be avoided.

"Coming out now I'd say.. some sort of guidance would help definitely... 'Cos you're left to your own devices and you're half afraid what to do and not to do." [QP03]

"And even to say well look you can do this but look for goodness sake don't do that." [QP04]

In addition to information provided by healthcare professionals, a recurrent suggestion related to the benefits of peer support. Speaking from their own experience of peer support, a number of participants strongly felt that interaction with and support from other survivors of oesophageal cancer would be hugely valuable.

"We have a cancer support group here in [hometown] and I go and do various therapies and once a month we had a men's discussion group and there was a women's discussion group and I found that quite beneficial." [QP05]

"There were a couple of friends of mine now had the same type of operation and I got to know them and they came along after me and had the same... and I went to them and I had a bit of a chat with them and I reckon I helped them you know." [QP10]

"What I found very useful was, on my visits to the hospital afterwards, waiting outside [the surgeons] office, on the corridor there, you might meet another patient that has had oesophageal cancer surgery and the amount of information that you can get from each other, it's unbelievable you know. You know 'did you suffer from this' or 'did you get that?' and they more than likely would have done." [QP14]

"I remember when I was in the HDU, [the cancer nurse] brought in a man who was going to have the surgery in a day or two, just to show him what the HDU looked like and he came over and he was talking to me for a minute and I felt like saying to him 'lookit everything is going to be ok' because I remember I was in his position and you're worried sick." [QP14]

Structure of rehabilitation

Most participants felt that a rehabilitation programme would be most beneficial after all treatment had been completed. Furthermore as the initial weeks and months post discharge were described as being particularly difficult, the suggestion was that six months to one year

post completion of treatment may be the most feasible and appropriate time for survivors of oesophageal cancer to participate in a rehabilitation programme.

> *"I dunno whether I would have shook myself to do it in the first couple of weeks or not. Because well I know the first couple of days I was home by the time I got up out of bed and got myself dressed and washed and had a bit of breakfast I was only fit to sorta fall into the armchair." [QP12]*
>
> *"Exercise wouldn't have been a priority [in the first couple of months post surgery] or anything like it, it was just generally move around and see how you could keep the body and move around the house as much as you could." [QP16]*
>
> *"You're expecting yourself to be better after a year and next thing things stop going according to plan... so that's when the rehab would be huge. I'd say he'd be more physically able for it as well." [QP02Wife]*

In contrast, one participant felt that a rehabilitation programme would have been beneficial during treatment.

> *"Well maybe during the treatment... something maybe to keep you going." [QP10]*

More participants expressed an interest in a home based exercise programme as opposed to a hospital based class. However, a common reason for this preference was location; the majority of participants did not live in Dublin and therefore would find it difficult to travel to Dublin for a rehabilitation programme. Some of these participants did feel that if a class was available in their own town, they would be happy to attend it.

> *"If I got information on it and I could do it here in [home town]." [QP04]*

"From my distance up to Dublin that wouldn't work like you know. It would be alright if you were living closer to the hospital or somewhere like that but if you're far away like.. for anyone that has that... But to do a programme at home I'd say would be the best." [QP07]

"Well if there was something close by I'd probably have gone to it.. But Dublin would have been just too far for me." [QP08]

One participant felt that the hospital environment would provide more support for the exercise programme, particularly in the first few months and suggested that a home based programme may then follow the hospital programme for the exercise to be maintained.

"Well I suppose initially it would probably have been nice to come up and do something in the hospital environment perhaps.. initially and then it's something that you could continue yourself.. But I'd certainly say initially yea in the hospital environment...where you would have the support of the health professionals there with you." [QP05]

With the exception of suggesting that increased education and peer support would be beneficial, participants did not have any strong views on what a rehabilitation programme should consist of.

JG: "What do you think would be beneficial for a rehab programme to consist of?" "I haven't a clue really. Not a clue." [QP02]

However, a number of participants raised the point that recovery would be different for everybody and this would need to be an important consideration when planning rehabilitation programmes.

"I fully understand everybody's recovery or treatment or whatever is different." [QP05]

"Well it would also depend on..because if you told somebody my story and they were much worse, they might feel terrible after a while that they weren't in the same boat." [QP15]

"A handout from somebody like you that knows the programmes to do out for Mary Smith and Mary Jones... and say ok that programme will do her and that will do her and that'll do her... because we won't all be the same." [QP13]

5.5 Discussion

The extensive research into HRQOL in an oesophageal cancer population has highlighted the potential negative impact of treatment, particularly oesophagectomy, on most aspects of QOL. However there may be many important aspects of QOL that are not sufficiently covered by questionnaires and therefore patient narratives are growing in importance as additional descriptors of this complex group (Malmstrom et al., 2013). In recent years there have been some qualitative studies in an oesophageal cancer population with a focus primarily on the emotional and psychological impact of oesophageal cancer, changes in eating habits and the experience of supportive care. The aim of this study was to explore the experience of treatment and recovery in those with oesophageal cancer with a focus on physical functioning. The results of this study demonstrated that suboptimal physical functioning was prevalent in disease free survivors of oesophageal cancer and that this group experienced significant physical and lifestyle changes since diagnosis and treatment. This complements the objective data gathered on this cohort in Study 1 which also revealed low fitness and physical activity levels in this group.

The first objective of this study was to describe the effect of a cancer diagnosis and its treatment on participants' general health and physical functioning. Overall participants reported that treatment for oesophageal cancer had a substantial impact on their health and functioning. A prolonged recovery period after treatment was described with reports of taking up to three years to feel back to 'normal'. Participants described numerous physical changes as compared to pre-diagnosis including decreased stamina, fitness, strength and activity levels. Specific physical side effects of treatment experienced at various stages throughout the cancer continuum were also described and included respiratory, musculoskeletal and sensory

problems in addition to reflux, voice changes and pain. Some participants reported that their lifestyle was more restricted; daily activities required more planning and pacing and there was a general feeling of slowing down. Other lifestyle differences included occupational changes and altered eating habits. Despite this, participants reported that they were feeling positive, fortunate and were very happy with their progress overall since completing treatment.

The second objective of this study was to explore participants' knowledge of exercise recommendations and perceptions about their own level of physical activity. None of the participants in this study knew the correct physical activity guidelines recommended for health benefits; over 80% had never heard of physical activity guidelines and while a few were aware of the existence of activity guidelines, none knew exactly what they are. The majority of participants were aware of the benefits of exercise and recognised that exercise is important to increase fitness and general health. However, a small minority of participants were unsure about the benefits of exercise and queried whether it was necessary. These findings highlight the importance of increased education and awareness regarding physical activity and exercise in this cohort. The extensive contact healthcare professionals have with patients as they undergo treatment for cancer could be a prime opportunity for increased exercise counselling.

The third objective of this study was to identify potential barriers and facilitators to recommended physical activity levels and exercise. It is important to identify barriers and facilitators to exercise in any clinical population where exercise interventions may be warranted. While there are barriers and facilitators to exercise which are common to all populations such as the weather, interest and enjoyment, participation in sports and hobbies, walking the dogs etc., there are others which may be as a direct result of a clinical condition. These condition specific barriers and facilitators are particularly important to investigate as they may be unique to a certain disease and may need to be specifically targeted with an exercise intervention. In this study, a number of disease specific barriers to exercise were identified. These included a fear or reluctance by participants to 'push themselves' or exercise at a moderate or high intensity after cancer treatment, reduced fitness and stamina post treatment, reduced food intake, weight loss and other physical side effects of treatment. The majority of these barriers could be addressed with a multidisciplinary rehabilitation programme. For example a rehabilitation programme could include: education and information regarding exercise guidelines and benefits, input from dieticians regarding the optimal energy intake to facilitate increased activity and exercise and a supportive environment to facilitate a gradual and safe return to exercise.

Another noteworthy barrier to exercise that was mentioned by a number of participants was

ageing. Some participants reported that it was difficult to segregate physical changes that arose from ageing with those which arose from cancer treatment. This is an important consideration which raises the question of whether people who have been through cancer treatment are more aware of or focused on the ageing process and are therefore more willing to accept functional decline than other older adults with no comorbidities. This is also something which could be addressed with education and supervised or supported exercise programmes.

The discussion regarding facilitators to exercise in this population highlight the importance of personality with regards to exercise and activity levels. The majority of facilitators to the return to exercise after cancer treatment related to participants attitudes, interest in exercise and lifetime exercise habits. More general facilitators to exercise such as good weather, the use of exercise equipment and walking dogs reflected facilitators to exercise common to any population. Some participants did mention the importance of a gradual return to exercise and found that slowly building up activity levels was useful. This is important information which could be emphasised to patients at the time of discharge.

The final objective of this study was to obtain participants' views on the development of rehabilitation programmes for patients with oesophageal cancer. Information from the target population is extremely useful when developing programmes of this nature; taking into account patient needs and preferences should optimise the feasibility and acceptability of such programmes and potentially improve adherence rates. Overall rehabilitation was viewed very positively by this cohort; participants expressed a high level of interest in a programme and stated that they thought it would be beneficial for survivors of oesophageal cancer. Based on the results of this study, it would appear that the optimal timing of rehabilitation would be a number of months after the completion of treatment, to allow patients time to recover from the acute side effects of surgery. Participants described the initial few months after discharge as particularly difficult and a number of them felt that a rehabilitation programme would not be feasible at that time. In addition participants reported the need for stabilisation of eating habits prior to a rehabilitation programme. A number of participants stated that until eating normalised they would not have been able for an exercise programme. Preferences for the structure of a rehabilitation programme i.e. hospital based class versus home exercise programme were personal. Therefore if rehabilitation programmes were to become part of the standard of care it may be advisable to offer both home and hospital options. Participants in this study described reduced stamina, strength and physical activity levels when compared to pre diagnosis. These findings reflect the objective measurement of physical functioning in

Study 1 where survivors of oesophageal cancer demonstrated suboptimal fitness and physical activity levels. Therefore it would be advisable for rehabilitation programmes in this cohort to target these important components of physical functioning.

5.5.1 Limitations

Some methodological limitations should be considered when interpreting the results of this study. Firstly, the majority of interviews were carried out over the telephone. A limitation of this interview method is the absence of visual cues. This may result in loss of non-verbal data, loss of contextual data or loss or distortion of verbal data. However, a review by Novick (2008) revealed that despite the common perception that face-to-face interviews are superior to telephone interviews, there is very little formal evidence regarding the merits and shortcoming of one as compared to the other. Therefore this review concluded that until further well-designed studies have been carried out to compare interview modalities, there was no reason to favour a particular mode for qualitative interviews (Novick, 2008). Furthermore the advantages of telephone interviews are that they provide increased access to participants in a wide geographical region, they allow participants to remain in familiar comfortable surroundings and it has been reported that participants are relaxed on the telephone and willing to talk freely (Novick, 2008).

A further limitation of this study relates to the recruitment of participants. Survivors of oesophageal cancer who had taken part in Study 1 were invited to take part in Study 2 by the lead investigator (JG) (Section 5.3.2). When being informed of the study, potential participants were advised that participation was completely voluntary and there was no obligation to take part. If the participant was interested, he/she was provided with written information detailing the aims and requirements of the study. Participants were then given seven days to decide whether or not they would like to take part upon receipt of the study information. However, despite these efforts, it must be noted that survivors of oesophageal cancer who were invited to take part in the study by the lead investigator may have felt an obligation to take part. One potential reason for this may have been familiarity with the lead investigator (JG). Therefore, in future studies of a similar nature, it may be useful, where feasible, to employ an independent third party or 'gatekeeper' to inform potential participants about the study and give them the option of taking part. As the gatekeeper would be fully independent of the study, this may reduce any feelings of obligation on the part of the potential study participants to participate.

There was some selection bias associated with this study. Firstly, there is an unavoidable self

selection bias associated with studies where participants are required to volunteer to participate. Those who agreed to participate may have had a higher interest in exercise and activity and consequently the implementation of exercise interventions. These participants may also have been relatively well in their recovery and as a result felt able to participate in research. Those experiencing a poorer recovery may have been less likely to agree to participate. A further bias may have resulted from the fact that these participants had also participated in Study 1. Accordingly they might have previously received information regarding physical activity, exercise and expected functional recovery from the researcher (JG). However, the primary focus of this interview was on the participants' own opinions and experiences. Furthermore as the potential participants for this study were geographically disparate, telephone interviews were necessary to maximise recruitment. It has been suggested that establishing contact or rapport, in person, prior to conducting telephone interviews is important (Novick, 2008). Therefore having previously taken part in Study 1 was also beneficial. As participants had previously met the study investigator (JG), they may have been more comfortable and willing to complete a telephone interview.

There are some limitations associated with criterion sampling which should be acknowledged. Criterion sampling involves the selection of information rich cases that meet a predetermined criterion of importance. Participants are selected on the assumption that they possess knowledge and experience with the phenomenon of interest. However, criterion sampling can narrow the range of variation and focus primarily on similarities and therefore is less useful to identify and expand on the range of variation or differences (Palinkas et al., 2015). By including only individuals who meet a specific criterion, on the basis of having a specific experience of a process, the views of other individuals with different experiences of the same process may not be captured. In this study the criteria for inclusion was that participants were disease free survivors of oesophageal cancer who were at least one year post completion of curative treatment. These participants had also already taken part in Study 1 in this thesis. Therefore these participants represent those who were successfully treated, were doing relatively well into survivorship and were interested in and physically able to participate in research. This limits the generalisabilty of the study results as these findings may not represent the experience of all patients who undergo treatment for oesophageal cancer. However this was the group who would most likely be targeted with interventional programmes and therefore represented the cohort of primary interest for this primary exploratory research. Furthermore it was of interest to the research in this thesis to compare quantitative and qualitative data and the use of the same participants in both studies facilitated this.

To address the limitations of criterion sampling Palinkas et al. (2015) recommend also using other types of purposive sampling to place greater emphasis on breath and variation. For example maximum variation sampling is more focused on exploring differences and therefore can increase the breadth and variation of the results. Accordingly, to address some of the limitations associated with criterion sampling, maximum variation sampling was also used in this study. This aimed to ensure the inclusion of participants with a range of ages, treatment types, surgery types and time post surgery.

Due to the retrospective nature of the study, some participants may have had difficulties recalling specific information about their treatment and recovery, which could lead to inaccuracies. However it has been shown that those who have experienced special or traumatic events often remember those quite well, even though time has passed since they occurred (Christianson and Loftus, 1991).

5.6 Conclusion

The results of this study demonstrated that patients with oesophageal cancer experienced significant physical and lifestyle changes as a result of treatment for oesophageal cancer. These changes were found to continue up to five years post completion of treatment. This complements the objective measurements of poor fitness and physical activity levels which have been previously demonstrated in this group. The qualitative data gathered in this study has provided a comprehensive understanding of some of the potential reasons for the suboptimal physical functioning observed. This study cohort had a limited knowledge of activity guidelines and the wide ranging benefits of exercise and faced a number of disease specific and general barriers to increased activity and exercise. These are areas which can be specifically targeted with multi-disciplinary rehabilitation programmes. The findings of this study indicate that rehabilitation programmes are feasible and would be well received in an oesophageal cancer population a number of months post completion of treatment. The potential implications of the findings in this study are discussed in more detail in Chapter 8.

Chapter 6 Study 3: Modifiers of functional performance during treatment for oesophageal cancer

6.1 Introduction

The systematic review in Chapter 1 revealed the limited amount of data currently available regarding the impact of chemotherapy, radiotherapy and surgery on objective measures of physical performance in patients with oesophageal cancer. The review identified a small number of recent studies which investigated the effect of either neoadjuvant treatment or surgery on fitness and strength levels in patients with oesophageal cancer. One study by Tatamatsu and colleagues (2013) also subjectively measured physical activity levels pre and post neoadjuvant chemotherapy, however to the authors' knowledge no study has investigated the impact of treatment on objectively measured physical activity levels. While the results of these studies primarily indicated that treatment for oesophageal cancer had a negative impact on physical performance, there were conflicting results regarding the effect of neoadjuvant treatment on fitness levels. No study to date has carried out a longitudinal analysis of the physical performance of one cohort of oesophageal cancer patients from diagnosis and throughout the treatment trajectory to investigate and compare the effect of both neoadjuvant treatment and surgery on physical performance.

The results of Study 1 in this thesis identified suboptimal physical performance outcomes into longer term survivorship after oesophageal cancer. However, due to the cross sectional design of the study, a direct cause-effect relationship between treatment for cancer and the low fitness and physical activity levels observed could not be established. It is clear that more research is needed in this area to investigate exactly how, when and to what extent treatment for oesophageal cancer might impact on physical performance. Longitudinal data on the strength, fitness and physical activity levels of patients with oesophageal cancer during treatment will assess the immediate physical side effects of treatment and highlight any prehabilitative or early rehabilitative needs this group may have.

6.2 Study aims and objectives

The aim of this study was to investigate changes in physical performance during curative multimodal treatment for oesophageal cancer. The specific objectives were:

- To measure exercise capacity, physical activity levels and muscle strength at diagnosis, post neoadjuvant treatment (chemotherapy and/or radiotherapy) and post oesophagectomy.
- To investigate any changes in the measurements of exercise capacity, physical activity levels and muscle strength across all study time points.
- To measure body weight, waist circumference and BMI at diagnosis, post neoadjuvant treatment (chemotherapy and/or radiotherapy) and post oesophagectomy.

6.3 Methods and measures

6.3.1 Study design

A longitudinal study design was used to describe the changes in physical performance experienced by patients with oesophageal cancer throughout the treatment trajectory. Participants were assessed at the following time points during treatment and recovery:

1. At diagnosis, prior to commencing neoadjuvant treatment (T1)
2. Post neoadjuvant treatment and prior to surgery (T2)
3. At least four weeks post surgery and post hospital discharge (T3)

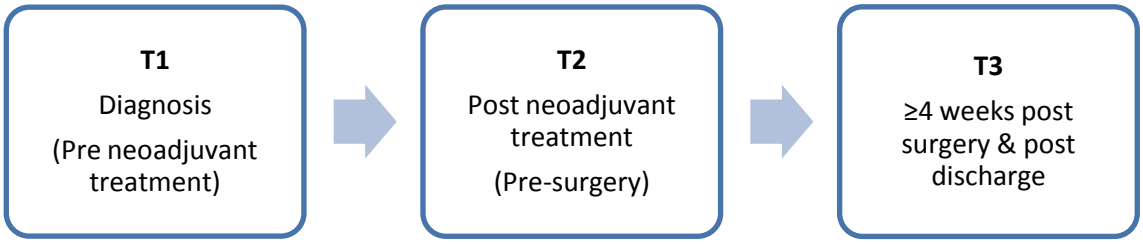

Figure 6.1 Study assessment time-points

The inclusion criteria for participants in this study were that they: (1) were >18 years of age (2) had a diagnosis of oesophageal cancer and (3) were scheduled to receive multimodal treatment (including oesophagectomy) with a curative intent. Exclusion criteria included: (1) a neurological or musculoskeletal condition limiting independent mobility or (2) contraindications to exercise testing as per the American College of Sports Medicine guidelines (Pescatello, 2013).

6.3.2 Sampling and recruitment

Eligible participants were identified at multidisciplinary team meetings and upper gastrointestinal surgical clinics at St. James's Hospital. These patients were informed of the study at clinics by either the surgical team or nurse specialist, were provided with a participant information leaflet and invited to take part (Appendix XVI). If the participant was agreeable, the study investigator then met or telephoned him/her to further explain the study and establish his/her interest in participation. When participants agreed to take part, an appointment was made for the initial assessment (T1). When participants returned to clinic post neoadjuvant treatment and again approximately four weeks post discharge, they met with the study investigator again and appointments were made for the follow up assessments (T2 & T3). Recruitment for this study began in April 2014 and is ongoing as part of a Health Research Board funded Health Research Award. The results presented here represent the preliminary data from this study.

6.3.3 Ethical approval

Ethical approval was granted by the SJH/AMNCH research ethics committee and all participants provided written, informed consent (Appendix XV & Appendix XVI).

6.3.4 Measurement and testing protocol

All study appointments took place in the Clinical Research Facility, St. James's Hospital. During each assessment the measurements outlined below were completed:

- **Hand grip strength** was measured using a Jamar dynamometer according to the procedures outlined in Section 2.3.2.3.

- **Exercise capacity** was measuring using the 6MWT as outlined in Section 2.3.1.5.
- Habitual **physical activity levels** over five to seven days were measured using the ActiGraph triaxial accelerometer as outlined in Section 2.3.3.4.
- **Standing height**, **body weight, waist circumference** and **BMI** were measured according to the procedures outlined in Section 2.4.3.

Socio-demographic and past medical history details were gathered from medical charts, computer records at St. James's Hospital and through participant interviews.

6.3.5 Data analysis

Data analysis was performed using SPSS (version 20) (IBM, Armonk, New York, USA). Data normality was assessed using normality plots and the Shapiro-Wilk test ($p>0.05$). Means and standard deviations (SD) are presented for each variable with a normal distribution. Medians and interquartile ranges are presented for each variable with a skewed distribution. A one-way repeated measures ANOVA was conducted to determine whether there were statistically significant differences in outcomes across the treatment trajectory. The assumption of sphericity was assessed by Mauchly's test of sphericity. Post hoc analysis with a Bonferroni adjustment was carried out to assess all pairwise comparisons. Statistical significance was set at $p<0.05$.

6.4 Results

6.4.1 Participant characteristics

To date, 20 participants scheduled for neoadjuvant treatment have been recruited to the study at time of diagnosis. Of these, four did not attend for further study assessments due to disease progression (n=3) or no further interest in study participation (n=1). Sixteen participants completed the T2 study assessment and progressed to surgery. However, five participants did not compete the T3 assessment because they either underwent a gastrectomy (n=2), were too medically unwell to complete an assessment (n=1) or were lost to study follow up (n=2). Accordingly, to date, 11 participants have completed all three study assessments and were included in this preliminary descriptive analysis (Figure 6.2).

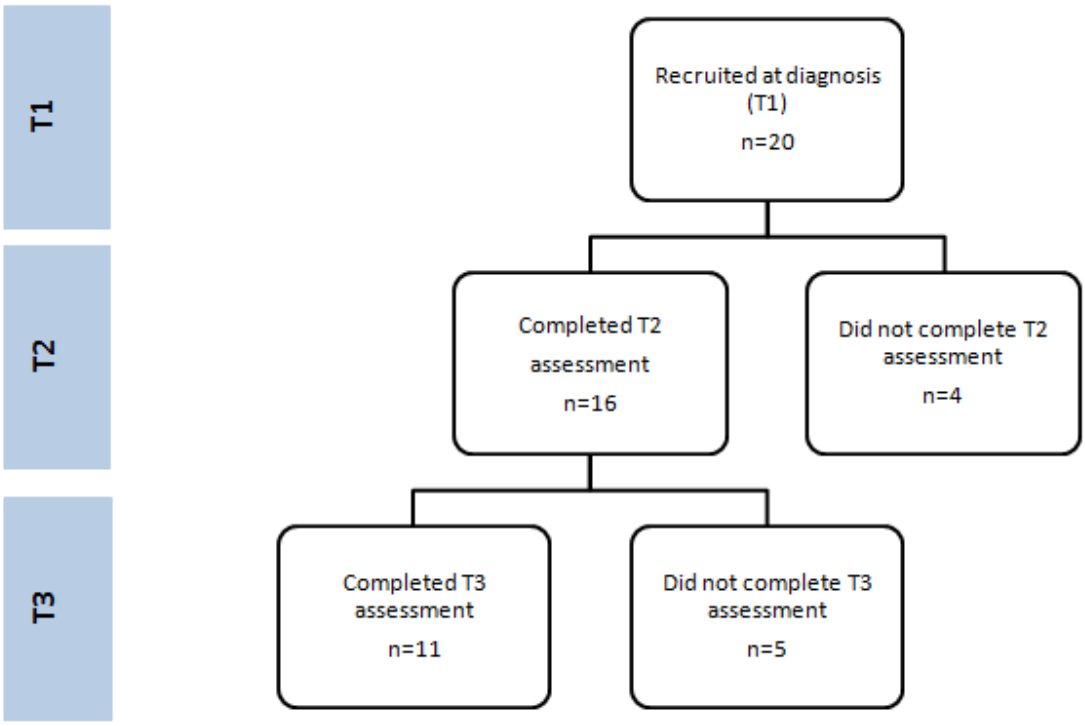

Figure 6.2 Recruitment of study participants

Eleven patients with oesophageal cancer (two female) with a mean (SD) age of 64.55 (8.24) have completed the study protocol. Participant demographics are detailed in Table 6.1.

Table 6.1 Participant demographics and disease related information

Demographics (n=11)	
Age (years)*	64.55 (8.24)
Range	50-75
Gender *n (%)*	
Male	9 (82)
Female	2 (18)
Employment status *n (%)*	
Working (sick leave)	6 (55)
Retired	5 (45)
Co-morbidities *n (%)*	
Cardiac	3 (27)
Respiratory	0 (0)
Metabolic	0 (0)
Cancer Type n (%)	
Adenocarcinoma	10 (91)
Squamous Cell Carcinoma	1 (9)
Neoadjuvant Treatment Regimen n (%)	
MAGIC protocol	9 (82)
CROSS protocol	2 (18)
Surgery Type *n (%)*	
2-stage oesophagectomy	8 (73)
3-stage oesophagectomy	2 (18)
2-stage oesophago-gastrectomy	1 (9)

*mean (standard deviation)

6.4.2 Data normality and assumption of sphericity

The following data were non normally distributed ($p<0.05$): average time spent in vigorous intensity activity per day, average time spent in bouts of moderate-vigorous activity per day. Accordingly these data are described as median (inter-quartile range). No outliers were identified in the results for HGS and the 6MWT and Mauchly's test of sphericity indicated that the assumption of sphericity had not been violated.

6.4.3 Results for body weight, BMI and waist circumference measurements

The results for the body weight, BMI and waist circumference measurements for this cohort at each study time point are detailed in Table 6.2. The average (SD) height of this group was 168.91 (6.22) cm. This group had an average (SD) weight of 79.14 (14.79) kg at diagnosis, which decreased to 76.55 (14.25) kg post neoadjuvant treatment and to 72.85 (12.96) kg post surgery. Accordingly, the average BMI measurement for this group also decreased consistently across the study period with an average BMI of 27.62 (4.11) kg/m^2 at diagnosis, 26.68 (3.71) kg/m^2 post neoadjuvant treatment and 24.93 (3.42) kg/m^2 post surgery. The average (SD) waist circumference was 90.08 (11.80) cm at diagnosis, 93.24 (13.24) cm post neoadjuvant treatment and 99.65 (2.54) post surgery.

Table 6.2 Results for body weight and BMI measurements

Variable	**Diagnosis (T1)** **(n=11)**	**Post neoadjuvant treatment (T2)** **(n=11)**	**≥ 4 weeks post surgery (T3)** **(n=8)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Weight (kg)	79.14 (14.79)	76.55 (14.25)	72.85 (12.96)
BMI kg/m^2	27.62 (4.11)	26.68 (3.71)	24.93 (3.42)
Waist circumference (cm)	90.08 (11.80)[a]	93.24 (13.24)[b]	99.65 (2.54)[c]

[a]n=7, [b]n=9, [c]n=2 Abbreviations: *SD* standard deviation, *BMI* body mass index, *kg* kilogram, *m* metre.

6.4.4 Results for the measurement of the 6MWT and HGS

The mean values for 6MWT distance (6MWD) and HGS for each study time point are detailed in Table 6.3. Eight participants completed a 6MWT at each of the three study time points. Three participants declined to complete the 6MWT at the T3 study time point due to dizziness or fatigue. All 11 study participants completed HGS measurements at each study time point. Treatment for oesophageal cancer elicited significant changes in 6MWT distance, right HGS and left HGS over time (p=0.037, p=0.002 and p=0.005 respectively) indicating a decrease in both fitness and strength levels across the treatment trajectory in this cohort. The distance on the 6MWT decreased from 536.12 (63.01) metres at diagnosis to 532.87 (74.39) metres post neoadjuvant treatment and further to 473.25 (62.08) ≥ four weeks post surgery (p=0.037) (Figure 6.3). Right HGS decreased from 39.86 (10.47) kg at diagnosis to 35.64 (7.86) post neoadjuvant treatment and to 33.20 (8.85) kg ≥ four weeks post surgery (p=0.002) (Figure 6.4).

Similarly, left HGS decreased from 37.64 (8.35) kg at diagnosis to 34.15 (5.73) kg post neoadjuvant treatment and to 32.48 (8.45) kg ≥ four weeks post surgery (p=0.005) (Figure 6.5).

Table 6.3 Results for 6MWT and HGS measurements

Variable		Diagnosis (T1)	Post neoadjuvant treatment (T2)	≥ 4 weeks post surgery (T3)	P value
	n	Mean (SD)	Mean (SD)	Mean (SD)	
6MWD (m)	8	536.12 (63.01)	532.87 (74.39)	473.25 (62.08)	.037*
Right HGS (kg)	11	39.86 (10.47)	35.64 (7.86)	33.20 (8.85)	.002*
Left HGS (kg)	11	37.64 (8.35)	34.15 (5.73)	32.48 (8.45)	.005*

Abbreviations: *SD* standard deviation, *6MWD* Six Minute Walk Test distance, *HGS* hand grip strength, *kg* kilogram, *m* metre.

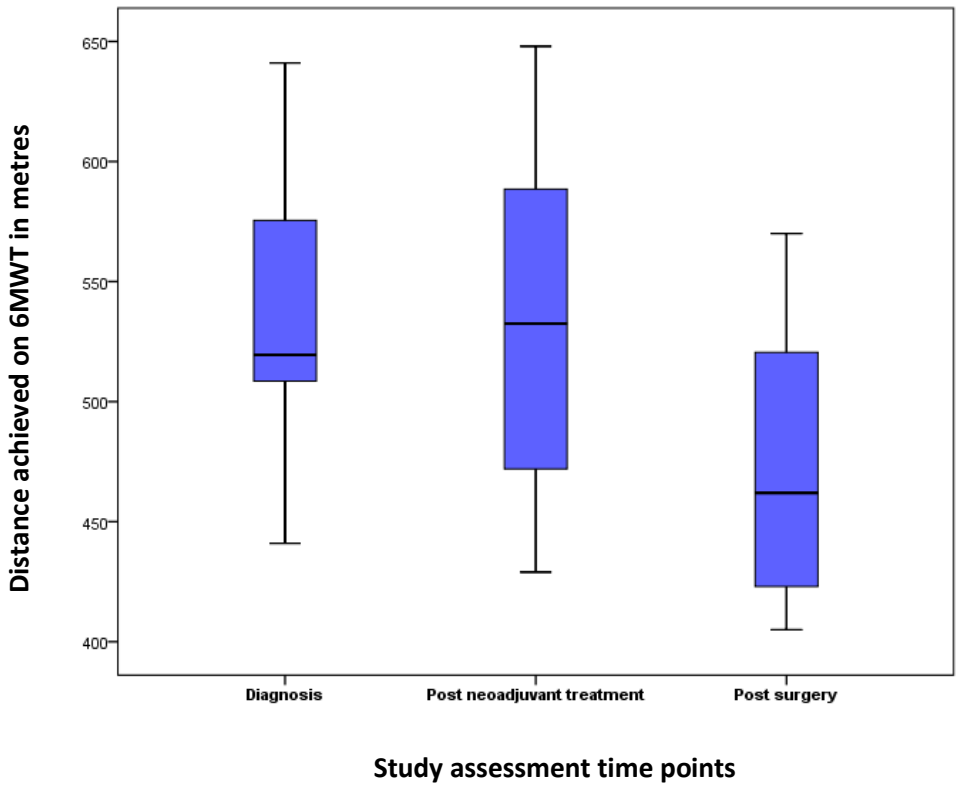

Figure 6.3 Changes in 6MWT distance over time (metres) (represented as median and interquartile range)

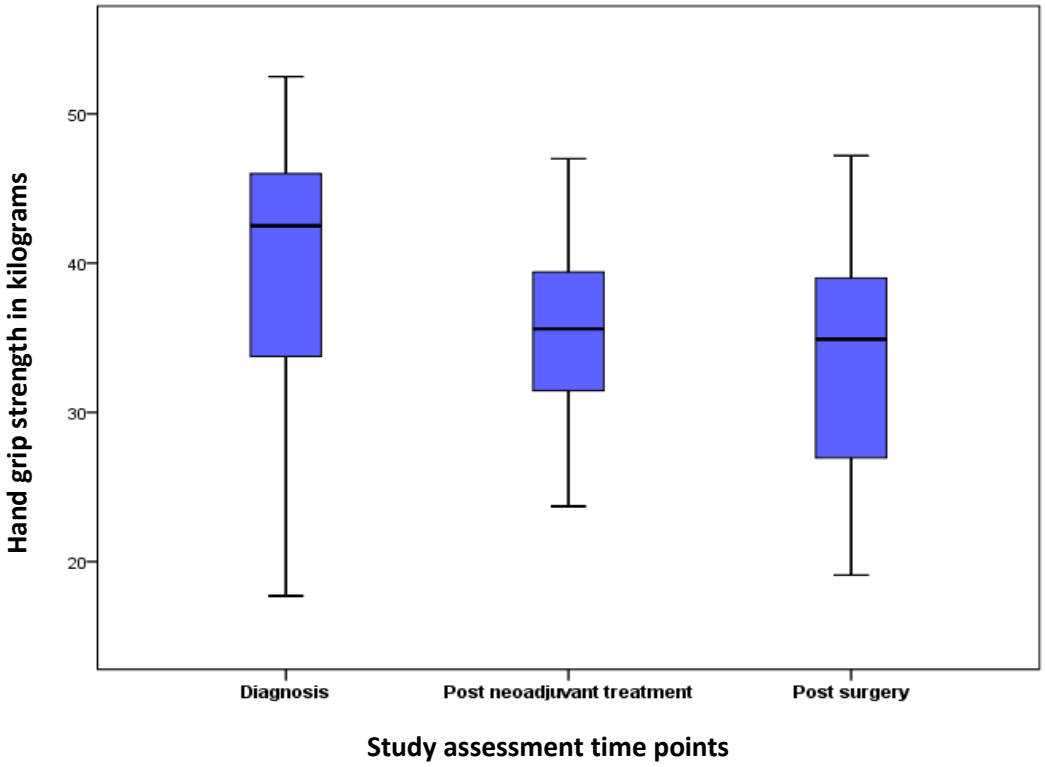

Figure 6.4 Changes in right HGS measurements over time (kg) (represented as median and interquartile range)

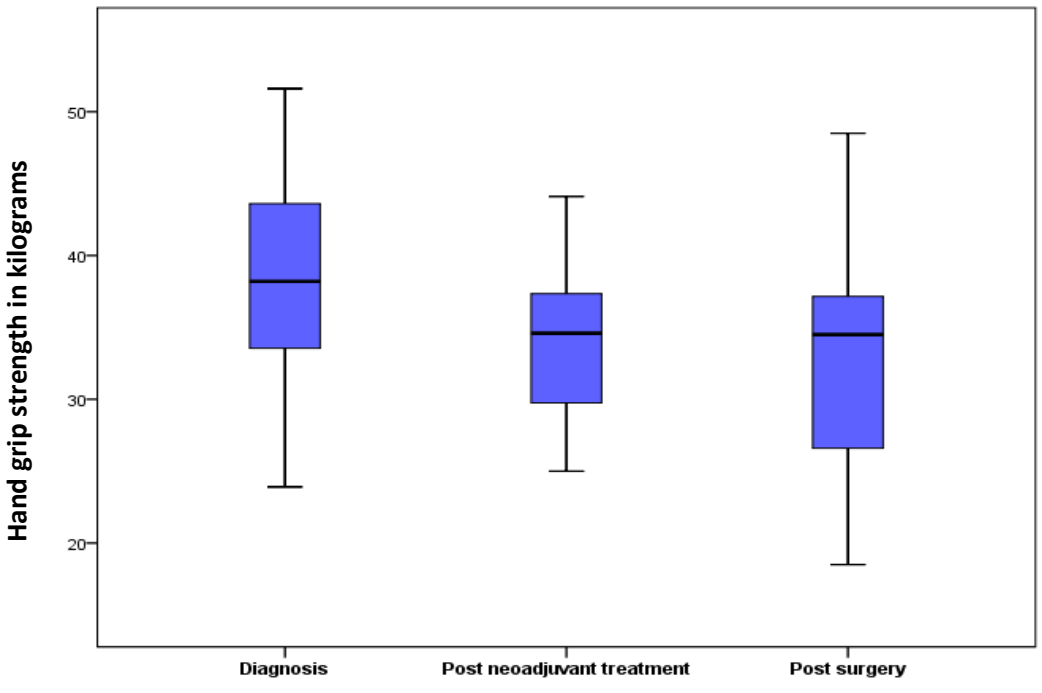

Figure 6.5 Changes in left HGS measurements over time (represented as median and interquartile range)

While a significant change in 6MWT results across all three study time-points was observed, post hoc analysis revealed no statistically significant difference between the distances achieved on the 6MWT for each pairwise comparison of study time-points (Table 6.4). However the 6MWT distance decreased by a mean of 59.62 (95% CI, -120, 0.75) metres from pre to four weeks post surgery which was approaching statistical significance (p=0.053) and exceeds the minimal clinically important difference of 50 metres reported for this test (Perera et al., 2006). Post hoc analysis of the right HGS measurements demonstrated that there was a statistically significant decrease from diagnosis to ≥ four weeks post surgery (-6.66 (95% CI -10.88, -2.44) kg, p=0.003) but not from diagnosis to post neoadjuvant treatment (p=0.197) or from post neoadjuvant treatment to ≥ four weeks post surgery (p=0.257) (Table 6.5). Similarly, post hoc analysis of the left HGS measurements demonstrated that there was a statistically significant decrease from diagnosis to ≥ four weeks post surgery (-5.16 (95% CI -8.34, -1.99) kg, p=0.003) but not from diagnosis to post neoadjuvant treatment (p=0.173) or from post neoadjuvant treatment to ≥ four weeks post surgery (p=0.861) (Table 6.6).

Table 6.4 Post hoc pairwise comparisons for 6MWT

6MWD (metres)	**Mean Difference (95% C.I)**	**P value**
Difference from diagnosis to post neoadjuvant treatment (T2-T1)	-3.25 (-83.73, 77.23,)	1.00
Difference from post neoadjuvant treatment to ≥ 4 weeks post surgery (T3-T2)	-59.62 (-120.00, 0.75)	.053
Difference from diagnosis to ≥ 4 weeks post surgery (T3-T1)	-62.87 (-148.46, 22.71)	.166

Abbreviations: *6MWD* Six Minute Walk Test distance.

Table 6.5 Post hoc pairwise comparisons for right HGS

RHGS (kg)	Mean Difference (95% C.I)	P value
Difference from diagnosis to post neoadjuvant treatment (T2-T1)	-4.22 (-10.08, 1.64)	.197
Difference from post neoadjuvant treatment to ≥ 4 weeks post surgery (T3-T2)	-2.44 (-6.12, 1.23)	.257
Difference from diagnosis to ≥ 4 weeks post surgery (T3-T1)	-6.66 (-10.88, -2.44)	.003*

Abbreviations: *RHGS* right hand grip strength, *kg* kilogram.

Table 6.6 Post hoc pairwise comparisons for left HGS

LHGS (kg)	Mean Difference (95% C.I)	P value
Difference from diagnosis to post neoadjuvant treatment (T2-T1)	-3.49 (-8.16, 1.18)	.173
Difference from post neoadjuvant treatment to ≥ 4 weeks post surgery (T3-T2)	-1.67 (-5.94, 2.59)	.861
Difference from diagnosis to ≥ 4 weeks post surgery (T3-T1)	-5.16 (-8.34, -1.99)	.003*

Abbreviations: *LHGS* left hand grip strength, *kg* kilogram.

6.4.5 Results for the measurement of habitual physical activity levels

Results for objectively measured habitual physical activity levels at each study time point are detailed in Table 6.7. Participants wore the ActiGraph accelerometer for an average (SD) of 6.3 (0.95) days at T1, 6.27 (1.35) days at T2 and 6.17 (1.33) days at T3. An ActiGraph was worn at each time-point by all participants with the exception of one at T1 as the participant was overseas and declined to wear a monitor. At the T3 time point one monitor had not been returned at the time of study analysis. In addition, four of the ActiGraphs which were worn and

returned by participants at the T3 time point did not meet the requirements for wear time validation in the ActiLife software and therefore were unsuitable for analysis. These accelerometers had a daily wear time of less than 10 hours and therefore, as outlined in Section 2.3.3.5, were not valid for inclusion in the analysis (Troiano et al., 2007). As valid physical activity data was only available for a small number of participants at all three time-points (n=5), an ANOVA analysis was not carried out and all available data was presented descriptively (Figure 6.6, Figure 6.7, Figure 6.8 and Figure 6.9).

Table 6.7 Results for objectively measured habitual physical activity levels

Physical Activity Levels	**Diagnosis (T1)** **(n=10)**	**Post neoadjuvant treatment (T2)** **(n=11)**	**≥ 4 weeks post surgery** **(n=6)**
Sedentary behavior (min.day^{-1})	498.26 (57.61)	505.78 (57.96)	523.04 (110.59)
Sedentary behavior (% of total wear time)	64.76 (9.18)	67.54 (5.73)	75.54 (11.56)
Light activity (min.day^{-1})	250.45 (80.77)	221.81 (57.74)	156.32 (80.64)
Moderate activity (min.day^{-1})	24.46 (16.75)	24.24 (23.15)	13.89 (15.25)
Vigorous activity (min.day^{-1}) ‡	0.00 (0.79)	0.00 (0.00)	0.00 (0.04)
Mod-to-vig activity (≥10 minute bouts) (min.day^{-1})‡	4.64 (11.12)	5.33 (25.33)	4.93 (7.61)

Data are displayed as mean (standard deviation) unless indicated otherwise. ‡ Variable not normally distributed, data presented as median (interquartile range). Abbreviations: *min.day^{-1}* minutes per day

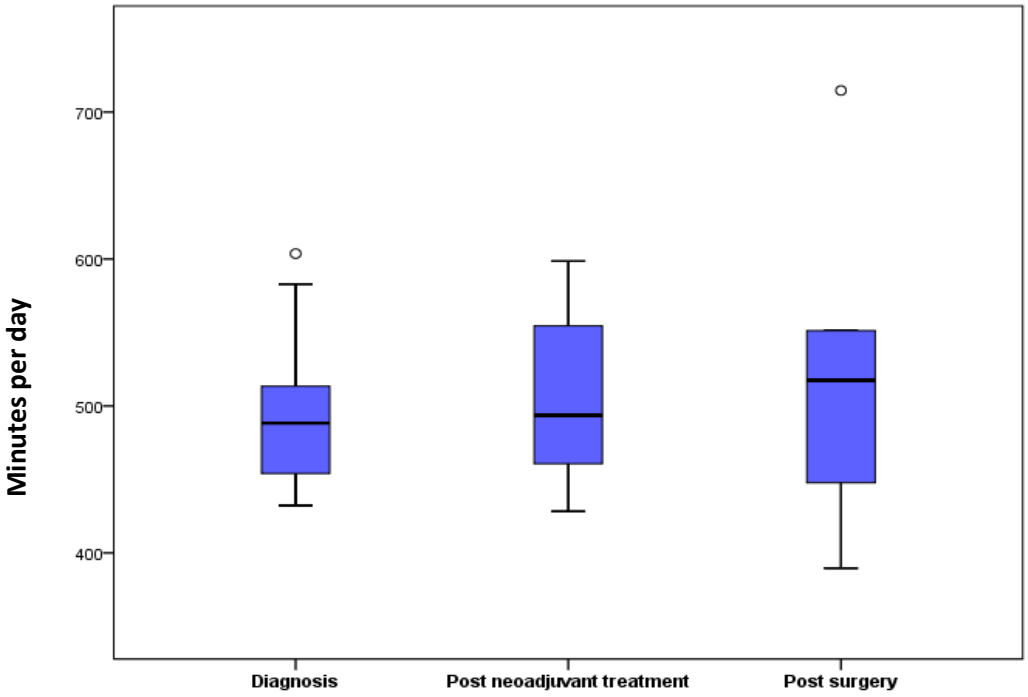

Figure 6.6 Minutes per day spent in sedentary behaviour at each study time point (represented as median and interquartile range)

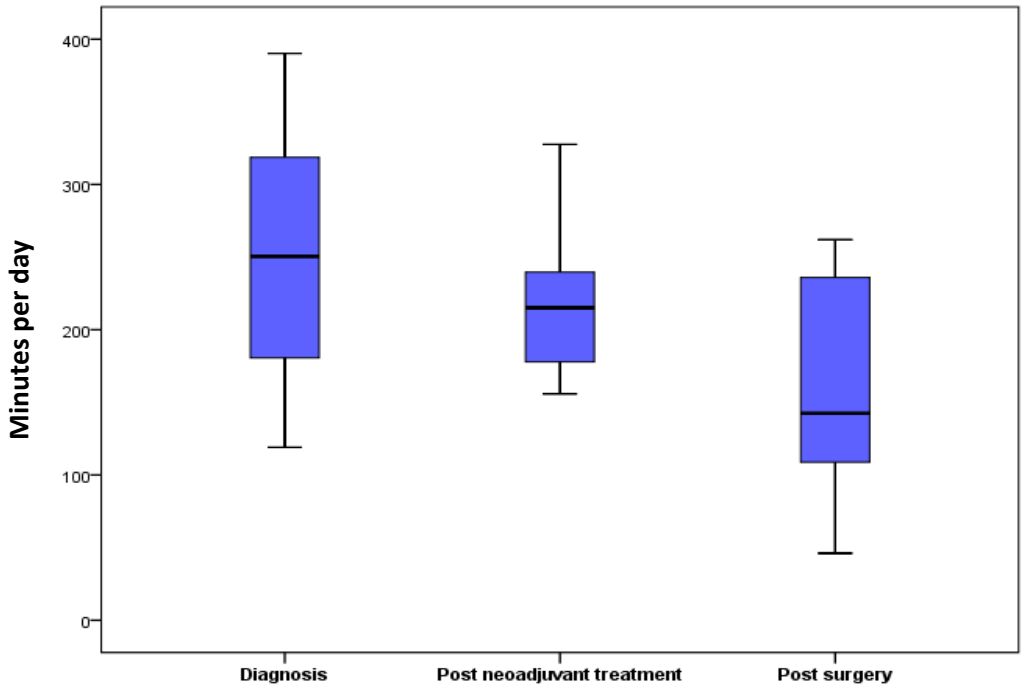

Figure 6.7 Minutes per day spent in light intensity activity at each study time point (represented as median and interquartile range)

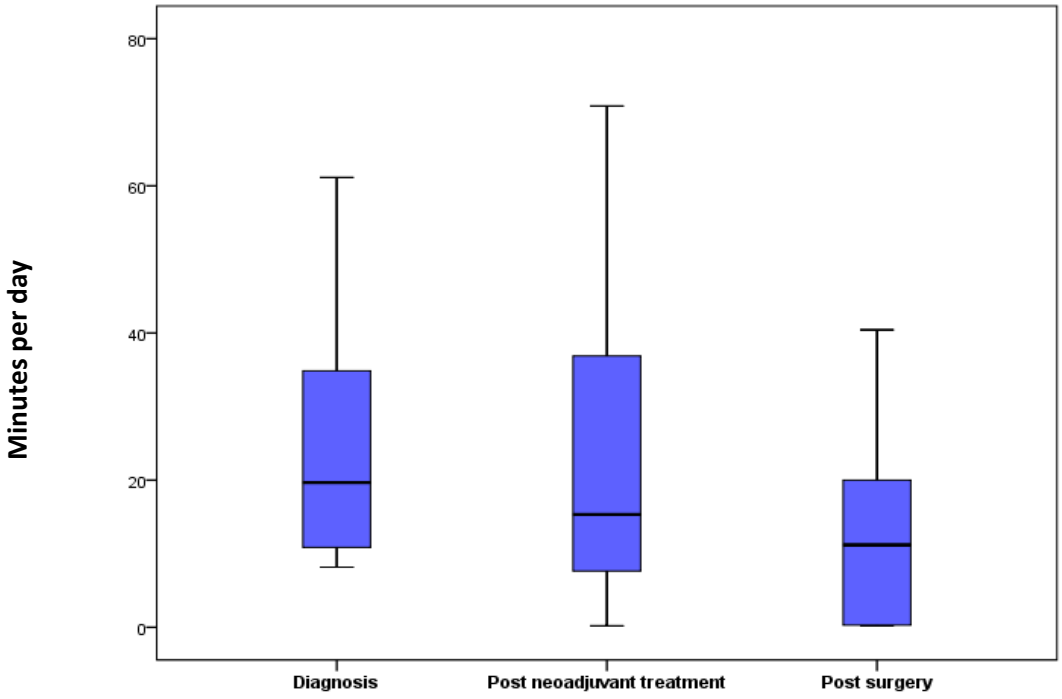

Figure 6.8 Minutes per day spent in moderate intensity activity at each study time point (represented as median and interquartile range)

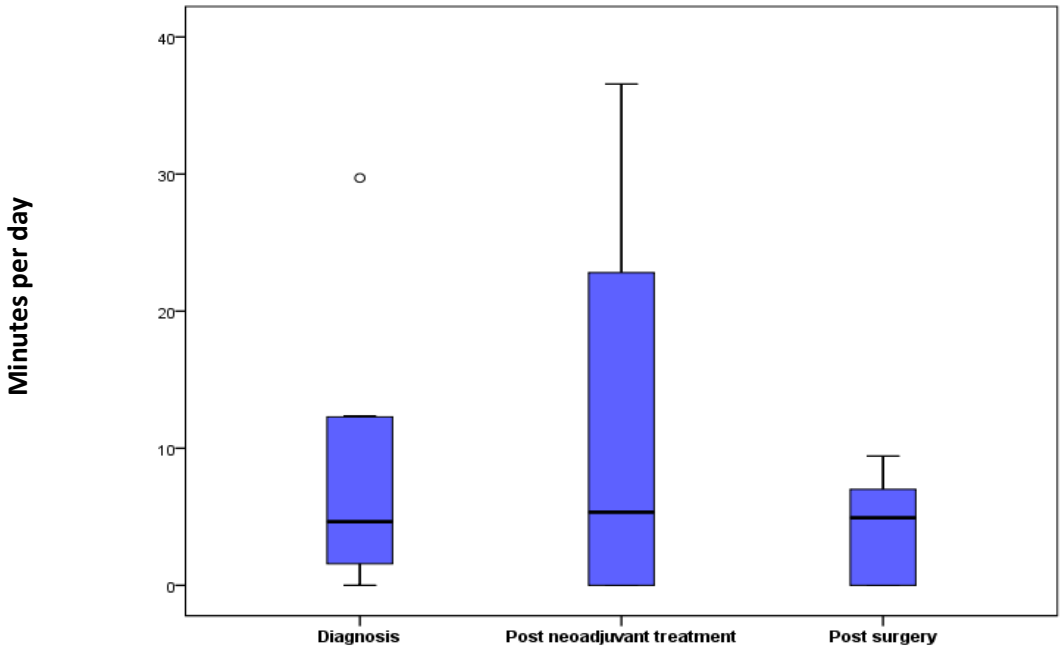

Figure 6.9 Minutes per day spent in bouts of moderate - vigorous intensity activity at each study time point (represented as median and interquartile range)

At diagnosis, this cohort spent 65% of their time sedentary, with this figure increasing to 67% post neoadjuvant treatment and further to 75% at least four weeks post surgery and discharge from hospital. The average time spent engaged in moderate intensity activity was the same at diagnosis and post neoadjuvant treatment (24.46 (16.75) minutes per day and 24.24 (23.15) minutes per day respectively). However, for those who wore a monitor at least four weeks post surgery the average time in moderate intensity activity dropped to 13.89 (15.25) minutes per day. The median time spent in vigorous intensity activity was zero minutes per day across all three study time points. When the data was analysed for time spent in bouts (≥10minutes) of activity, it revealed that this cohort spent a very small minority of their time engaged in bouts of moderate-to-vigorous intensity activity across all study time points. A median of 4.64 (11.12) minutes per day at T1, 5.33 (25.33) minutes per day at T2 and 4.93 (7.61) minutes per day at T3, was recorded. Accordingly this group were not meeting the PA guidelines recommended for cancer survivors at any study time-point.

6.5 Discussion

The aim of this study was to assess the impact of curative multimodal treatment for oesophageal cancer on physical performance. While this is an ongoing study, the preliminary results presented here indicate that fitness, strength and physical activity levels are adversely affected by these cancer treatments. These results are consistent with previous literature which has reported significant decreases in both fitness and strength after neoadjuvant therapy and surgery (Jack et al., 2014, Lund et al., 2015, Liedman et al., 2001, Taguchi et al., 2003, Tatematsu et al., 2013b). The results in this study indicate that physical performance is more adversely affected by oesophagectomy than chemotherapy and radiotherapy.

In this cohort, both fitness and physical activity levels were preserved from diagnosis to post neoadjuvant treatment. These findings are similar to those reported by Tatematsu et al., (2013a) where both 6MWT distance and subjectively measured physical activity levels remained the same from pre to post neoadjuvant chemotherapy. Similarly in a study by Rawat et al., (2011) the distance in the 6MWT decreased by less than would be considered clinically meaningful from pre to post neoadjuvant therapy. However, these findings differ from three studies which measured fitness pre and post neoadjuvant treatment for oesophageal cancer using a CPET or maximal working capacity test and reported significant losses in fitness levels (Jack et al., 2014, Lund et al., 2015, Liedman et al., 2001). As discussed in Section 1.3.4, the discrepancy between these results may be due to the lower sensitivity of the 6MWT, as compared to a CPET, to treatment effects. It has been suggested that walking tests may not be sensitive enough to assess changes in exercise capacity in patients with early-stage disease or in those without concomitant comorbid disease because they may not sufficiently stress the cardiovascular system (Jones et al., 2008a). The participants in this study cohort were eligible for curative treatment and had minimal comorbidities and therefore the 6MWT may not have been sensitive enough to identify changes in fitness in the early stages of treatment. As physical activity levels were also maintained from pre to post neoadjuvant treatment in this group, it could be hypothesised that the effect, if any, of chemotherapy and radiotherapy on fitness levels was too small to be picked up by the 6MWT.

The results of this study demonstrated that oesophagectomy had a more profound impact on fitness and physical activity levels than neoadjuvant treatment. A clinically meaningful decrease of greater than 50 metres was observed in 6MWT distance from pre to at least four weeks post surgery in this study cohort, indicating a clinically meaningful decrease in fitness levels, which also approached statistical significance ($p=0.053$). Furthermore, sedentary

behaviour increased from 67% to 75% of total wear time and time engaged in moderate intensity activity dropped from an average of 24 minutes per day to 13 minutes per day from pre to at least four weeks post surgery in this group. These findings show that participants were highly sedentary in the initial weeks post surgery and discharge from hospital and engaged in almost no moderate or vigorous intensity activity. This reflects the results in Study 2, where long term survivors of oesophageal cancer described the initial weeks and months post surgery as particularly difficult and reported that their activity levels were very low during this time.

The strength levels of this cohort were also negatively affected by treatment for oesophageal cancer. There was a significant loss in both right and left HGS from diagnosis to post oesophagecomy. As the HGS measurements decreased consistently across the three study time-points, these findings indicate that losses in strength can occur with both neoadjuvant treatment and surgery. It has been established that sarcopenia is prevalent in patients with oesophageal cancer. Recent studies have reported increases of 17% to 24% in the number of patients classified as sarcopenic from pre to post neoadjuvant chemotherapy (Awad et al., 2012, Yip et al., 2014), with similar findings demonstrated in Study 1 in this thesis. Therefore these patients could be experiencing a loss of muscle mass throughout the treatment trajectory with resulting in losses in strength. As expected in this cohort, consistent weight loss was observed throughout the treatment trajectory, with average body weight and BMI measurements decreasing after both neoadjuvant therapy and surgery.

Finally it was noteworthy that suboptimal fitness and physical activity levels were prevalent in this group from diagnosis and throughout the treatment trajectory. The highest distance achieved in the 6MWT by this cohort was 536 metres at the diagnosis time point. This is lower than the distance that would be expected for healthy older adults. Normal values for the 6MWT range from 576 metres to 659 metres (Enright and Sherrill, 1998, Camarri et al., 2006, Troosters et al., 1999). Furthermore, the median time spent engaged in bouts of moderate to vigorous intensity activity ranged from four to five minutes per day at all study time points. This amounts to an average of 28 to 35 minutes per week engaged in these important activity intensities, which falls far short of the figure of 150 minutes per week which is recommended for health benefits in patients with cancer (Schmitz et al., 2010). These findings indicate that prehabilitation and rehabilitation programmes targeting fitness and physical activity levels are indicated in this group in order to optimise physical performance both prior to surgery and post completion of treatment.

6.5.1 Limitations

This study has a number of limitations which warrant discussion. Due to the use of a field walking test, fitness levels were measured indirectly. As discussion in Section 6.5, this test may not have been sensitive enough to identify small changes in fitness from pre to post treatment in this group. This test however is clinically meaningful and is easily reproducible in a variety of settings and was deemed the most appropriate test for this study for the reasons outlined in Chapter 2 (Section 2.3.1.1). As the results presented here are preliminary results from an ongoing study the sample size is small, however this study provides informative early data on a limited, under researched group. Furthermore due to the inclusion of participants who completed all three study assessments only, this study consists of a somewhat biased sample. Those who were able to attend all three study assessments represent those who successfully completed treatment, were discharged from hospital and were generally doing relatively well post-operatively. However, this is the patient type who will likely be targeted with interventional programmes and therefore represents the cohort of primary interest for this research.

It must be noted that the results presented here are as a result of an interim analysis of the preliminary data from an ongoing longitudinal study. There may be some bias associated with this as the study assessors continuing the study will be aware of the initial trend of the results. However this study contains an inherent bias as it is observational only and the assessments are unblinded. Therefore the study investigators may already be aware of trends in the data due to clinically meaningful and noticeable changes in performance observed in participants throughout the progression of the study. Another inherent bias associated with this study arises from the fact that the research team are acutely aware of the patient's medical status and those who are most unwell are less likely to complete assessments at designated timepoints. As this study does not include a comparison of an intervention and control group, early trends in the study results known to investigators cannot bias the assessment of one group as compared to another. The study assessments are conducted according to a strict pre-defined protocol and this will remain the same throughout the entire study period. Therefore it is anticipated that this preliminary interim analysis will have no significant impact on the overall study results.

6.6 Conclusion

The preliminary data presented in this study has revealed that physical performance is adversely affected by curative treatment for oesophageal cancer. These results suggest that interventional programmes targeting strength, fitness and physical activity levels are indicated in this cohort in order to optimise physical functioning both prior to surgery and post completion of treatment.

Chapter 7 Study 4: Treatment experiences and patient perspectives on physical functioning during curative multimodal treatment for oesophageal cancer

7.1 Introduction

The aim of Study 3 in this thesis was to objectively measure the impact of multimodal treatment for oesophageal cancer on physical performance. The aim of this study was to complement these results with a qualitative exploration of patient perspectives on the impact of a cancer diagnosis, and commencement of treatment, on their lifestyle and physical functioning. The aim was to explore potential reasons for the changes in physical functioning which occur during treatment for oesophageal cancer. Changes in physical functioning may be as a direct result of the physical impact of treatment, due to conscious lifestyle changes made by patients after a cancer diagnosis or due to other reasons. In addition, this study aimed to examine participants' knowledge and understanding of exercise and activity and their role across the cancer continuum and to determine the importance they placed on them.

It has been shown that decreased exercise tolerance and activity levels pre oesophagectomy are associated with an increased occurrence of post-operative complications (Feeney et al., 2011, Murray et al., 2007, Moyes et al., 2013). Increasing patient fitness and activity levels before surgery through a prehabilitation programme may reduce the risk of post-operative complications (Singh et al., 2013). However the implementation of a prehabilitation programme poses many practical issues, some of which were identified in the initial stages of this PhD. Patients may be undergoing chemotherapy and radiotherapy in the proposed prehabilitative period. While it has been shown that exercise is safe during chemotherapy and radiotherapy, the side effects of these treatments are well documented and include fatigue, cachexia, myopathies and neuropathies. These side effects may impact on patient's ability and willingness to exercise. In addition it is unclear what an optimal prehabilitation programme should consist of in terms of type, location, duration, frequency and intensity. Qualitative research in this patient cohort may address some of these issues from a patient perspective. By interviewing patients immediately post completion of neoadjuvant treatment this study aimed to gain valuable information on patients' physical functioning and willingness to complete an exercise intervention in this time period. This study also aimed to investigate any physical challenges patients encountered and any concerns or suggestions they had regarding

exercise and activity at this time.

7.2 Study aims and objectives

The overall aim of this study was to describe the treatment experiences of patients with oesophageal cancer while undergoing curative multimodal treatment. The specific objectives of the study were:

- To describe the effect of a cancer diagnosis and its treatment on participants' lifestyle and physical functioning.
- To explore participants' knowledge of physical activity guidelines and perceptions about their own level of physical activity.
- To identify potential barriers and facilitators to recommended physical activity levels and exercise.
- To obtain participants' views on the development of prehabilitation programmes for patients with oesophageal cancer.

7.3 Methods and measures

7.3.1 Study design

As discussed in Chapter 3 (Section 3.2), a qualitative descriptive study design was used in this study and individual semi structured interviews with open ended questions took place.

7.3.2 Sampling and recruitment

Criterion purposive sampling, as described in Section 3.4 was used in this study. The criterion for inclusion was that participants were undergoing curative multimodal treatment for oesophageal cancer at the time of the study. Eligible participants had completed neoadjuvant therapy and were scheduled for surgery. Patients receiving multimodal therapy only were selected for inclusion in this study because the provision of neoadjuvant treatment provides a window of opportunity between diagnosis and surgery when a prehabilitation programme could potentially be introduced. Therefore in order to investigate patient perspectives on the

feasibility of such a programme, it was necessary that they had completed neoadjuvant treatment.

This qualitative study formed part of a larger longitudinal study carried out from diagnosis, throughout treatment and into recovery in this cohort. Preliminary results from this longitudinal study are presented in Study 3 in this thesis. Accordingly, details about the qualitative component of the study were included in the original PIL which participants received at the beginning of the study (Appendix XVI). When participants had successfully completed neoadjuvant therapy and were scheduled for surgery, they were invited to complete an interview. When potential participants agreed to take part, they were given the option of completing the interview in person or over the phone and asked to nominate the day and time that best suited them. All participants who took part in Study 3 were considered for inclusion in Study 4. However not all participants who completed an interview and are included in Study 4 were included in the preliminary results reported in Study 3 in this thesis. Reasons for this included: (1) some participants completed an interview in the pre-operative period but were not able to attend for a post-operative study assessment for Study 3 and therefore were not included in the preliminary analysis in this thesis or (2) some participants completed an interview for Study 4 but subsequently went on to have a gastrectomy and therefore were not included in the preliminary analysis in this thesis.

7.3.3 Interview schedule

The development of the interview schedule involved (1) examining the literature on qualitative descriptive research in general and in an oesophageal cancer population and (2) referring to the study objectives listed in Section 7.2. As discussed in Section 3.3, questions were designed to be simple, open-ended and flexible. Additional questions designed to probe for more depth were included in the schedule, to be used if deemed necessary. The interview schedule is contained in Appendix XVII.

7.3.4 Ethical approval

Ethical approval was granted by the SJH/AMNCH research ethics committee and all participants provided written, informed consent (Appendix XVI & Appendix XV).

7.3.5 Data analysis

Data analysis of the interview transcripts was carried out as described in Section 3.7.

7.4 Results

7.4.1 Participant selection and identification of saturation

Nine participants were interested in participating in the study and were available for interview post neoadjuvant therapy and prior to surgery. Recruitment took place between July 2014 and June 2015. As described in Chapter 3, recruitment continued until data saturation was reached. It was clear from the analysis of the 7th - 9th interviews that no new information, perspectives or themes were found from the data and therefore recruitment was stopped at nine participants.

7.4.2 Participant characteristics

Nine participants (seven men) with an average age of 62 years completed an individual semi-structured interview with the lead investigator (JG). Participant demographics and interview details are presented in Table 7.1. Eight face-to-face interviews took place and one interview was carried out over the phone. Eight participants completed the interviews independently and one participant attended for a face-to-face interview with his wife. All participants had completed neoadjuvant therapy and were scheduled for surgery. The average interview duration was 12 minutes with a range from 6 - 29 minutes. Over 20,000 words of original content was transcribed.

Table 7.1 Participant characteristics and interview details

Participant ID	Gender	Age	Current occupational Status	Cancer Type	Neoadjuvant treatment type	Interview Type	People present	Interview Duration (minutes)
G2QP01	Male	74	Retired	AC	CROSS protocol	Face-to-face	Participant only	8
G2QP02	Female	60	Sick leave	SCC	CROSS protocol	Face-to-face	Participant only	9
G2QP03	Female	57	Retired	AC	MAGIC protocol	Face-to-face	Participant only	12
G2QP04	Male	64	Sick leave	AC	CROSS protocol	Telephone	Participant only	6
G2QP05	Male	64	Sick leave	AC	MAGIC protocol	Face-to-face	Participant only	15
G2QP06	Male	69	Working	AC	CROSS protocol	Face-to-face	Participant only	10
G2QP07	Male	62	Sick leave	AC	CROSS protocol	Face-to-face	Participant & wife	29
G2QP08	Male	59	Working	AC	CROSS protocol	Face-to-face	Participant only	11
G2QP09	Male	53	Sick leave	SCC	CROSS protocol	Face-to-face	Participant only	11

Abbreviations: *AC* adenocarcinoma, *SCC* squamous cell carcinoma.

7.4.3 Inter-rater and intra-rater reliability

Section 3.7.3 outlined the methods used to examine the reliability of the coding and the formula used to calculate the inter-rater and intra-rater reliability. The results are presented in Table 7.2 and Table 7.3. Most discrepancies were errors of omission, where one or the other coder overlooked text that could be coded. All disagreements that were not an error of omission were resolved through discussion.

$$\frac{\text{Number of agreements x 100}}{\text{Total number of agreement + disagreements}}$$

$$= \frac{102 \text{ x } 100}{102 + 21}$$

$$= 83\%$$

Table 7.2 Inter-rater reliability of the coding system (Miles and Huberman, 1994)

$$\frac{\text{Number of agreements x 100}}{\text{Total number of agreement + disagreements}}$$

$$= \frac{108 \text{ x } 100}{108 + 8}$$

$$= 93\%$$

Table 7.3 Intra-rater reliability of the coding system (Miles and Huberman, 1994)

It is common to expect that inter-rater reliability be ≥70%, while intra-reliability would be expected to be ≥80% (Miles and Huberman, 1994). The results obtained demonstrate the reliability, both inter-rater and intra-rater, of the coding system.

7.4.4 Themes and sub-themes

Three primary themes and a number of sub themes were identified from the analysis of the interview transcripts. These themes and sub-themes are presented in Table 7.4.

Table 7.4 Themes and sub-themes generated through interview analysis

Themes	1. Experiences of oesophageal cancer and its treatment	2. Physical activity and exercise during treatment for oesophageal cancer	3. The role of prehabilitation during treatment for oesophageal cancer
Sub-themes	• Physical impact • Lifestyle impact • Emotional impact	• Barriers to exercise • Facilitators to exercise • Exercise knowledge & understanding	• Feasibility of prehabilitation • Interest in prehabilitation • Structure of prehabilitation

7.4.4.1 Theme 1: Experiences of oesophageal cancer and its treatment

The first theme which emerged from the data in this study was 'experiences of oesophageal caner and its treatment'. This was divided into three major subthemes: the physical impact, the lifestyle impact and the emotional impact.

Physical impact

Participants discussed the impact that a cancer diagnosis and the subsequent commencement of treatment had on their physical functioning. For the majority of participants, treatment had some impact on their physical functioning, even if only temporarily. Fatigue was mentioned frequently with participants noticing a decrease in their strength, stamina and fitness levels, particularly as treatment progressed. Activity limitations discussed included: having difficulty with heavy lifting, chopping wood or cutting grass, being restricted in the distance they could walk or being restricted in a particular hobby e.g. playing golf.

"Coming towards the end of the treatment I was finding that a bit harder to walk...not a great distance now you know... about quarter of a mile maybe." [G2QP01]

"Well at one time there...I'd be dead tired after about the third or fourth hole [of golf], I'd be dead tired... I gave it up for... a month [during] chemotherapy." [G2QP08]

"I just have to be careful, not lifting anything awkward, not overexerting, at the moment but I don't physically feel strong enough to be lifting anything compared to what I would be." [G2QP07]

Other more specific side effects of treatment were also reported and included low blood pressure and dizziness, sensory problems, altered bowel movements, inflamed lungs, sore throats and infections.

"I tend to have low blood pressure anyway and it was completely exacerbated by the chemo and by I suppose just not being able to eat and so if I did anything at all.. if I was out in the garden and I was bending down and I knew if I stood up...I'd be feeling dizzy and faint and I'd have to sit down for 10 minutes or something. So that was kind of constant throughout the chemo." [G2QP03]

However, for some participants the treatment effects were only temporary and they described the overall experience as generally positive with a negligible long term physical impact and minimal side effects overall.

"It wasn't bad at all now you know...not bad. Because I kind of sailed through that, that was no problem, the chemo." [G2QP01]

"I was working during my treatment, but em.. no I was lucky I had just the right dosage or something. It was very bearable indeed." [G2QP06]

"I haven't been sick during this... since the treatment started, I haven't been sick." [G2QP08]

A number of participants reported that while they had no particular problems during the neoadjuvant treatment, they began to experience side effects once the treatment had finished. In the initial few weeks post completion of neoadjuvant treatment, some participants described being completely 'wiped out' and feeling unable to do anything.

> *"Only when I came out...For two weeks or a little more I just couldn't do anything... and that was the first time that I had felt like that." [G2QP01]*
>
> *"During the chemo, during the treatment I was fairly active, it was just after the treatment that my activity levels dropped completely...immediately post chemo.. my activity levels were zero." [G2QP02]*
>
> *"When I was in the hospital you couldn't keep me in the bed...It wasn't until I got home that it hit me. Everything hit me at once." [G2QP09]*

For those who experienced this post treatment drop in energy levels, most reported that their activity levels gradually started to increase again over a period of two to six weeks and at the time of interview, were almost back to normal.

> *"Oh I'd say about five to six weeks after the chemo. It's only in the last two to three weeks that I actually feel I'm back to my original level of activity." [G2QP02]*
>
> *"As soon as I got out of the hospital... I couldn't do anything...call it fatigue...I made a cup of tea and I had to go and sit down... I couldn't do anything and I was like that for about four weeks... It's only just recently, I'd say in the last three weeks that I'm getting back to normal." [G2QP09]*

Accordingly, at the time of interview, the majority of participants described themselves as an 'active person'. Some described their current exercise habits which primarily included walking and playing golf. Others described how they had endeavoured to maintain a good level of activity during their treatment thus far.

"At the moment, I'd be doing...roughly I'd be walking four miles a day...sometimes more, sometimes less, seven days a week." [G2QP09]

"Well I'm active alright because I play the golf still so...now I played it three times last week." [G2QP08]

"Even when I was on the chemo on my good days I'd be trying to go out...when we had beautiful weather...with friends, I'd go for a walk for an hour around the...park and that was ok I could do that." [G2QP03]

Lifestyle impact

In addition to the changes in physical functioning, the impact, if any, oesophageal cancer and its treatment had on the participants' lifestyle was described. Some reported no problems with maintaining a relatively normal lifestyle and completing household tasks while others reported that they were 'minding themselves' somewhat and therefore were restricted in some activities.

"I do a lot of cooking and that.. so that's fine now. Pottering around." [G2QP01]

"I'm working away as normal as such, doing the usual chores around the house." [G2QP04]

"He's very good at doing housework and stuff like that...like he'd potter in the garden...he'd vacuum and clean the bathrooms and stuff like that so he still does that." [G2QP07Wife]

"But I haven't been able to do the things I like doing...I'm still minding myself I suppose really." [G2QP01]

"I was kinda minding myself a bit, maybe too much!" [G2QP05]

For some, the most significant lifestyle change was going on sick leave from work during their treatment. In some cases, this was described as a reason for a reduction in activity levels.

"No I'm not doing a lot of exercise you know, I didn't actually work officially since I got ill you know." [G2QP04]

"Because I'm not working now at the minute and you know you are lazing about the house and that and there's only so much you can do." [G2QP05]

"The only thing I gave up was work. I couldn't go to work. That was just too strenuous, I packed that in you know...That's...the only main change, is giving up the work." [G2QP09]

Another difference in lifestyle described was changes in eating habits. Some had experienced significant dysphagia which resulted in a very limited or restrictive diet. Others described experiencing significant weight loss and feeling that they had to eat large amounts of food just to maintain their weight.

"I'd say...I have lost over three stone...that was before the treatment...before the treatment I just couldn't eat. I was on liquids...the weight just fell off me. Over three stone...and it's very hard to get it back on, especially when you are on liquids...you're not eating proper." [G2QP09]

"It was hard to put that back up so I got back to 50 [kilograms] but I found that very hard particularly when I started to eat again and I wasn't on the feed.. just eating enough to keep it on.. I could just maintain and I thought I was eating a huge amount and that I was...and I was sure that I was going to be piling on the pounds...particularly with the kind of food that I was eating but in fact no I was really surprised that I was just maintaining." [G2QP03]

"I'm on over 3000 calories a day. There's no way you'd burn them all off...But you wouldn't think it to look at me." [G2QP09]

Emotional impact

The emotional impact of a cancer diagnosis was discussed, with some participants describing feeling upset and anxious, particularly initially after receiving the diagnosis. However, as time went on and they commenced treatment, the importance of having a positive attitude and a good sense of humour was discussed. This was deemed particularly important when any

problems arose during treatment. Participants felt it was important not to focus on the negative and to look towards recovery.

> *"It does affect you naturally enough, when you hear the word like cancer or that or you have to go for chemo, it knocks you, it does knock you...But I feel myself I was strong enough to get around that. I might have had the odd cry in the corner now, I have to say that now...but in general then I just said to myself 'lookit that's life you know', you get up and you get on with it now.. You have to be positive." [G2QP05]*
>
> *"I've put it out of my mind, what I have, I didn't let it get to me. If someone asks me 'how do you feel' and I say 'sure I'm alright sure I'm able to do what I want to do and that's it you know'." [G2QP08]*
>
> *"But he has a great sense of humour through it all, I have to say he never lost his sense of humour, which is brilliant." [G2QP07Wife]*

With neoadjuvant treatment successfully completed and the side effects of treatment diminishing over time there was a strong overall sense of 'feeling good' at the time of interview.

> *"But as I say I do feel good now." [G2QP01]*
>
> *"I'm working away the finest. Healthy enough I think." [G2QP04]*
>
> *"I feel 100% now." [G2QP06]*

One participant and his wife talked about the importance of receiving information and support from healthcare professionals who they found to be very approachable. They felt that any question they had was answered and this was described as a great source of comfort and reassurance.

"But it's nice to know that there is people there to turn around and say... and you can talk and if they're in the ward 'can I ask you something', 'yea that's grand' and they'll sit there and talk to you and they'll help you out." [G2QP07]

"Because all the information makes a difference because you're not the whole time in your mind thinking I wonder.. or this or that.. it's already answered and you know.. So you're not afraid to sleep because you can't, you're afraid of what the next thing is or whatever." [G2QP07Wife]

"The horror... Yea what if, what if, what if and you're assuming.. It's the assumptions yea, the assumptions are the frightening part" [G2QP07]

"The information is incredibly valuable" [G2QP07Wife]

7.4.4.2 Theme 2: Exercise and activity during treatment for oesophageal cancer

The second theme to emerge from the data was 'exercise and activity during treatment for oesophageal cancer'. This included the following subthemes: barriers to exercise, facilitators to exercise and exercise knowledge and understanding.

Barriers to exercise

Any barriers to exercise which participants experienced at the time of data collection were discussed. Some of these were specifically related to the fact that participants had cancer and were undergoing treatment, while others were more general barriers to exercise. Concerns regarding weight loss and changes in eating habits were the primary disease related barriers to exercise in this cohort. Some participants described restricting their activity in an effort to maintain their weight.

"It's nice to maintain a certain level of activity but at the same time you just have to kind of try and hold on to the calories at the same time...I'm purposefully slowing down in order to maintain the calories." [G2QP02]

On the other hand, some did recognise the benefits of exercise for building up muscle strength and therefore were keen to maintain it, regardless of any concerns with their weight.

"I think exercise builds up muscle and it builds up strength rather than you know...that wouldn't be an issue for me at all, you know I'd see the benefits." [G2QP03]

Restrictive eating habits such as a liquidised or dairy based diet were also reported as a reason for a reduction in energy levels and therefore a barrier to exercise.

"It's so limited what he can take in and that's why he doesn't, it's not enough to give him good energy." [G2QP07Wife]

Some participants reported that their activity was limited as they had been told to 'take it easy' during their treatment.

"But I haven't been able to do the things I like doing...because I was told just to take things easy." [G2QP01]

Finally, being unable to go out for a walk due to bad weather was also described as more general barrier to exercise.

"I'd say I am active, now there is days of course as I say weather permitting again that you can't get out." [G2QP05]

Facilitators to exercise

A number of facilitators to maintaining exercise and activity levels during treatment were discussed. Participants spoke about wanting to maintain fitness levels in the lead up to surgery and as a result had made a conscious effort to exercise habitually.

"I kind of...try to get into a routine and make it a habit that no matter what way you're feeling you get up and go out and do it...I like to keep myself active so...I'm trying to keep as fit as I can for the operation that's coming up." [G2QP05]

This attitude and determination to maintain normal activity levels during treatment was a very important facilitator.

"I tell ya actually the only exercise I ever got was going from my bed.. down to the radiotherapy treatment..And the first day they sent up a wheelchair for me.. 'what's this for'...'we have to take you'.. 'no way'... it was a dietician...a dietician said it's too much of a walk...you're not taking enough in...you'll be losing weight.. I said I won't be losing weight... I never once in the five weeks used the wheelchair, I refused it." [G2QP09]

Improvements in eating habits were also described as an important facilitator to exercise. Some participants reported that when problems such as dysphagia had improved or had been resolved this facilitated an increase in energy and activity levels.

"Because I'm eating like a horse now...Because I have no blockage and it's going down normally you know so I'm eating normal food and quite a lot of it...I feel a lot brighter...I can certainly walk better." [G2QP01]

Other more general facilitators to exercise included good weather, having to cut the grass or having to walk the dogs.

Exercise knowledge and understanding

Participants' knowledge and understanding with regards to exercise and activity were explored. The majority of participants recognised the benefits associated with exercise and reported feeling better when they engaged in exercise.

"I'd know that there are health benefits if you do a certain amount of exercise." [G2QP02]

"I feel much better and as the weeks went on, doing the exercise as I say and the walking and just getting up for the game of golf and getting out as well.. I felt much better as the weeks went on." [G2QP05]

One participant was particularly surprised at how beneficial exercise was for improving cancer related fatigue, as he had thought the opposite to be true.

"Now I couldn't believe it when they told me, go and exercise, you won't be so tired...I thought it would be the opposite but actually you have more energy when you come back from your walk...I mean I'm out digging the garden and everything!" [G2QP09]

Seven out of the nine participants included in the study had not heard of physical activity guidelines and did not know what they were. Two participants had a vague awareness of the guidelines and explained their understanding of them.

"Well I suppose I'd be aware in a general way...but I wouldn't have specific figures for different age groups or anything like that, I would just know that a certain amount of physical activity every day is good and 20 minutes maybe of increased heart rate or whatever...so that sort of thing." [G2QP03]

"I think there is consensus now that something like 10-15 minutes moderately vigorous exercise per day is about the optimum...about 10 minutes a day, minimum moderate exercise, which is what I do anyway." [G2QP06]

7.4.4.3 Theme 3: Role of prehabilitation

The final theme in this study was 'the role of prehabiliation in an oesophageal cancer cohort'. Prehabilitation was discussed in terms of feasibility, interest and structure (location and timing).

Feasibility of prehabilitation

Participants were asked if they felt they would have been able to complete a prehabilitation programme in the time period between diagnosis and surgery, during which time they received neoadjuvant chemotherapy and radiotherapy. There were varied responses regarding the feasibility of an exercise programme in the pre-surgery period but the majority of participants felt that they would have been able for some sort of programme at certain times during this period. However they clarified it would depend on the exact timing and components of the programme.

> *"So yea there were times when I could have done something yes. But now it depends on what it was." [G2QP03]*

Some participants described when they felt they might not have been able for an exercise programme. This was primarily when significant side effects of treatment were experienced or when they felt their stamina was particularly low.

> *"Em.. I don't know if that would have been on now to be honest with you, you know... 'cos...coming towards the end of the treatment I was finding that a bit harder to walk...not a great distance now you know." [G2QP01]*

> *"Em maybe not...certainly not during the worst times of it, there were...like obviously there's the day of the chemo itself...that really knocked me for six. So I had the very strong symptoms on the day, the tingling fingers and the cramps in the legs and all that, the eye difficulties and then...so then as the week went on they sort of grew less but then the second week like whatever 10, 12 days afterwards for 3 or 4 days I was just completely knocked out." [G2QP03]*

One participant felt that it would be hard to take on an additional programme on top of the activity she tried to maintain herself.

> *"I don't think I would have been able for it. When I look back at how I went through it I don't think I would have been able for any kind of a programme other than what I have just been doing." [G2QP02]*

Interest in prehabilitation

There was a high level of interest in a prehabilitation programme within this study group with six out of nine participants stating they would most likely have taken part in such a programme, especially if they 'thought it would help'. Some participants spoke about what they considered the benefits of such a programme would be, including motivation or a 'push' for people to exercise who may not do so independently or to 'build up' or prepare, both physically and mentally, for surgery.

> *"I'd have loved a thing like that." [G2QP09]*
>
> *"I think I'd be well up for an exercise programme...even quite a, well I won't say strenuous, but you know." [G2QP03]*
>
> *"Well I'd say it would benefit people, maybe if they did need a bit of a push, if they have people around them, you know class wise, one might feel down and out in themselves and another might push them along, 'come on we'll go and do..', you know get them up and get them out of it...some people are like that and they need that little bit of a push." [G2QP05]*
>
> *"Yea anything that could build up strength or mental...physical or mental." [G2QP07]*

One participant described the reassurance of exercising in a supervised environment with staff who were knowledgeable and where the exercise prescribed was safe and beneficial.

“Anything where you can get the help, like if you're in a class or something like that and something happens...If something happens when you’re there, there's someone there to say to you ‘that's normal’ or ‘oh no don't do that then, that's not right’. Where you're not pushing something to the boundary that you're not able for because you think you should...Anything where you can get the help to do it right...especially when you're unwell.” [G2QP07Wife]

In addition to the support provided by healthcare professionals as part of a prehabilitation programme, participants discussed the importance of peer support. Participants felt that completing an exercise programme with peers to support and motivate each other would be beneficial.

“With people around them, it might be easier for them then to...or rather it might be harder just to sit back and that if they have other people around them trying to encourage them to get out and 'come on we're going, you go, come on with us' and that. So some people need a bit of a push like that.” [G2QP05]

One participant discussed the support he had received from another patient during neoadjuvant treatment and described how that it had helped him greatly. Therefore the perceived advantage of a prehabilitation programme was that it was seen as an opportunity to increase peer support in this cohort.

“I met [other patient with oesophageal cancer]...he has a similar situation to me and we're helping each other out now...we're in hospital together...we're both going through the same thing...so we were supportive of each other that way...we kept each other a bit of company...it's all important...we helped each other in our own little ways.” [G2QP07]

In contrast, a small number of participants reported that they would rather do their 'own thing' and preferred to drive their own recovery and return to habitual activity levels. They felt motivated enough themselves to maintain a good level of activity and didn't need anyone to 'push' them.

> *"I was literally only able to do what I have just achieved myself, without anyone else introducing anything...I think it's up to everyone to get back to their own level of activity and do it in their own time and their own pace." [G2QP02]*

> *"I'd say at this stage...I would like to just go ahead with it myself...I don't think that I would get any more benefit out of it being in with a group of people.. I don't think I would. I think myself that I'd be motivated enough myself to get out and do it." [G2QP05]*

Structure of prehabilitation

Participants had varied responses regarding the optimal timing for a prehabilitation programme. Overall participants felt that they would be able to participate in a programme during the pre surgery period but it may be more difficult at certain times when they were experiencing treatment side effects. One participant stated he would have felt most able for a programme after completion of neoadjuvant treatment.

> *"Well the last two weeks I would have [been able for it]...well I think I would have been anyway." [G2QP01]*

Another participant suggested commencing a programme at a lower intensity during treatment with a gradual increase when treatment was finished and while awaiting surgery.

> *"I could have started maybe very gently while the chemo was going on and then maybe got more intense maybe as it came to the end." [G2QP03]*

One participant felt that an intervention would be more suitable after surgery, when treatment was completed and they were on the 'road to recovery'.

> *"I think I would be interested post-operatively because with the chemo it just completely wipes your system out whereas surgically I feel...I know it won't be. I know it's a long road to recovery but at the same time I don't think you'll be wiped out...your whole system won't be wiped out as much and if I thought it would speed up the road to recovery post surgery I would be interested in a programme like that yea." [G2QP02]*

More participants had a preference for a home based programme over a hospital based class for a variety of reasons including: not liking the gym, not enjoying exercising in a group setting and being 'told what to do' and not being able to travel to Dublin for a class.

> *"Oh I'd prefer to do it on my own...gyms don't appeal to me." [G2QP01]*
>
> *"A programme from home for me, you see I'm so far away." [G2QP04]*
>
> *"I've been self employed, I've worked on my own and all that...and I can't come to these classes with people telling you what to do.. I wouldn't put up with that, couldn't put up with that." [G2QP09]*

One participant felt a home based walking programme would be the most feasible to maintain and incorporate into his lifestyle.

> *"Well a walking programme would suit me particularly because, not because I'm a keen walker but my wife is and we often go for walks or that sort of thing but I would keep it up religiously, I am the sort of person, I would do, even if I didn't like doing it, I would do it if I had undertaken to do it." [G2QP06]*

Another participant talked about the benefits of a hospital based class in order to facilitate adherence to the programme, particularly for patients with low self-motivation.

> *"Well for me, just me because of the person I am, a class would be much better because if you give it to me you know a list of things to do at home I'd go oh yea great and I'll do it the first day and I might do it the second day and then the third day forget it! So no I'm not self motivated but yea if there was a class I would." [G2QP03]*

One participant who had completed his neoadjuvant treatment as an inpatient felt that his stay in hospital would have been an ideal time for an exercise programme to be completed. He reported feeling well throughout his treatment and having a lot of free time while in hospital and therefore would have benefitted from, and enjoyed an exercise intervention.

> *"I definitely would have been interested in that, because I sat in that hospital bed for 5 weeks with nothing to do. The only thing I could do was walk up and down the corridors, the weekends, they'd let me out for a few hours and I'd go down to the museums and stuff like that and come back. But if you had something like that up there [referring to hospital exercise class] just even a basic... something that you could... spend an hour in. .you know instead of just sat in that bed." [G2QP09]*

7.5 Discussion

This study has provided a description of the experiences of a cohort of patients with oesophageal cancer since commencing their treatment with neoadjuvant chemotherapy and radiotherapy. Study 2 in this thesis was also a qualitative exploration of the experiences of patients with oesophageal cancer, however it provided a more broad overview of the entire treatment and recovery experience. The retrospective account provided by long term survivors may not be a good representation of the salient challenges experienced during or immediately post treatment (Clarke et al., 2011). Therefore, by carrying out the interviews for this study

during active treatment for oesophageal cancer, an in-depth exploration of acute treatment effects and experiences was possible. This information is very useful regarding the feasibility of interventional programmes in this time period, particularly given the difficulties encountered previously with implementing a prehabilitation programme in this research centre (Section 1.5). The results of this study demonstrate that neoadjuvant treatment had an impact on physical functioning in the majority of participants. The findings of this study complement the growing body of objective data regarding the physical impact of treatment, and provide a more comprehensive overview of the acute treatment experience for patients with oesophageal cancer.

A primary objective of this study was to investigate the impact of a cancer diagnosis and neoadjuvant chemotherapy and radiotherapy on physical functioning, from the patients' perspective. In this cohort, the impact of treatment varied, with some reports of 'sailing through' and other reports of becoming very physically deconditioned during treatment. However, treatment did have some impact on the majority of participants, if only temporarily. Participants reported decreases in strength and stamina and other physical side effects such as sensory problems, low blood pressure and altered bowel movements. For some, the biggest physical impact occurred during treatment, while for others it occurred in the initial few weeks after neoadjuvant treatment was completed. By the time of interview however, approximately one to three weeks pre surgery, the majority of participants were feeling well and had made a recovery from the impact and side effects of treatment. These results indicate that while treatments such chemotherapy and radiotherapy do have an impact on physical functioning, it appears that this impact may be reasonably temporary and self limiting. However it must also be considered that getting back to a 'normal' level of activity may not be a high or healthy level of activity. Some participants in this study reported that they did not exercise frequently pre diagnosis and therefore had not experienced significant changes in their activity levels during treatment. Consequently, despite reports of returning to 'normal', this cohort may still be physically deconditioned going in to surgery. Previous studies have shown low fitness levels and physical activity levels are common in patients with oesophageal cancer prior to surgery (Murray et al., 2007, Feeney et al., 2011, Moyes et al., 2013). Furthermore, low fitness physical activity levels in the pre-operative period were demonstrated in patients with oesophageal cancer in Study 3 in this thesis.

Participants' knowledge of physical activity guidelines and perceptions about their own level of physical activity were also explored in this study. Overall, knowledge of physical activity guidelines was very poor with none of the study cohort accurately describing the guidelines

recommended for health benefits. Despite this, the majority of the study cohort was aware of the benefits of exercise, particularly for building up strength and 'feeling good'. Most study participants described themselves as an 'active person' and there was a strong sense of participants trying to maintain their normal exercise habits e.g. walking regularly, playing golf, as much as was possible during treatment. Notwithstanding these efforts, participants did report barriers to exercise which they experienced. Both disease specific and more general barriers to exercise were described. The primary disease specific barriers were quite unique to oesophageal cancer and included concerns regarding weight loss and changes in eating habits. For those struggling with maintaining their weight during treatment, a fear of losing more weight as a result of exercise was reported as a reason for having consciously reduced their activity levels. In addition, those who experienced dysphagia or were on restrictive diets, perceived their energy levels to be lower as a result of reduced food intake and therefore reported this to have been a barrier to exercise. More general barriers to exercise described were for example, not being able to go out for a walk in bad weather. The identification of both general and disease specific barriers in this cohort is very useful as it highlights important issues to address with any interventional programme.

Finally, an important objective of this study was to investigate participants' opinions regarding the feasibility of a prehabilitation programme in the pre oesophagectomy time period. An encouraging finding was that there was a very high level of interest in prehabilitation in this study cohort. A number of participants recognised the potential benefits of a multidisciplinary interventional programme and felt that it may be useful as a support and a motivator to exercise during treatment. The majority of participants felt that such a programme would be feasible in the pre-operative period. However when looking back over their treatment, participants did report that their ability to participate would have depended on the timing and structure of the programme. Overall participants felt they would have been physically able for an intervention of this nature between diagnosis and surgery but cautioned that there were certain times when it would have been more difficult to maintain an exercise programme. This was primarily when they were particularly fatigued or were experiencing certain treatment side effects. A small minority of the study cohort were not interested in a prehabilitation programme as they preferred to maintain their own activity levels and drive their own recovery. This finding reflects the differences in personalities which could be expected in any population.

Overall it appears that a prehabilitation programme would be feasible in this population as participants reported being physically able and interested in participation. This is an interesting

finding as it contrasts with the previous experiences of this research group with regards to the implementation of a preoperative exercise intervention (Section 1.5). In the preliminary work involved in this PhD, recruitment of patients with oesophageal cancer to a prehabilitation programme was very poor. The majority of patients approached declined participation as they were unable to attend additional hospital appointments or felt they would be unable to take on an exercise programme while undergoing treatment. A potential explanation for these conflicting findings could relate to timing. When patients were invited to take part in the prehabilitation programme, they had just received a diagnosis of cancer and were about to commence treatment. Therefore these patients may have been anxious or upset and may have felt unable to take on anything else. In contrast, the patients interviewed for this study were a few months post diagnosis and had successfully completed their initial treatment. Therefore they may have been in a better position to reflect on the potential benefits of an exercise programme and express an interest.

7.5.1 Limitations

There was an unavoidable self selection bias associated with this study as participants were required to volunteer to participate. Therefore those who participated may have had a higher interest in exercise and activity and consequently the implementation of exercise interventions than other patients with oesophageal cancer. In addition, one participant in this study completed the interview over the telephone. As described in Section 5.5.1, there is a loss of visual cues associated with telephone interviews which may result in the loss of non-verbal data, loss of contextual data or the distortion of verbal data.

It is acknowledged that the sample size of this study was small. However a key characteristic of qualitative samples are that they are relatively small in size as this enables an in-depth exploration of the phenomena under investigation. Furthermore, numbers don't necessarily guarantee quality in qualitative research; one well placed articulate informant could advance research further than a randomly chosen much larger sample. The research question in this study was restricted to the investigation of participant experiences over a period of weeks to months and therefore was a narrower research question than that of Study 2 in this thesis. In Study 2, participants' experiences of treatment and up to five years of recovery were explored. This may explain why data saturation was reached with fewer participants in this study as compared to Study 2. During the analysis of the 7^{th} – 9^{th} interview transcripts in this study there was no additional data emerging from the data which was found to be developing or

changing the properties of the themes and categories. Therefore recruitment was stopped. However the concept of 'data saturation' is always provisional as there is always the potential that a few more participants will add some new property and this is a bias inherently associated with all qualitative research of this nature. The sample size of this study is similar to others reported in the relevant literature; qualitative research previously carried out in an oesophageal cancer population have included sample sizes of five, six, nine and ten participants respectively (Missel and Birkelund, 2011, Watt and Whyte, 2003, Hodgson, 2006, Olsson et al., 2002).

The results of this study have provided a useful account of the experiences and opinions of patients with oesophageal cancer who met the specific criteria for inclusion (Section 7.3.2), and represented the cohort of interest for this research. There are however limitations associated with criterion sampling, as outlined in Section 5.5.1, and accordingly these findings may not represent the experience of all patients who undergo treatment for oesophageal cancer. Further research is warranted to investigate the specific experiences of patients with oesophageal cancer who meet different criteria, however this was beyond the scope of this study.

7.6 Conclusion

The results of this study demonstrated that physical functioning was affected by a diagnosis of and treatment for oesophageal cancer and that this was recognised by patients. In addition this study cohort demonstrated a limited knowledge of physical activity guidelines and faced a number of general and disease specific barriers to increased exercise and activity during treatment. As a result, interventional programmes to increase education and optimise physical performance across the cancer continuum are likely to grow in importance in this clinical cohort. The feasibility of an interventional programme during treatment was investigated in this study and overall it appears that a prehabilition programme would be feasible and generally well received in an oesophageal cancer population but may need to be tailored to the individual and reasonably flexible in terms of timing, structure and components. The potential implications of the findings in this study are discussed in more detail in Chapter 8.

Chapter 8 Discussion

8.1 Introduction

Increasing incidence and improved outcomes in oesophageal cancer has resulted in a marked increase in the number of people living with and beyond this disease in the past decade. Therefore there is a need for a more comprehensive understanding of the outcomes of oesophageal cancer and its treatment, beyond post-operative morbidity, mortality and survival rates. In recent years there has been a steady increase in research examining HRQOL in this cohort. Physical functioning is a component of HRQOL which has been shown to be particularly affected by cancer and its treatment. While patients with cancer experience losses in all functional domains, it has been shown that their losses are often most profound in the area of physical functioning (Hewitt et al., 2003) and that a leading cause of emotional distress in cancer survivors is physical disability (Silver et al., 2013). Therefore, optimising physical functioning in any cancer cohort is important.

While physical functioning has been extensively investigated in cancers such as breast and colorectal there is a paucity of evidence regarding physical functioning across the oesophageal cancer continuum. The systematic review in Chapter 1 demonstrated that, to date, physical functioning has predominantly been subjectively reported as a subscale of a HRQOL questionnaire. These questionnaire subscales provide very basic information relating to the ability to take a short or long walk, needing to rest, the presence of activity limitations, the ability to carry out activities of daily living and the ability to complete self care activities. Therefore data from these studies are quite limited in the extent to which they can comprehensively describe the physical performance and functioning of this cohort. Furthermore, due to the discrepancies often identified between subjective perception of health and objective measurement of health outcomes, there is a need for objective measures of physical performance to complement the HRQOL data available, particularly for the purposes of informing specific rehabilitation strategies in this cohort. In other cancer populations, objective measurements of physical functioning have resulted in a greater understanding of the physical needs of survivors. In recent years a small number of studies have emerged which have objectively measured the acute effect of treatment for oesophageal cancer on strength and fitness levels. These studies are summarised in the systematic review in Chapter 1 and provide useful initial data on this under researched group.

Overall the results of the systematic review in Chapter 1 revealed the predominantly negative effect oesophageal cancer treatment has on both subjectively and objectively measured physical functioning in the initial weeks and months post treatment. However, results from these studies were varied with regards to the recovery of subjectively reported physical functioning to baseline levels into longer term survivorship. To date there have been no studies examining the long term impact of treatment on objectively measured physical functioning. The current paucity of literature comprehensively describing physical functioning in an oesophageal cancer population highlighted the need for further research in this complex clinical cohort. The improving survival rates associated with this disease have lead to a growing clinical cohort about which very little is known. This is a cohort who has changed over recent decades as a result of the ongoing improvements in treatments. Therefore in order to optimise outcomes in this group, it is necessary to investigate their current functioning and needs.

The aim of this thesis was to comprehensively describe the physical functioning and needs of oesophageal cancer patients across the cancer continuum. This thesis had a mixed methods approach which involved the collection of both quantitative and qualitative data. This approach provides a better understanding of this group than would be achieved through either quantitative or qualitative investigation alone. While the studies in this thesis were individual and designed independently of each other, there is opportunity for the triangulation of findings in the discussion of the thesis in its entirety. Triangulation refers to the use of more than one approach to the investigation of a research question in order to enhance confidence in the ensuing findings. The rationale behind triangulation is that it helps overcome the deficiencies that are inherent in one method (Denzin, 1970). When more than one method is used and there is convergence, confidence in the results grows considerably. The gathering of both quantitative and qualitative data has provided an in-depth, specific, quantifiable and contextualised picture of this growing clinical cohort. The key points which emerged from the four studies in this thesis are outlined in the following sections.

8.2 Analysis of key points

8.2.1 Impact of oesophageal cancer and its treatment on physical functioning

In Study 1 in this thesis, survivors of oesophageal cancer (11 - 36 months post surgery) demonstrated significantly lower fitness and physical activity levels than their age and gender matched counterparts with no history of cancer. To the authors knowledge, this was the first

study to objectively measure physical functioning into longer term survivorship and compare results to those measured in non cancer controls. The systematic review in Chapter 1 revealed the inconsistencies in the current literature regarding the long term recovery of physical functioning after successful completion of treatment for oesophageal cancer. Therefore the results of Study 1 have provided very useful information about this cohort. Low fitness levels in survivors of oesophageal cancer were revealed by the poorer performance of this group in the ISWT as compared to controls. In addition, while the cancer cohort were comparable to the control group in terms of time spent sedentary and engaged in light intensity activity, they spent significantly less time engaged in moderate and vigorous intensity activity. Therefore the majority were not meeting the physical activity guidelines recommended for health benefits in cancer survivors (Schmitz et al., 2010). HRQOL was also measured in this study and the results complemented the objective measures of physical performance, with the cancer cohort reporting significantly lower scores than controls on the physical functioning subscale. The poor physical functioning observed in the months and years post completion of treatment highlighted the importance of continued investigation into the factors associated with physical functioning across the cancer continuum in this group. The deleterious physical impact of complex treatment for oesophageal cancer is likely a factor in the suboptimal physical functioning observed. However due to the cross sectional nature of the study, a direct cause effect relationship between cancer treatment and the poor fitness and physical activity levels in this group could not be established. Therefore the subsequent studies in this thesis aimed to further elucidate on this matter.

The second study in this thesis, Study 2, involved a qualitative exploration of the impact of treatment on physical functioning from the perspectives of survivors who were one to five years post surgery. These results provided a richer description of the impact of treatment on physical functioning which added to the findings of Study 1. Physical changes and side effects of treatment which had been experienced by participants across the cancer continuum were discussed. The physical changes and side effects reported included: reduced strength and fitness levels, changes in body composition, pain, musculoskeletal and sensory issues and gastrointestinal issues. Participants described how these physical changes had a negative impact on their physical functioning and had led to a reduction in regular physical activity levels and exercise. Accordingly these results provide more context and understanding regarding the low fitness and physical activity levels objectively measured in Study 1.

In order to investigate when changes in physical functioning may occur across the cancer continuum, Study 3 prospectively measured the acute impact of multimodal treatment on

physical performance in patients undergoing curative treatment for oesophageal cancer. The preliminary results from this ongoing study suggest that fitness, HGS and physical activity levels remain the same during neoadjuvant treatment. However a significant loss of hand grip strength was observed in participants four weeks post oesophagectomy as compared to baseline measures. Similarly, a clinically meaningful decrease in fitness levels was observed from pre surgery to four weeks post surgery. In addition, this study recorded low physical activity levels across the study period; at diagnosis, post neoadjuvant treatment and four weeks post surgery. Overall this study demonstrated that treatment for oesophageal cancer had an adverse effect on physical functioning.

The final study in this thesis, Study 4, qualitatively explored the patients' perspectives on their physical functioning from diagnosis and throughout their neoadjuvant treatment. This study gave a more in-depth evaluation of the impact of chemotherapy and radiotherapy on physical functioning and revealed that for most participants, neoadjuvant treatment did have some physical impact. Participants reported decreases in strength and stamina and other physical side effects such as low blood pressure, sensory problems and altered bowel movements. However the majority of the participants in this study reported that the physical impact of neoadjuvant treatment was reasonably temporary and self limiting. Most participants stated that they were able to build their strength and fitness levels back up in the weeks following the completion of neoadjuvant treatment, and felt almost back to normal at two to three weeks pre surgery. This finding is complemented by the objective data in Study 3 where strength, fitness and physical activity levels remained the same at diagnosis and post neoadjuvant treatment.

The thorough quantitative and qualitative investigation of the impact of oesophageal cancer on physical functioning in this thesis has demonstrated that physical performance is affected to varying degrees across the cancer continuum, from diagnosis up to five years post surgery. The results of the studies in this thesis would suggest that oesophagectomy has a marked adverse impact on physical functioning but that chemotherapy and radiotherapy have a lesser impact. This is unsurprising given the complexity of oesophageal resection and the high morbidity rates associated with this surgery (Section 1.1.6). Overall, it is of concern that suboptimal physical performance in the form of decreased strength, fitness and physical activity levels, is prevalent in patients with oesophageal cancer from diagnosis up to five years post completion of treatment. These findings are similar to other cancer populations (Broderick et al., 2014a, Jones et al., 2008b, Sanchez-Jiminez et al., 2014, Lynch et al., 2010, Lynch et al., 2011) and put this group at increased risk of disability and activity limitation, in

addition to decreased QOL, particularly in the domain of physical functioning. These results highlight the need for targeted exercise interventions in this group with the aim of optimising physical functioning both during and after treatment for oesophageal cancer. This is discussed further in Section 8.2.4.

8.2.2 Physical activity and exercise across the oeosphageal cancer continuum

It is well established that physical activity and exercise can improve QOL for cancer patients both during treatment and into survivorship (Mishra et al., 2012a, Mishra et al., 2012b). Furthermore physical activity has been shown to reduce symptoms and treatment side effects, and to expedite recovery in patients with cancer (Schmitz et al., 2010, Courneya, 2003). Despite the growing body of evidence regarding the important role of physical activity in other cancers, very little is known about activity and exercise in an oesophageal cancer population. An aim of this thesis was to determine physical activity levels in survivors of oesophageal cancer and to explore perceptions and knowledge regarding physical activity and exercise in this group. In addition, barriers and facilitators to exercise and optimal physical activity were investigated.

The habitual physical activity levels of people with oesophageal cancer were measured objectively both during treatment (Study 3) and after completion of treatment (Study 1). The benefits of the objective measurement of physical activity levels over subjective reporting were outlined in Chapter 2 (Section 2.3.3.1) and therefore the results of these studies have provided very novel and informative data on this cohort. As discussed in Section 8.2.1, the results of the studies in this thesis revealed low physical activity levels are prevalent throughout treatment and recovery in an oesophageal cancer population. The vast majority of participants were not meeting physical activity guidelines for health benefits either during treatment (Study 3) or into longer term survivorship (Study 1). Furthermore both study cohorts spent the majority of their time engaged in sedentary behaviour (57% in Study 1 and from 65% - 75% in Study 3). These findings are similar to recent studies which have objectively measured habitual physical activity levels in survivors of breast and prostate cancer and reported high sedentary behaviour and poor adherence to physical activity guidelines in these cohorts (Broderick et al., 2014a, Lynch et al., 2010, Lynch et al., 2011). However, low physical activity levels are also common in healthy normal populations. Only 41% of Irish adults take part in regular moderate or vigorous intensity activity (Morgan et al., 2008). Often survivors of cancer are no more inactive than the normal population (Broderick et al., 2014a, Neil et al., 2014).

Therefore the significantly lower physical activity levels observed in the cancer cohort as compared to controls in Study 1 highlights the particularly poor physical activity levels in an oesophageal cancer population, perhaps as a result of the complexity of this specific cancer type and its treatment.

The suboptimal physical activity levels observed in this cohort could be due to a number of factors, some of which were explored in this thesis. Prior to their diagnosis, this population may have already demonstrated low physical activity levels. Physical inactivity has been shown to be a risk factor for developing oesophageal and numerous other cancers (Kushi et al., 2012, Behrens et al., 2014). In Study 3, physical activity levels measured at diagnosis were low. However, as pre diagnosis activity levels were not measured it was not possible to determine whether this level of activity was normal for this group. At the time of measurement this cohort had recently received a diagnosis of cancer and patients were due to commence treatment. Both of these factors may have caused a change from the participants' usual physical activity routine.

Physical activity levels and exercise habits may have been reduced as a result of a cancer diagnosis and treatment. This has previously been shown in a breast and colorectal cancer populations (Irwin et al., 2003, Courneya and Friedenreich, 1997, Demark-Wahnefried et al., 1997) and the results of the studies in this thesis support this hypothesis. Participants reported changes in their physical activity and exercise habits as a result of their diagnosis and treatment, both during treatment (Study 4) and into longer term survivorship (Study 2). These changes generally involved a reduction in habitual physical activity levels such as walking shorter distances or less regularly. Some longer term survivors in Study 2 spoke about hobbies such as golf or handball which they had given up since their diagnosis. Similarly some participants, who were currently receiving treatment (Study 4), reported giving up hobbies such as golf during chemotherapy due to reduced stamina levels. The prospective measurement of physical activity levels during and shortly after treatment in Study 3 demonstrated a noticeable drop in physical activity levels from pre to post surgery, further indicating the negative impact of cancer treatment, particularly surgery, on physical activity levels.

Other factors which may contribute to low activity levels could be a lack of knowledge regarding the amount of exercise and physical activity which is recommended for health benefits or concerns regarding the safety of exercise both during and after cancer treatment. These factors are explored further in Section 8.2.2.2. Finally, in order to investigate any other potential causes for low physical activity levels in this cohort, any barriers or facilitators to

exercise and activity from the patients' perspectives were explored in Study 2 and Study 4. These are outlined in the following section.

8.2.2.1 Barriers and facilitators to physical activity and exercise

Understanding and addressing barriers to physical activity is important in enabling cancer survivors to be physically active. It is particularly important to understand the unique barriers faced by any clinical cohort when developing exercise interventions, so that they can be taken into account and potentially addressed by the healthcare professional prescribing the exercise (Fisher et al., 2015). There is a body of evidence available regarding barriers to exercise in cancer survivors, however these studies are primarily in a breast cancer population and are frequently carried out using surveys or checklists. The disadvantage of using checklists of potential barriers hypothesised by the researchers is that other barriers relevant to the participants, and not considered by researchers, may be missed. Therefore a qualitative methodology has been recommended as a better way to explore all potential barriers to physical activity in cancer populations (Lynch et al., 2010b).

The qualitative studies included in this thesis provided an opportunity to explore some of the barriers and facilitators to exercise and optimal physical activity levels in an oesophageal cancer population. Barriers and facilitators to exercise and activity were discussed with participants both during treatment (Study 4) and into survivorship (Study 2). Both general and disease specific barriers and facilitators to exercise were discussed in these studies and there were a number of common findings.

Some barriers described were unique to the physiology and pathology of oesophageal cancer. These particularly related to weight loss and changes in eating habits. Body weight was identified as a barrier to exercise for two distinct reasons. Firstly, as shown in Study 1, long term survivors of oesophageal cancer are generally a relatively healthy weight. Participants interviewed one to five years post completion of treatment (Study 2) who were at a healthy weight reported that they did not see the need for exercise as they were not overweight or obese. For them, exercise was viewed primarily as a means to lose weight and therefore was not seen as necessary when they were maintaining a healthy weight. Secondly, patients at any stage of the cancer continuum (Study 2 and Study 4) who were actively concerned about weight loss reported consciously avoiding physical activity and exercise in case it induced further weight loss. Some participants perceived the maintenance of their weight to be more important than being more physically active. Changed eating habits and reduced food intake

were also reported as barriers to exercise both during (Study 4) and long after the completion of treatment (Study 4). As people were eating less, they felt they lacked sufficient energy levels for increased physical activity. Correspondingly, eating well, reduced dysphagia or returning to more normal eating habits were all cited as an important facilitators to exercise.

In addition to the barriers specific to oesophageal cancer, barriers which are common to a number of cancers were discussed. Commonly reported barriers to exercise in breast and colorectal cancer populations include treatment side effects and fatigue (Hefferon et al., 2013, Fisher et al., 2015, Courneya et al., 2005, Lynch et al., 2010b). Similar findings were reported in Study 2 in this thesis, where long term survivors of oesophageal cancer reported that they found reduced stamina and fitness levels post diagnosis and physical side effects of treatment, such as pain and altered bowel habits, to be significant barriers to exercise and optimal physical activity. In addition, some participants in Study 2 reported having a fear or reluctance to 'push themselves' or to exercise at a moderate or high intensity. This is an interesting finding and could reflect a lack of education and awareness around the role, safety and benefits of exercise in this population. Similarly, a study by Jones and Courneya (2002) found that 56% of cancer survivors preferred to exercise at a moderate rather than a high intensity.

More general barriers to exercise were also mentioned in both qualitative studies and included ageing, a lack of interest, 'laziness' and bad weather. These barriers are also frequently mentioned in the literature in both cancer and non cancer cohorts (Ottenbacher et al., 2011). The knowledge of general and disease specific barriers to exercise in survivors of oesophageal cancer is extremely useful. Once specific barriers have been identified, they can be targeted as part of clinical care and exercise and educational interventions. Potential strategies to address some of these barriers are discussed in Section 8.2.4.

The facilitators to exercise described in Study 2 and Study 4 were mainly related to personal attributes of participants and highlight the importance of personality and attitude with regards to exercise and activity. Some other facilitators discussed include: goal setting, building exercise up slowly, eating normally, making exercise a habit and the use of exercise equipment. As the participants themselves reported that these methods were useful to promote exercise and activity in their lives, it is important to take them into account when developing interventions. These strategies could be incorporated into exercise programmes in this cohort in order to potentially increase adherence.

8.2.2.2 Knowledge and understanding regarding physical activity and exercise

In order to get a sense of the knowledge and understanding of this cohort with regards to physical activity and exercise, participants were asked about their awareness and knowledge of physical activity guidelines and what they perceived the benefits of exercise to be. None of the participants interviewed during treatment (Study 4) or after completion of treatment (Study 2) could accurately describe the correct physical activity guidelines recommended for health benefits. Over 80% of participants in Study 2 and 78% of participants in Study 4 reported that they had never heard of physical activity guidelines. Of the few who were aware of the existence of activity guidelines, none knew exactly what they are. This finding, while noteworthy, is not completely surprising, as it has been shown that the general public have a very poor knowledge of physical activity guidelines. Recent studies carried out in the UK and Northern Ireland revealed that, despite the efforts of public health promotion, only 18% and 8.4% of the respective study populations could accurately recount the physical activity guidelines (Knox et al., 2013, Hunter et al., 2014). However as patients with cancer have extensive contact with healthcare professionals over the course of their treatment and recovery, this could be an opportunity to increase awareness of activity guidelines in this group. While knowledge alone is unlikely to stimulate a behaviour change, individuals are unlikely to change their behaviour unless they become aware that their behaviours are not optimal (Snyder, 2007). The combination of qualitative and quantitative studies in this thesis has provided a greater understanding of the potential link between knowledge and behaviour. The majority of participants interviewed both during and up to 5 years after treatment had poor knowledge and awareness of physical activity guidelines (Study 2 and Study 4). When physical activity levels were measured at these time points (Study 1 and Study 3), over 70% of participants were not exercising to physical activity guidelines. Therefore it could be suggested, based on the literature, that increased education in this cohort could play a role in improving physical activity levels. In a study by Hefferon et al., (2013) breast cancer patients reported that if they felt exercise had been part of their 'prescribed recovery programme' they would have been more likely to engage with it.

Physiotherapists as exercise specialists are ideally placed to increase education and awareness regarding physical activity and therefore may need to play a larger role in this area in future. There is evidence to suggest that patients would be amenable to receiving information regarding exercise from health care professionals. Interests and preferences for exercise counselling have been explored previously in a cancer population and it has been reported that 76% - 84% of cancer survivors were interested in receiving exercise counselling at some

point throughout their cancer experience (Jones and Courneya, 2002, Gjerset et al., 2011). In terms of timing, one study found that survivors would have preferred exercise counselling prior to treatment (Jones and Courneya, 2002) while in another study participants reported a preference for immediately after treatment (Gjerset et al., 2011). It is likely that the ideal timing for exercise counselling will vary depending on the cancer diagnosis, treatment plan and personal attributes of the patient. More research is warranted regarding the optimal timing of exercise counselling in an oesophageal cancer population, particularly given the complexity of the disease.

An encouraging finding in this thesis was that the majority of participants interviewed in Study 2 and Study 4 were aware that exercise is beneficial. Benefits of exercise discussed included 'feeling good' and improved fitness and strength levels. These are similar to the benefits of exercise cited by other cohorts of cancer survivors in previous research (Craike et al., 2013, Fisher et al., 2015). These findings are expected as these are most likely the benefits of exercise commonly perceived in any population. However, it is worth noting that some participants were not aware of the wider ranging benefits of exercise beyond improving strength and fitness and maintaining a healthy body weight. An important barrier to exercise identified in this specific population was the relationship between exercise and weight loss, in particular the fact that participants did not need to lose weight and therefore felt they did not need to exercise (Section 8.2.2.1). In Study 1, longer term survivors of oesophageal cancer exhibited a relatively healthy body composition but also low fitness and physical activity levels. Another noteworthy belief about exercise was highlighted in Study 4 where one participant spoke about the beneficial effect of exercise for improving cancer related fatigue which he perceived to be very counterintuitive. Similarly, despite the substantial evidence regarding the benefits of exercise for cancer related fatigue (Cramp and Byron-Daniel, 2012), a study by Fisher and colleagues (2015), found that only 7% of colorectal cancer patients suggested that physical activity may be beneficial in reducing tiredness or increasing energy levels. Since fatigue is commonly reported as a significant barrier to exercise, these findings suggest that cancer survivors may be in a vicious cycle of becoming less active and more fatigued as a result of cancer treatments and this then presents as a primary barrier to increasing activity levels. Therefore it is clear that education regarding the need for and wide ranging benefits of exercise is hugely important in any cancer population. Of particular importance in this population, given the high prevalence of sarcopenia and cachexia, would be education regarding the benefits of exercise for building up muscle mass.

8.2.2.3 Subjective perceptions of activity versus objective measurement of activity

The mixture of qualitative and quantitative investigation in this thesis has highlighted the potential discrepancy between subjective perceptions of being 'active' and meeting physical activity guidelines or exercising regularly at a moderate or high intensity. Physical limitations and reduced activity and exercise levels were reported by participants both undergoing active treatment and into survivorship (Study 2 and Study 4). This was reflected in the objective measures of physical performance in these cohorts which revealed low strength, fitness and physical activity levels (Study 1 and Study 3). Despite this, the vast majority of participants in both Study 2 and Study 4 described themselves as an 'active person'. In this particular cohort, it appears descriptions of being 'active' most likely relate to completing normal household tasks and maintaining a relatively normal lifestyle. A similar finding was reported by Lynch et al., (2010b) in survivors of colorectal cancer, where a significant barrier to exercise in that group was the fact that participants believed they were already doing enough physical activity, however only 33% the study cohort were meeting physical activity guidelines.

Furthermore, while participants answered questions about exercise and activity, they were more likely to talk spontaneously about eating changes, weight changes and the emotional impact of cancer. All participants interviewed both during or at least one year after treatment (Study 2 and Study 4) were very positive overall when discussing their treatment and recovery. Therefore while they reported physical and lifestyle changes, these did not appear to be a primary concern. This finding is similar to the HRQOL results of participants who had completed their treatment at least 11 months previously in Study 1, where the overall QOL score for the cancer survivors was high and similar to controls, despite a significantly lower score for the physical functioning subscale. These findings highlight the fact that survivors of oesophageal cancer may not be aware of, or concerned about, their physical functioning. Subjective perceptions and reporting of being an 'active person' may mask underlying compromise in strength, fitness and activity levels.

Healthcare professionals may also perceive patients to be more active than they are. This was shown in a study by Broderick et al., (2014a) where there was low correlation observed between physician assigned Eastern Cooperative Oncology Group (ECOG) performance status scores and objectively measured physical activity levels in patients with cancer. When assigning performance status scores, health care professionals may classify patients as 'fully active' when it fact they are quite sedentary. The authors argued that assigning a top score of 0 or 'fully active' may reflect what a patient could potentially do, as opposed to what they are actually doing. In modern society it is relatively easy to participate fully in activities of daily

living while being habitually inactive (Broderick et al., 2014a). Therefore the participants in this thesis may have been fully functioning in daily life with no major limitations in activities of daily living and would therefore describe themselves as an active person when they are habitually sedentary.

8.2.3 The relationship between food intake, body weight and exercise in oesophageal cancer

A strong theme emerging from the studies in this thesis was the importance of the relationship between food intake, body weight and exercise throughout treatment and recovery for people with oesophageal cancer. Symptoms such as anorexia, dysphagia and malnutrition are frequently experienced by patients with oesophageal cancer. In addition oesophageal cancer is associated with a particularly high prevalence of weight loss, sarcopenia and cachexia. Furthermore following oesophagectomy patients must adapt to profound physical changes that affect a major bodily function and eating habits can be affected long into survivorship. The research in this thesis aimed to investigate changes in body composition and eating habits and examine how they may impact on physical functioning.

In Study 1, survivors of oesophageal cancer demonstrated relatively healthy body weight and BMI measurements which were comparable to non cancer controls. This differs from other cancer cohorts such as breast cancer survivors who often present as overweight or obese in the months and years after treatment (Vance et al., 2011). While obesity is a risk factor for developing oesophageal cancer, these relatively healthy body weight and BMI measurements may be due to the weight loss experienced by this cohort during and after treatment. The medical record review in Study 1 provided an overview of the changes in body composition experienced by patients with oesophageal cancer from diagnosis, throughout treatment and recovery and into longer term survivorship. The study cohort exhibited a decrease in body weight and BMI at one, three and six months post-operatively with body weight continuing to be decreased up to three years post surgery. These findings support previous research which has shown that nearly two-thirds of survivors of oesophageal cancer lose at least 10% of their preoperative BMI (Martin et al., 2007) and 54% lose more than 10% of their body weight (D'Journo et al., 2012) during the first six months post-operatively. It has also been shown that weight loss is protracted after oesophagectomy and can continue up to three years post-operatively (Martin and Lagergren, 2009). Similarly, the prospective measurement of body weight and BMI during treatment in Study 3 demonstrated mean decreases in body weight

and BMI after both neoadjuvant treatment and surgery. The changes in body composition measured in Study 1 and 3 were reflected in Study 2 and 4 where the majority of participants reported experiencing significant weight loss at some point in their cancer journey.

The presence of sarcopenia in patients receiving curative treatment for oesophageal cancer was also investigated in Study 1. The review of available CT scans in this group revealed a loss of fat free mass during their treatment. Over 30% of the total study cohort was classified as sarcopenic prior to surgery. This figure is higher than would be expected in the general population where the prevalence of sarcopenia is approximately 13% in people under the age of 70 and 19-26% in people aged 70-80 (Baumgartner et al., 1998). For the patients in Study 1 who underwent neoadjuvant therapy the number of patients who were sarcopenic doubled from before to after this treatment. These figures are similar to the findings of recent studies in oesophageal cancer populations where the number of patients classified as sarcopenic increased by 24% (Awad et al., 2012) and 17% (Yip et al., 2014) from pre to post neoadjuvant chemotherapy. Sarcopenia is associated with reduced strength, physical performance and exercise capacity (Prado et al., 2008, Collins et al., 2014). Therefore the evidence of extensive weight loss and sarcopenia during treatment in patients with oesophageal cancer must be considered in the context of the suboptimal physical functioning observed across the cancer continuum in this cohort.

In patients with cancer, changes in body weight can indicate the progress of disease or the process of recovery and weight loss can be ascribed different meanings according to the point on the pathway at which it occurs (Wainwright et al., 2007). For patients with oesophageal cancer there may be incentives beyond physical appearance and performance to maintain, increase or lose body weight. Therefore when planning exercise interventions in this cohort it is important to consider the patients' perspective on the relationship between food intake, body weight and physical activity. The qualitative studies in this thesis provided an opportunity to do this. As described in Section 8.2.2.1, concerns and beliefs regarding body weight were identified as important barriers to physical activity and exercise in patients with oesophageal cancer both during and after treatment (Study 2 and Study 4). Changed eating habits and reduced food intake were also reported as barriers to exercise in these studies while reduced dysphagia or returning to more normal eating habits were mentioned as important facilitators to exercise. It is clear from the results of the qualitative studies that body weight and eating habits play an important role in the lives of people with oesophageal cancer and can have a considerable effect on physical functioning. This highlights the important of addressing these issues with any exercise intervention in this clinical cohort.

8.2.4 Exercise interventions in oesophageal cancer

The findings of the studies in this thesis have demonstrated the adverse effect oesophageal cancer and its treatment can have on physical functioning across the cancer continuum. As discussed in Chapter 1 (Section 1.4), physiotherapy can play an important role to ameliorate the negative impact of treatment on physical functioning particularly through the implementation of exercise based interventions such as prehabilitation and rehabilitation programmes. Prehabilitation and rehabilitation programmes provide an opportunity to optimise health and function at every step along the cancer care continuum and it has been recommended that these programmes become an integral and continuous part of cancer care (Hellbom et al., 2011). However, prehabilitation and rehabilitation needs can vary considerably between different cancer cohorts. Therefore there is a need to investigate the specific needs of each cancer group in order to design evidence based and targeted interventional programmes. To date, there has been a paucity of evidence regarding the physical functioning of patients with oesophageal cancer specifically. Therefore there has been a lack of data to inform the setting up of interventional programmes in this group. The studies in this thesis have made a valuable contribution to the evidence regarding physical functioning and oesophageal cancer and have provided an overview of the specific prehabiltative and rehabilitative needs of this cohort.

Prehabilitation

The process of enhancing the functional capacity of the individual to enable him/her to withstand an upcoming stressor has been termed 'prehabilitation' (Section 1.4). Prehabilitation programmes are increasingly being introduced in a number of surgical populations in order to optimise outcomes. For example prehabilition programmes are commonly used in orthopaedic patients in order to optimise strength and fitness prior to joint replacement surgeries (Ditmyer et al., 2002). In addition, recent studies have implemented prehabilition programmes in lung and colorectal cancer populations (Jones et al., 2007, Carli et al., 2010, West et al., 2015). The studies in this thesis highlighted the indications for and potential benefits of prehabilitation programmes in an oesophageal cancer population.

The prospective study examining the modifiers of physical performance during treatment for oesophageal cancer (Study 3) revealed suboptimal fitness and physical activity levels in this cohort in the preoperative period. While strength, fitness and physical activity levels were not significantly affected by chemotherapy and radiotherapy in this study, these measures were

already low at diagnosis. As a result, this cohort may be an increased risk of post-operative complications. Suboptimal physical fitness is associated with poorer outcomes following major surgery; it has been established that less fit patients have a greater risk of complications and death (Jack et al., 2011). Survivors of major surgery and critical illness tend to have a higher cardiac index, oxygen delivery and oxygen consumption than non survivors (Davies and Wilson, 2004). In an oesophageal cancer specific population, a recent study found that those who developed a PPC were significantly less active preoperatively than those who did not (Feeney et al., 2011). Furthermore it has been suggested that increasing inspiratory muscle strength prior to surgery may reduce PPCs (Inoue et al., 2013). Given that PPCs and cardiac complications are particular threats to patients recovering from oesophageal surgery, an intervention that would improve strength, physical activity and fitness pre-operatively may positively influence these complications. Accordingly it could be recommended that any preoperative exercise intervention targets these aspects of physical performance in this cohort.

Due to the potential difficulties involved in setting up a programme of this nature (Section 1.5), patients with oesophageal cancer were interviewed during the pre-operative period (Study 4) in order to assess the feasibility of a prehabilitation programme from the patients' perspective. The results of this study were encouraging; two thirds of those interviewed reported that they would have been interested in participating in such a programme and felt that it would have been beneficial. In terms of the feasibility of a prehabilitation programme, most participants felt that they would have been physically able to complete at a programme at some point in the preoperative period.

While the results overall indicated that a programme would be feasible between diagnosis and surgery, an important finding of this study was that the side effects of neoadjuvant treatment were experienced to varying degrees and at different times by participants during this period. While some participants reported the greatest treatment side effects occurred during neoadjuvant treatment, others reported that they only experienced side effects once treatment had been completed. This finding is important as some participants reported that when they were particularly affected by treatment side effects they would not have been able to complete an exercise intervention. Therefore the timing of a prehabilitation programme in this population is a key consideration. The findings of Study 3 in this thesis could not identify an optimum time-point for a prehabiliaton programme from the patients' perspectives. Therefore timing of interventions may have to be varied according to a patient's response to therapy.

Study 1 in this thesis, in agreement to other literature (Yip et al., 2014, Awad et al., 2012), has shown the high prevalence of sarcopenia in patients with oesophageal cancer. Therefore an important aim of any interventional programme would be to optimise body composition and increase muscle strength. This is particularly important as sarcopenia is associated with increased morbidity both during and after treatment for oesophegeal cancer. Sarcopenia has been shown to be a significant predictor of dose-limiting toxicity in patients undergoing neoadjuvant chemotherapy (Tan et al., 2015). In addition sarcopenia has been identified as a potential risk factor for increased risk of PPCs after oesophagectomy (Ida et al., 2015). Finally sarcopenia has been associated with a poorer prognosis after treatment for oesophageal cancer, in those without lymph node involvement (Harada et al., 2015). It is well established that exercise, particularly resistance exercise, is very effective for eliciting increases in both strength and lean body mass (Peterson and Gordon, 2011). Therefore resistance training would be an important element of a prehabilitation programme in this cohort to target sarcopenia.

As shown in Study 4, none of the participants interviewed in the preoperative period could accurately describe physical activity guidelines and had limited knowledge of the wide ranging benefits of exercise. Education regarding these topics may increase engagement and adherence to exercise programmes and therefore should be incorporated into any prehabilitation programme.

Prehabilitation could be implemented as a home exercise programme or as a hospital based class. Participants currently receiving treatment in Study 4 were asked what their preference for the location of a rehabilitation programme would be. The majority reported that they would prefer a home exercise programme as opposed to a hospital based class. Personal reasons and location were the primary reasons for a preference for a home based programme. These results demonstrate that, while some patients do prefer the support and motivation to exercise that a supervised group setting provides, interventional programmes in the form of an exercise class may not suit all. Therefore it could be recommended that a home exercise programme may be available as a valuable alternative to an exercise class, particularly for patients living a significant distance from the hospital. An interesting suggestion from a participant in Study 4 was that a prehabilitation programme may be beneficial for those receiving neoadjuvant treatment as an inpatient. As these patients are based in the hospital for a number of weeks, this could be a prime opportunity to implement a regular exercise class under the supervision of local physiotherapists.

The components of a proposed prehabiltation programme with suggestions for frequency, intensity, time and type are summarised in Table 8.1.

Table 8.1 Components of proposed prehabilitation programme

Frequency	• 3 - 6 sessions per week. • Tailored to patients response to therapy**
Intensity	• Light (30-39% HRR) – moderate intensity (40-59% HRR) exercise • Progressive • Tailored to patients response to therapy**
Type	• Aerobic exercise • Resistance training • Dietary advice and support • Education sessions • Option of supervised and home based programmes.
Time	• 20 - 60 minutes per session • 2 - 12 week programme prior to progression to surgery • During and/or after neoadjuvant treatment

** important consideration. Abbreviation: *HRR* heart rate reserve.

Rehabilitation

Rehabilitation involves preventing and addressing the late and long-term effects of cancer and its treatment (Section 1.5). Due to the growing number of cancer survivors worldwide, oncology rehabilitation programmes are growing in importance to address treatment-induced physical impairments that can lead to disability. In addition to addressing the long term sequelae of cancer treatments, it has been suggested that a cancer diagnosis may be a "teachable moment" to encourage healthy lifestyle behaviours in cancer survivors (Demark-Wahnefried et al., 2005). However, behavioural changes may not be independent or spontaneous in this group. A large population-based study of cancer survivors in the UK found no evidence that a cancer diagnosis was associated with sustained improvements in lifestyle

from before diagnosis to at least two years after diagnosis (Williams et al., 2013). Similar findings have been demonstrated in breast cancer specific populations in Ireland and Canada (Broderick et al., 2014b, Sabiston et al., 2014). This highlights the important role of structured cancer rehabilitation programmes designed to actively engage the individual in the recovery process. In cancers such as breast and colorectal, the teachable moment refers to making long term diet and lifestyle changes with the aim of preventing other chronic disease and cancer recurrence. While this could also apply to an oesophageal cancer population, the teachable moment in this group may relate more so to providing the education and support to enable survivors to actively engage in their own recovery, to promote functional independence and to optimise physical functioning.

All of the studies in this thesis have shown the adverse effects of treatment for oesophageal cancer on strength, fitness and physical activity levels. These results highlight the important targets for improvement in survivors of oesophageal cancer in order to optimise physical functioning and enhance QOL. Any rehabilitation programme in this cohort should consist of aerobic exercise and an increase in habitual physical activity levels. Furthermore as discussed in Section 8.2.3, loss of muscle mass frequently occurs during treatment in patients with oesophageal cancer. Therefore resistance training would also be recommended as an important component of a rehabilitation programme in order to increase strength and optimise body composition and muscle mass into survivorship.

To complement the quantitative data gathered regarding the specific physical rehabilitative needs of this cohort, an aim of Study 2 was to obtain the views of survivors of oesophageal cancer on the structure and implementation of rehabilitation programmes. The majority of those interviewed reported that they would have been interested in a rehabilitation programme and felt that it would have been beneficial. Participants in Study 2 spoke about the importance of education and information as part of an interventional programme. Some reported that they would have liked more specific information regarding exercise, particularly when they were discharged home after completing treatment. These participants were unsure about the type of exercise recommended or safe after cancer treatment. Accordingly some revealed that they restricted their exercise or didn't 'push themselves' as a result of fear or uncertainty. Therefore, similar to prehabiliation, an educational component should be an essential element of any rehabilitation programme. Education should address: the safety of exercise, the wide ranging benefits of exercise, physical activity guidelines and how to gradually commence an exercise programme and progress it as able.

It is important to consider the appropriate timing for the implementation of a rehabilitation

programme. This was explored from the perspectives of the survivors of oesophageal cancer interviewed in Study 2. In this study participants reported a period of being very deconditioned in the initial weeks and months after discharge from hospital post oesophagectomy. In addition to feeling fatigued participants had to come to terms with a new eating routine which was often described as challenging in this early post-operative period. Therefore the prevailing opinion was that it would have been difficult to participate in an exercise intervention during this period. The physical performance measures taken in Study 4 reflect this finding as participants demonstrated very low fitness and physical activity levels at approximately four weeks post surgery. The study cohort spent on average 75% of their waking hours sedentary. Accordingly, before the commencement of a rehabilitation programme, it would be important to allow time, possibly at least six months post completion of treatment, for eating habits to stabilise and participants to make an initial recovery from the acute side effects of surgery. An additional consideration in relation to timing would be to avoid any exercise interventions near meal times as a number of participants reported not being able to exercise or needing to rest for some time after eating a large meal. Finally, similar to prehabilitation, it may be useful, where possible, to have both home based and hospital based rehabilitation programmes available to account for varying geographical locations and preferences. The components of a proposed rehabilitation programme with suggestions for frequency, intensity, time and type are summarised in Table 8.2.

Table 8.2 Components of proposed rehabilitation programme

Frequency	• 5 - 7 sessions per week.
Intensity	• Light (30-39% HRR) – moderate intensity (45-59% HRR) exercise • Progressive
Type	• Aerobic exercise • Resistance training • Dietary advice and support • Education sessions • Option of supervised and home based programmes.
Time	• 30 - 60 minutes per session • 8 – 12 week programme • Approximately ≥ 6 months post completion of treatment

Abbreviation: *HRR* heart rate reserve.

There are a number of considerations common to both prehabilitation and rehabilitation programmes in patients with oesophageal cancer. Firstly it would be important for any intervention in this cohort to be multi-disciplinary. In an oesophageal cancer population in particular, input from dieticians, in addition to physiotherapists, would be recommended. The important relationship between eating habits, body composition and exercise in this group has been highlighted (Section 8.2.3). Patients with oesophageal cancer require a lot of support with diet and nutrition due to the significant changes in the gastro-intestinal system which occurs with oesophagectomy. Concerns that unwanted weight loss would result from an increase in activity levels was reported as a barrier to exercise by participants in Study 2 and Study 4. Participants in these studies also reported that reduced food intake had resulted in low energy levels and this was perceived as another significant barrier to exercise. Consequently, given these nutritional concerns, it may be more difficult to set up exercise interventions with input solely from physiotherapists. Additional input provided by dieticians working alongside physiotherapy colleagues would provide participants with support and information on how to sufficiently increase energy intake to facilitate an increase in aerobic

exercise and physical activity. Increased nutritional support and guidance would also help participants with the maintenance of a healthy weight while simultaneously increasing activity. Furthermore, exercise for maintaining or increasing muscle mass is most effective when coupled with appropriate nutrition (Solheim and Laird, 2012, Penna et al., 2011) and therefore nutritional support should be combined with exercise advice to address sarcopenia or strength deficits in this cohort.

A strong theme to emerge from participant interviews both during treatment and into survivorship (Study 2 and Study 4) was the benefits of peer support. A number of participants reported that meeting and speaking with other patients with oesophageal cancer both during and after treatment was extremely helpful. Participants were reassured when other patients described similar experiences and concerns. It has been shown that peer support groups provide shared understanding, positive role models and information regarding coping, which would not be available from friends and family (Dakof and Taylor, 1990). Previous research in an oesophageal cancer population reported that peers could provide normalisation of feelings, support, reassurance, non-defensive relating, hope and inspiration (Clarke et al., 2011, McCorry et al., 2009). Accordingly it would appear that, in addition to the support provided by healthcare professionals, class based interventional programmes would be an ideal opportunity to increase peer support in this cohort. The camaraderie of a group may provide valuable mental and emotional support for survivors of oesophageal cancer.

A number of barriers to exercise common to participants both during and after completion of treatment for oesophageal cancer were described in Study 2 and Study 4. It would be important for any interventional programmes in this cohort to address these barriers where possible. It has been shown that an intervention to target barriers in a breast cancer population was effective in improving physical activity levels (Rogers et al., 2011). For example, strategies to overcome the barrier of fatigue could include prescribing shorter duration bouts (e.g. 10 minutes at a time), performing interval exercise (i.e. alternating exercise and rest bouts), and exercising when fatigue is at its lowest (e.g. early in the morning) (Courneya et al., 2005). Strategies to overcome the barrier of altered bowel habits may include lower intensity and shorter duration exercise, not exercising after meals, and exercising in locations where toilets are convenient and private (e.g. at home) rather than sparse and public (e.g. outdoors, gyms) (Courneya et al., 2005). In order to address persuasive issues such as lack of motivation and lack of confidence in engaging with exercise and activity, exercise programmes could involve a psycho-educational component on self-regulations and self efficacy.

Finally, as highlighted by a participant in Study 2 “everyone’s recovery is different” and

therefore any exercise interventions in an oesophageal cancer population should be tailored to the individual and their specific abilities and needs. The concept of individualised or precision medicine is growing in importance, particularly in the treatment of cancer. This is as a result of an increasing ability to characterise patients using methods such as proteomics, genomics and mobile health technologies (Collins and Varmus, 2015). In recent years, a number of targeted therapies have been developed for cancer and these have been associated with significant benefits. While personalised medicine primarily applies to tailoring treatments according to the phenotypic characteristics of an individual patient, the concept can be applied to other treatment modalities including physiotherapy or exercise interventions. As different patients can respond very differently to interventions such as rehabilitation programmes, a 'one size fits all' approach may not provide optimal outcomes for all patients. Therefore future research may involve a move from exercise training protocols based on general principles to individually tailored or personalised programmes (Ambrosino and Clini, 2015). Personalised exercise programmes could take into account the individuals clinical, functional, environmental and social factors and prescribe more targeted interventions. The structure of a personalised pulmonary rehabilitation programme has been outlined by Ambrosino and Clini, (2015). In this proposed programme as the patients symptoms become more severe, the programme and activities are progressively and specifically adapted to the patient's characteristics. The authors suggest that a personalised programme of this nature would allow resource savings for poor responders or first-stage patients and optimal treatment for responders and more severe patients. An important area for future research would be the multidimensional profiling of response to therapies and suggestions of how to personalise activities and/or motivate participants in these programme to achieve the goals they perceive as most important (Ambrosino and Clini, 2015).

8.3 Critical analysis of this work

There are a number of limitations to the work in this thesis. A convenience sample was recruited for all studies in this thesis. This method of recruitment was adopted due to the limited number of people receiving curative treatment for oesophageal cancer in Ireland. Survivors of oesophageal cancer who had an interest in oesophageal cancer or were of higher physical functioning may have been more likely to volunteer for the studies in this thesis, which could have biased the results. This would, however, mean that the prevalence of

suboptimal physical functioning could be higher in survivors of oesophageal cancer than indicated in this thesis. This potential bias could also have occurred with the control participants in Study 1.

Compared to larger trials investigating outcomes in survivors of more common cancers, the sample sizes in the studies presented in this thesis were relatively small. Much of the work was exploratory in nature however and recruitment in this population is difficult due to the poor prognosis and complexity of treatment. However these studies have provided useful preliminary data on an under researched cohort and have laid the foundations for ongoing and future research in this group.

The outcome measures used in this thesis have some limitations. Body composition was measured using BIA, which has been shown to be a valid measure (Section 2.4.4). The BIA system used in this thesis was more advanced than other models due to the incorporation of eight electrodes to facilitate segmental measurement, however BIA lacks precision and accuracy compared to measurements taken by DEXA, CT or MRI. The addition of the use of CT scans to identify sarcopenia in Study 1 provided valuable additional information regarding body composition in this cohort at pre and post treatment time points. The criterion method of measuring cardiorespiratory fitness is the direct measurement of VO_2 during a graded maximal exercise test. The walking tests used in the studies in this thesis provide an indication of fitness levels and therefore as discussed in Section 6.5 may have had lower sensitivity to small changes in fitness.

The use of two different walking tests, the ISWT in Study 1 and the 6MWT in Study 3, reduces the comparability of these two studies. The ISWT is incremental and externally paced. This minimises the effects of participant motivation, which may be different between cancer survivors and control participants and therefore this test was chosen for Study 1. However, some limitations were observed with the use of the ISWT in survivors of oesophageal cancer (Section 4.5.1). Minor difficulties were reported by some of the older and more deconditioned participants in relation to keeping in synchrony with the beeps and turning at the cone every 10 metres. Due to these issues it was hypothesised that the use of the 6MWT may be more appropriate for use in patients with cancer. With the 6MWT, participants can pace the test themselves, do not need to keep in synchrony with external pacing and only need to turn around the cone every 30 metres. A study validating and recommending the use of the 6MWT in cancer populations was published after the commencement of Study 1 (Schmidt et al., 2013). In addition, comparable studies investigating the effect of treatment for oesophageal cancer on fitness used the 6MWT and therefore this test was chosen for Study 3. The 6MWT

was carried out successfully with participants in Study 3 and participants reported no significant issues with completing the test. Therefore, the results of the studies in this thesis would suggest that while the ISWT is also a valid test, the 6MWT may be more feasible and less complex field walking test for use with patients with cancer.Similarly, due to the discontinuation of the RT3 accelerometer, different accelerometers were used in the studies in this thesis: the RT3 in Study 1 and the ActiGraph in Study 3. However, as the aim of Study 1 was to compare fitness and physical activity levels between cases and controls and the aim of Study 3 was to compare changes in fitness and physical activity levels over time, both studies provided individual results which answered the particular research question which pertained to each study.

Finally, researcher bias is an inevitable factor that must be considered in all qualitative research. The researcher can be regarded as the research instrument and therefore is subject to biases which may reduce the reliability or validity of the results. It is very important for the researcher to actively reflect on his or her biases and consider how they might influence the overall research process. Therefore a number of strategies, previously discussed in Chapter 3, were used in both Study 2 and Study 4 to promote participant-driven data and data-driven analysis. These included probing for clarification and depth during interviews, ensuring accurate transcription and a data driven approach to coding and categorising. In particular, the processes of peer review and respondent validation were carried out to ensure that the participants rather than the researcher's perceptions were represented. In Study 2 and Study 4, member checking was carried out during each interview to clarify points that participants made. The process of peer review was also used to ensure that results stayed close to the data. The codes developed for the studies were reviewed with a colleague to ensure they reflected what was truly in the data. Themes were discussed with colleagues to ensure that they flowed logically from findings. Alternative interpretations of codes and themes were also discussed. Finally, direct quotations were used extensively throughout the study reports in order to give readers a sense of the data and to allow them to judge the credibility.

8.4 Implications for future research

The data gathered from the early work in this thesis were used to inform an application for HRB grant funding. This grant was successfully attained and this has enabled research to continue in this centre (TCD) with the ReStOre trial. In particular, the results of Study 1 and Study 2 were used to plan the later work in this thesis (Study 3 and Study 4), in addition to the ongoing and planned future research at this centre. Study 1 and Study 2 in this thesis identified suboptimal physical functioning, activity limitations and lifestyle restrictions in disease free survivors of oesophageal cancer. These initial findings highlighted the need for further research in this area; firstly to investigate exactly when, how and to what extent treatment for oesophageal cancer can impact on physical functioning and secondly to examine whether a comprehensive rehabilitation programme could improve physical performance and HRQOL in this cohort. The preliminary results of an ongoing longitudinal study were presented in Study 3 in this thesis. This study is part of the HRB grant and data collection continues and the results from the total study cohort will be a very valuable descriptor of this cohort. In addition the study will reassess participants for an additional study time-point at six months post surgery. This data will reveal how participants recover from the significant decrease in physical performance observed at four weeks post surgery.

When this longitudinal study has been completed, an RCT will be carried out to investigate the implementation of a multidisciplinary rehabilitation programme. The results of the studies in this thesis have been used to inform the design of this rehabilitation programme. The important relationship between food intake, body weight and exercise in patients with oesophageal cancer has been highlighted by the studies in this thesis (Section 8.2.3). These findings particularly highlighted the importance of input from both physiotherapists and dieticians in the management and rehabilitation of patients with oesophageal cancer. Therefore the rehabilitation programme has been designed to be multidisciplinary and will consist of both exercise sessions and dietary sessions with input from physiotherapist and dieticians.

Deficits in physical functioning were identified in survivors of oesophageal cancer in Study 1 and these results have provided important targets to address with exercise component of the rehabilitation programme. Firstly, as significant deficits in fitness and physical activity levels were observed in survivors of oesophageal cancer in Study 1, the rehabilitation programme will include an aerobic exercise component with the aim of improving both fitness and activity levels. The results of Study 1 also revealed significant changes in body composition, loss of

muscle mass and a high prevalence of sarcopenia across the treatment trajectory in patients with oesophageal cancer. Accordingly the rehabilitation programme will include resistance training aimed at improving body composition and increasing muscle mass and strength.

When developing interventional programmes, information from the target population is extremely useful. Taking into account patients preferences and suggestions should optimise the feasibility and acceptability of such programmes. Study 2 in this thesis explored patient perspectives on the implementation of rehabilitation programmes and very useful data was gathered with helped inform the design of the programme. An important finding from Study 2 was that participants described the initial few weeks and months post completion of treatment as particularly difficult and accordingly a number of participants reported that they did not feel that they would have been able to participate in a rehabilitation programme at this time. It was suggested by the participants that rehabilitation programmes not be commenced until approximately six months or more post completion of treatment and discharge from hospital. This influenced the timing of the ReStOre rehabilitation programme and accordingly the rehabilitation programme will be implemented in participants who are >12 months post completion of treatment. The participants in Study 2 had a very limited knowledge of activity guidelines and the wide ranging benefits of exercise (Section 8.2.2.2) and faced a number of barriers to increased activity and exercise (Section 8.2.2.1). These findings highlighted the importance of education in this cohort to increase awareness and understanding among cancer survivors of the important role that exercise can play across the cancer continuum and to target common barriers to exercise. Consequently the proposed ReStOre rehabilitation programme will also include educational sessions.

The preliminary work in this thesis (Section 1.5) highlighted some of the potential recruitment issues in this complex cohort and the difficulties which can arise with the implementation of an RCT. Therefore given the learning which occurred as a result of this early work, certain procedures were put in place with the aim of optimising recruitment and reducing the logistical challenges associated with working with a complex population. Firstly, it was very important that there was good communication between the research and clinical staff working with patients with oesophageal cancer. A system has been put in place to identify each potential research participant attending clinics to ensure that they meet a member of the research staff and are informed of ongoing studies. In addition improved teamwork between researchers from different disciplines has been implemented; in particular research physiotherapy and dietetic colleagues work closely together to ensure measurements are not repeated unnecessarily and that study visits are coordinated to take place on the same day

where possible. In order to further ease participant burden and minimise hospital visits, study assessments are arranged on a day that the patient is in the hospital for another clinical appointment where possible. Finally a Clinical Research Facility was opened in SJH in 2014 and therefore study assessments can now take place in a safe, clinical environment which is accessible from the main hospital. This has facilitated patients being able to attend both clinical and research appointments on the same day with ease. With these systems in place, recruitment for the ongoing longitudinal study is progressing well. However it must be noted that the longitudinal study is an observational study and participants are not required to complete an intervention or attend for weekly exercise sessions during their treatment. Therefore this is likely to be a significant factor in improved recruitment rates. In addition, as the rehabilitation programme will take place at least one year post completion of treatment in those free of disease, it could be hypothesised that the same difficulties observed with recruitment for the prehabilitation programme (Section 1.5), will not be present to the same extent for the rehabilitation programme. When patients were invited to take part in the prehabilitation programme, they had just received a diagnosis of cancer and were about to commence treatment. Therefore these patients were probably anxious or upset and may have felt unable to take on anything else. In contrast, the patients who will be invited to take part in the rehabilitation programme will be at least one year post completion of treatment and therefore may be in a better position to reflect on the potential benefits of an exercise programme, express an interest in such a programme and feel physically able to take part. This is reflected in the results of Study 2 where the majority of participants reported that they would prefer to take part in an exercise programme only after all treatment had ended.

In relation to the ReStOre trial, JG played a role designing the longitudinal study, carried out recruitment and data collection for the initial months of the longitudinal study and carried out the interim analysis presented in this thesis. A brief overview of the study design for the rehabilitation programme is outlined below.

Study Design

An RCT is planned to examine the effect of a rehabilitation programme, incorporating an exercise intervention, individualised nutritional advice and education session, on functional status following curative treatment for oesophageal cancer. On completion of the longitudinal study participants will be re-assessed for suitability for enrolment to the rehabilitation programme through a review of medical records and discussion with the surgical team. If

interested, participants will be posted a copy of the PIL and consent and contacted one week later by telephone to answer further questions. Interested participants will then be booked in for screening and baseline assessments. Inclusion criteria for the participation in the RCT are (1) consented to be contacted by the research team regarding future studies (2) completed oesophagectomy +/- neo-adjuvant/adjuvant chemo/radiotherapy with curative intent and (3) medical approval to complete cardiopulmonary exercise testing and the prescribed exercise intervention. Exclusion criteria will include: (1) unsuccessful treatment outcome, (2) evidence of metastatic or recurrent disease (3) lack of medical consent or (4) co-morbidities that would preclude safe exercise participation. Participants will be randomised 1:1 to either the intervention or a control group. The primary outcome for the multidisciplinary rehabilitation programme will be a change in functional capacity as measured by aerobic capacity. Assessments will be completed at baseline, programme completion and six months post programme completion. Assessments will include functional capacity, body composition, nutritional status, dietary quality and HRQOL.

Rehabilitation Programme

The intervention in the rehabilitation programme will consist of three main components: (1) exercise sessions (2) dietary sessions and (3) education sessions. The exercise component will include a 12 week programme of supervised and unsupervised aerobic and resistance exercise sessions, 1:1 dietary sessions and group education sessions. The exercise component of the rehabilitation programme will take the form of a 12 week supervised and home-based intervention. The exercise programme will be led by a physiotherapist. Supervised group exercise sessions will be held twice weekly during the first four weeks of the programme to reintroduce exercise to participant's lives in a safe and structured manner. As the programme progresses the frequency of supervised sessions will decrease to increase participants' independence with the protocol. Initially, activity will be prescribed at a light intensity and will progress during the programme to a moderate aerobic intensity. Participants will wear Polar Heart Rate monitors during all sessions to ensure compliance with the exercise prescribed. Intensity will also be assessed using the Borg Perceived Scale of Exertion. The goal at programme completion will be participation in 30 minutes of moderate intensity activity five days per week, as per the ACSM physical activity guidelines. In addition participants will complete resistance training on two non-consecutive days per week at a volume of 12-17 repetitions maximum for 2-4 sets per exercise. All major upper limb and lower limb muscle groups will be exercised. Low-load high-repetition resistance training will be carried out with a

progression from 12RM to 17RM over the 12 week programme.

Nutrition sessions will be delivered during week one, week two and then fortnightly on a one to one basis. Weight and circumferential measures will be recorded at each session and dietary intake will be assessed as described previously. The education delivered in the nutrition sessions will be individualised to participants needs. The target for participants is optimal dietary intake in line with the World Cancer Research Fund guidelines for cancer survivors. Supporting literature detailing prescriptive dietary advice will be developed and provided to participants.

Education sessions will be delivered weekly during weeks one -four and fortnightly thereafter by a range of members of the multidisciplinary team and representatives of organisations that support people with oesophageal cancer including a representative of the surgical team, Cancer Nurse Specialist, dietician, physiotherapist, psychology of oncology, and a representative of the ARC cancer support centre. Education sessions will take place after the exercise session and cool-down, to monitor participant recovery following exercise and will be conducted at the Clinical Research Facility in St. James's Hospital.

Given the greater understanding of this population gained from the studies in this thesis, future research into the implementation of a prehabilitation programme is also warranted in an oesophageal cancer population. This centre is already participating in the PREPARE trial. This is an international multi-centre RCT which is investigating the effect of preoperative inspiratory muscle training on the incidence of postoperative pneumonia and respiratory function in patients undergoing oesophageal resection (Valkenet et al., 2014). As the PREPARE trial is focused on respiratory measures and outcomes and the ReStOre trial is focused on physical function measures and outcomes, these trials are being undertaken concurrently in this centre and participants may be enrolled in both.

8.5 Conclusion

In summary, the quantitative and qualitative findings in this thesis were complementary and indicated that physical functioning is adversely affected by treatment for oesophageal cancer. In particular, oesophagectomy, which is considered one of the most complex cancer surgeries, had a marked impact on physical performance with chemotherapy and radiotherapy having a lesser impact. Suboptimal strength, fitness and physical activity levels were prevalent in this cohort from diagnosis up to five years post completion of curative treatment. In addition, survivors of oesophageal cancer demonstrated consistent weight loss throughout the treatment trajectory with relatively healthy body weight and BMI measurements into survivorship.

Exercise knowledge and awareness was low overall in this cohort and survivors of oesophageal cancer faced a number of disease specific and general barriers to increased activity and exercise. The relationship between food intake, body weight and exercise is particularly important in an oesophageal cancer population given the pathology and physiology of the disease and the changes in the gastrointestinal system which occur as a result of oesophagectomy. Concerns and beliefs regarding weight loss were identified as important barriers to exercise and it is clear that survivors of oesophageal cancer require considerable support to effectively manage and maintain a healthy energy balance.

The findings of this thesis demonstrate that this complex clinical cohort have multi-faceted needs across the cancer continuum. Therefore multidisciplinary interventional programmes such as prehabilitation and rehabilitation are indicated in order to: maintain or restore physical performance, optimise body composition, remediate functional loss and enable full participation in activities of daily living. Further research into the implementation and effectiveness of such programmes is warranted. On the basis of the studies reported herein such a programme has been initiated at this Centre, and the objective data recorded and targets for recovery lend itself to further prospective study within collaborative networks.

References

AARONSON, N. K., AHMEDZAI, S., BERGMAN, B., BULLINGER, M., CULL, A., DUEZ, N. J., FILIBERTI, A., FLECHTNER, H., FLEISHMAN, S. B., DE HAES, J. C. & ET AL. 1993. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.,* 85**,** 365-76.

ABIZANDA, P., NAVARRO, J. L., GARCIA-TOMAS, M. I., LOPEZ-JIMENEZ, E., MARTINEZ-SANCHEZ, E. & PATERNA, G. 2012. Validity and usefulness of hand-held dynamometry for measuring muscle strength in community-dwelling older persons. *Arch Gerontol Geriatr,* 54**,** 21-7.

ADAMS, R. 1999. Revised Physical Activity Readiness Questionnaire. *Can Fam Physician,* 45**,** 992, 995, 1004-5.

ALLUM, W. H., BLAZEBY, J. M., GRIFFIN, S. M., CUNNINGHAM, D., JANKOWSKI, J. A. & WONG, R. 2011. Guidelines for the management of oesophageal and gastric cancer. *Gut,* 60**,** 1449-72.

ALY, A., JAMIESON, G. G., WATSON, D. I., DEVITT, P. G., ACKROYD, R. & STODDARD, C. J. 2010. An antireflux anastomosis following esophagectomy: a randomized controlled trial. *J Gastrointest Surg,* 14**,** 470-5.

AMBROSINO, N. & CLINI, E. M. 2015. Response to pulmonary rehabilitation: toward personalised programmes? *Eur Respir J,* 46**,** 1538-40.

AMERICAN CANCER SOCIETY. 2015. Cancer Facts & Figures 2015. Atlanta. American

Cancer Society.

AMERICAN THORACIC SOCIETY. 2002. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med,* 166**,** 111-7.

AMERICAN THORACIC SOCIETY/AMERICAN COLLEGE OF CHEST PHYSICIANS. 2003. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med,* 167**,** 211-77.

ANCONA, E., CAGOL, M., EPIFANI, M., CAVALLIN, F., ZANINOTTO, G., CASTORO, C., ALFIERI, R. & RUOL, A. 2006. Surgical complications do not affect longterm survival after esophagectomy for carcinoma of the thoracic esophagus and cardia. *J Am Coll Surg,* 203**,** 661-9.

ANDERSON, S. E., MINSKY, B. D., BAINS, M., HUMMER, A., KELSEN, D. & ILSON, D. H. 2007. Combined modality chemoradiation in elderly oesophageal cancer patients. *British Journal of Cancer,* 96**,** 1823-1827.

ANDREASSEN, S., RANDERS, I., NASLUND, E., STOCKELD, D. & MATTIASSON, A. C. 2006. Patients' experiences of living with oesophageal cancer. *J Clin Nurs,* 15**,** 685-95.

ARNOTT, S. J., DUNCAN, W., GIGNOUX, M., HANSEN, H. S., LAUNOIS, B., NYGAARD, K., PARMAR, M. K., ROUSELL, A., SPILOPOULOS, G., STEWART, G., TIERNEY, J. F., WANG, M. & RHUGANG, Z. 2005. Preoperative radiotherapy for esophageal carcinoma. *Cochrane Database Syst Rev***,** CD001799.

AVERY, K. N., METCALFE, C., BARHAM, C. P., ALDERSON, D., FALK, S. J. & BLAZEBY, J. M. 2007a. Quality of life during potentially curative treatment for locally advanced oesophageal cancer. *Br J Surg,* 94**,** 1369-76.

AVERY, K. N. L., METCALFE, C., BARHAM, C. P., ALDERSON, D., FALK, S. J. & BLAZEBY, J. M.

2007b. Quality of life during potentially curative treatment for locally advanced oesophageal cancer. *Br J Surg,* 94**,** 1369-1376.

AWAD, S. & LOBO, D. N. 2011. What's new in perioperative nutritional support? *Curr Opin Anaesthesiol,* 24**,** 339-48.

AWAD, S., TAN, B. H., CUI, H., BHALLA, A., FEARON, K. C., PARSONS, S. L., CATTON, J. A. & LOBO, D. N. 2012. Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. *Clin Nutr,* 31**,** 74-7.

BALKE, B. 1963. A simple field test for the assessment of physical fitness *Rep Civ Aeromed Res Inst US***,** 1-8.

BARBOUR, A. P., LAGERGREN, P., HUGHES, R., ALDERSON, D., BARHAM, C. P. & BLAZEBY, J. M. 2008. Health-related quality of life among patients with adenocarcinoma of the gastro-oesophageal junction treated by gastrectomy or oesophagectomy. *Br J Surg,* 95**,** 80-4.

BAUMAN, A., PHONGSAVAN, P., SCHOEPPE, S. & OWEN, N. 2006. Physical activity measurement--a primer for health promotion. *Promot Educ,* 13**,** 92-103.

BAUMGARTNER, R. N., KOEHLER, K. M., GALLAGHER, D., ROMERO, L., HEYMSFIELD, S. B., ROSS, R. R., GARRY, P. J. & LINDEMAN, R. D. 1998. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol,* 147**,** 755-63.

BEHRENS, G., JOCHEM, C., KEIMLING, M., RICCI, C., SCHMID, D. & LEITZMANN, M. F. 2014. The association between physical activity and gastroesophageal cancer: systematic review and meta-analysis. *Eur J Epidemiol,* 29**,** 151-70.

BENZO, R., WIGLE, D., NOVOTNY, P., WETZSTEIN, M., NICHOLS, F., SHEN, R. K., CASSIVI, S. & DESCHAMPS, C. 2011. Preoperative pulmonary rehabilitation before lung cancer resection: Results from two randomized studies. *Lung Cancer,* 74**,** 441-5

BLAIR, S. N., KOHL, H. W., 3RD, PAFFENBARGER, R. S., JR., CLARK, D. G., COOPER, K. H. & GIBBONS, L. W. 1989. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA,* 262**,** 2395-401.

BLANCHARD, C. M., STEIN, K. D., BAKER, F., DENT, M. F., DENNISTON, M. M., COURNEYA, K. S. & NEHL, E. 2004. Association between current lifestyle behaviors and health-related quality of life in breast, colorectal, and prostate cancer survivors. *Psychol Health,* 19**,** 1-13.

BLAND, M. 2000. Significance Tests. In: BLAND, M. (ed.) *An Introduction to Medical Statistics.* 3rd ed. Oxford: Oxford University Press.

BLAZEBY, J. M., CONROY, T., HAMMERLID, E., FAYERS, P., SEZER, O., KOLLER, M., ARRARAS, J., BOTTOMLEY, A., VICKERY, C. W., ETIENNE, P. L. & ALDERSON, D. 2003. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. *Eur J Cancer,* 39**,** 1384-94.

BLAZEBY, J. M., FARNDON, J. R., DONOVAN, J. & ALDERSON, D. 2000. A prospective longitudinal study examining the quality of life of patients with esophageal carcinoma. *Cancer,* 88**,** 1781-1787.

BLAZEBY, J. M., SANFORD, E., FALK, S. J., ALDERSON, D. & DONOVAN, J. L. 2005. Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. *Cancer,* 103**,** 1791-1799.

BOHANNON, R. W. 2001. Dynamometer measurements of hand-grip strength predict multiple outcomes. *Percept Mot Skills,* 93**,** 323-8.

BOHANNON, R. W. 2008. Hand-grip dynamometry predicts future outcomes in aging adults. *J Geriatr Phys Ther,* 31**,** 3-10.

BOHANNON, R. W. 2012. Are hand-grip and knee extension strength reflective of a common construct? *Percept Mot Skills,* 114**,** 514-8.

BORG, G. A. 1982. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc,* 14**,** 377-81.

BOSETTI, C., LEVI, F., FERLAY, J., GARAVELLO, W., LUCCHINI, F., BERTUCCIO, P., NEGRI, E. & LA VECCHIA, C. 2008. Trends in oesophageal cancer incidence and mortality in Europe. *Int J Cancer,* 122**,** 1118-29.

BOVELLI, D., PLATANIOTIS, G. & ROILA, F. 2010. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. *Ann Oncol,* 21 Suppl 5**,** v277-82.

BOWER, M. R. & MARTIN, R. C., 2ND 2009. Nutritional management during neoadjuvant therapy for esophageal cancer. *J Surg Oncol,* 100**,** 82-7.

BRAUN, V. & CLARKE, V. 2006. Using thematic analysis in psychology. *Qualitative research in psychology,* 3**,** 77-101.

BRODERICK, J. M., HUSSEY, J., KENNEDY, M. J. & DM, O. D. 2014a. Patients over 65 years are assigned lower ECOG PS scores than younger patients, although objectively measured physical activity is no different. *J Geriatr Oncol,* 5**,** 49-56.

BRODERICK, J. M., HUSSEY, J., KENNEDY, M. J. & O'DONNELL, D. M. 2014b. Testing the 'teachable moment' premise: does physical activity increase in the early survivorship phase? *Support Care Cancer,* 22**,** 989-97.

BRODERICK, J. M., RYAN, J., O'DONNELL, D. M. & HUSSEY, J. 2014c. A guide to assessing physical activity using accelerometry in cancer patients. *Support Care Cancer,* 22**,** 1121-30.

BROOKS, J. A., KESLER, K. A., JOHNSON, C. S., CIACCIA, D. & BROWN, J. W. 2002. Prospective analysis of quality of life after surgical resection for esophageal cancer: preliminary results. *J Surg Oncol,* 81**,** 185-94.

BRUERA, E. 1997. ABC of palliative care. Anorexia, cachexia, and nutrition. *BMJ,* 315**,** 1219-22.

BRUTON, A., CONWAY, J.H., HOLGATE S.T. 2000. Reliability: What is it and how is it measured? . *Physiotherapy,* 86**,** 94-99.

BUTLAND, R. J., PANG, J., GROSS, E. R., WOODCOCK, A. A. & GEDDES, D. M. 1982. Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J (Clin Res Ed),* 284**,** 1607-8.

CAHALIN, L. P., MATHIER, M. A., SEMIGRAN, M. J., DEC, G. W. & DISALVO, T. G. 1996. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest,* 110**,** 325-32.

CAMARRI, B., EASTWOOD, P. R., CECINS, N. M., THOMPSON, P. J. & JENKINS, S. 2006. Six minute walk distance in healthy subjects aged 55-75 years. *Respir Med,* 100**,** 658-65.

CARLI, F., CHARLEBOIS, P., STEIN, B., FELDMAN, L., ZAVORSKY, G., KIM, D. J., SCOTT, S. & MAYO, N. E. 2010. Randomized clinical trial of prehabilitation in colorectal surgery. *Br J Surg,* 97**,** 1187-97.

CARTER, R., LUBINSKY, J., DOMHOLDT, E. (eds) 2011. *Rehabilitation Research: Principles and Applications,* St. Louis, Missouri, Elsevier Saunders.

CASANOVA, C., CELLI, B. R., BARRIA, P., CASAS, A., COTE, C., DE TORRES, J. P., JARDIM, J.,

LOPEZ, M. V., MARIN, J. M., MONTES DE OCA, M., PINTO-PLATA, V. & AGUIRRE-JAIME, A. 2011. The 6-min walk distance in healthy subjects: reference standards from seven countries. *Eur Respir J,* 37**,** 150-6.

CASPERSEN, C. J., POWELL, K. E. & CHRISTENSON, G. M. 1985. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep,* 100**,** 126-31.

CAWTHON, P. M., MARSHALL, L. M., MICHAEL, Y., DAM, T. T., ENSRUD, K. E., BARRETT-CONNOR, E. & ORWOLL, E. S. 2007. Frailty in older men: prevalence, progression, and relationship with mortality. *J Am Geriatr Soc,* 55**,** 1216-23.

CELIS-MORALES, C. A., PEREZ-BRAVO, F., IBANEZ, L., SALAS, C., BAILEY, M. E. & GILL, J. M. 2012. Objective vs. self-reported physical activity and sedentary time: effects of measurement method on relationships with risk biomarkers. *PLoS One,* 7**,** e36345.

CELLI, B. R., COTE, C. G., MARIN, J. M., CASANOVA, C., MONTES DE OCA, M., MENDEZ, R. A., PINTO PLATA, V. & CABRAL, H. J. 2004. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med,* 350**,** 1005-12.

CENSE, H. A., HULSCHER, J. B., DE BOER, A. G., DONGELMANS, D. A., TILANUS, H. W., OBERTOP, H., SPRANGERS, M. A. & VAN LANSCHOT, J. J. 2006. Effects of prolonged intensive care unit stay on quality of life and long-term survival after transthoracic esophageal resection. *Crit Care Med,* 34**,** 354-62.

CHANG, Y. L., TSAI, Y. F., WU, Y. C. & HSIEH, M. J. 2014. Factors relating to quality of life after esophagectomy for cancer patients in Taiwan. *Cancer Nurs,* 37**,** 4-13.

CHEN, C. H., HO, C., HUANG, Y. Z. & HUNG, T. T. 2011. Hand-grip strength is a simple and effective outcome predictor in esophageal cancer following esophagectomy with reconstruction: a prospective study. *J Cardiothorac Surg,* 6**,** 98.

CHRISTIANSON, S. & LOFTUS, E. 1991. Remembering emotional events: The fate of detail information. *Cogn Emot,* 5**,** 81-108.

CLARKE, C., MCCORRY, N. K. & DEMPSTER, M. 2011. The role of identity in adjustment among survivors of oesophageal cancer. *J Health Psychol,* 16**,** 99-108.

COLLINS, F. S. & VARMUS, H. 2015. A new initiative on precision medicine. *N Engl J Med,* 372**,** 793-5.

COLLINS, J., NOBLE, S., CHESTER, J., COLES, B. & BYRNE, A. 2014. The assessment and impact of sarcopenia in lung cancer: a systematic literature review. *BMJ Open,* 4**,** e003697.

COURNEYA, K. S. 2003. Exercise in cancer survivors: an overview of research. *Med Sci Sports Exerc,* 35**,** 1846-52.

COURNEYA, K. S. & FRIEDENREICH, C. M. 1997. Relationship between exercise pattern across the cancer experience and current quality of life in colorectal cancer survivors. *J Altern Complement Med,* 3**,** 215-26.

COURNEYA, K. S. & FRIEDENREICH, C. M. 2001. Framework PEACE: an organizational model for examining physical exercise across the cancer experience. *Ann Behav Med,* 23**,** 263-72.

COURNEYA, K. S. & FRIEDENREICH, C. M. 2007. Physical activity and cancer control. *Semin Oncol Nurs,* 23**,** 242-52.

COURNEYA, K. S., FRIEDENREICH, C. M., QUINNEY, H. A., FIELDS, A. L., JONES, L. W., VALLANCE, J. K. & FAIREY, A. S. 2005. A longitudinal study of exercise barriers in colorectal cancer

survivors participating in a randomized controlled trial. *Ann Behav Med,* 29**,** 147-53.

COURRECH STAAL, E. F., ALEMAN, B. M., BOOT, H., VAN VELTHUYSEN, M. L., VAN TINTEREN, H. & VAN SANDICK, J. W. 2010. Systematic review of the benefits and risks of neoadjuvant chemoradiation for oesophageal cancer. *Br J Surg,* 97**,** 1482-1496.

CRAIKE, M. J., HOSE, K., COURNEYA, K. S., HARRISON, S. J. & LIVINGSTON, P. M. 2013. Perceived benefits and barriers to exercise for recently treated patients with multiple myeloma: a qualitative study. *BMC Cancer,* 13**,** 319.

CRAMP, F. & BYRON-DANIEL, J. 2012. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev,* 11**,** CD006145.

CROMES, G. J. 1978. Implementation of Interdisciplinary Cancer Rehabilitation. *Rehabil Counseling Bull,* 21**,** 230-7.

CRUZ-JENTOFT, A. J., BAEYENS, J. P., BAUER, J. M., BOIRIE, Y., CEDERHOLM, T., LANDI, F., MARTIN, F. C., MICHEL, J. P., ROLLAND, Y., SCHNEIDER, S. M., TOPINKOVA, E., VANDEWOUDE, M. & ZAMBONI, M. 2010. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing,* 39**,** 412-23.

D'JOURNO, X. B., OUATTARA, M., LOUNDOU, A., TROUSSE, D., DAHAN, L., NATHALIE, T., DODDOLI, C., SEITZ, J. F. & THOMAS, P. A. 2012. Prognostic impact of weight loss in 1-year survivors after transthoracic esophagectomy for cancer. *Dis Esophagus,* 25**,** 527-34.

DAKOF, G. A. & TAYLOR, S. E. 1990. Victims' perceptions of social support: what is helpful from whom? *J Pers Soc Psychol,* 58**,** 80-9.

DALY, J. M., FRY, W. A., LITTLE, A. G., WINCHESTER, D. P., MCKEE, R. F., STEWART, A. K. & FREMGEN, A. M. 2000. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. *J Am Coll Surg,* 190**,** 562-72; discussion 572-3.

DAVIES, S. J. & WILSON, R. J. 2004. Preoperative optimization of the high-risk surgical patient. *Br J Anaesth,* 93**,** 121-8.

DE BOER, A. G., VAN LANSCHOT, J. J., VAN SANDICK, J. W., HULSCHER, J. B., STALMEIER, P. F., DE HAES, J. C., TILANUS, H. W., OBERTOP, H. & SPRANGERS, M. A. 2004. Quality of life after transhiatal compared with extended transthoracic resection for adenocarcinoma of the esophagus. *J Clin Oncol,* 22**,** 4202-8.

DEEKS, J. J., DINNES, J., D'AMICO, R., SOWDEN, A. J., SAKAROVITCH, C., SONG, F., PETTICREW, M. & ALTMAN, D. G. 2003. Evaluating non-randomised intervention studies. *Health Technol Assess,* 7**,** iii-x, 1-173.

DEMARK-WAHNEFRIED, W., AZIZ, N. M., ROWLAND, J. H. & PINTO, B. M. 2005. Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. *J Clin Oncol,* 23**,** 5814-30.

DEMARK-WAHNEFRIED, W., HARS, V., CONAWAY, M. R., HAVLIN, K., RIMER, B. K., MCELVEEN, G. & WINER, E. P. 1997. Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. *Am J Clin Nutr,* 65**,** 1495-501.

DENZIN, N. K. 1970. *The research act: A theoretical introduction to sociological methods. ,* Chicago, Aldine Publishing Company.

DEROGAR, M., ORSINI, N., SADR-AZODI, O. & LAGERGREN, P. 2012. Influence of major postoperative complications on health-related quality of life among long-term

survivors of esophageal cancer surgery. *J Clin Oncol,* 30**,** 1615-9.

DEVESA, S. S., BLOT, W. J. & FRAUMENI, J. F., JR. 1998. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer,* 83**,** 2049-53.

DISHMAN, R. K., WASHBURN, R. A. & SCHOELLER, D. A. 2001. Measurement of physical activity. *Quest,* 53**,** 295-309.

DITMYER, M. M., TOPP, R. & PIFER, M. 2002. Prehabilitation in preparation for orthopaedic surgery. *Orthop Nurs,* 21**,** 43-51; quiz 52-4.

DOHERTY, T. J. 2003. Invited review: Aging and sarcopenia. *J Appl Physiol (1985),* 95**,** 1717-27.

DONOHOE, C. L., MCGILLYCUDDY, E. & REYNOLDS, J. V. 2011a. Long-term health-related quality of life for disease-free esophageal cancer patients. *World J Surg,* 35**,** 1853-60.

DONOHOE, C. L., RYAN, A. M. & REYNOLDS, J. V. 2011b. Cancer cachexia: mechanisms and clinical implications. *Gastroenterol Res Pract,* 2011**,** 601434.

DOWNS, S. H. & BLACK, N. 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health,* 52**,** 377-84.

EDGE, S.B, COMPTON, C.C. 2010. The american joint committee on cancer: the 7th edition of teh AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*, 17, 1471-1474.

EGBERTS, J. H., SCHNIEWIND, B., BESTMANN, B., SCHAFMAYER, C., EGBERTS, F., FAENDRICH, F., KUECHLER, T. & TEPEL, J. 2008. Impact of the site of anastomosis after oncologic esophagectomy on quality of life - A prospective, longitudinal outcome study. *Ann Surg Oncol,* 15**,** 566-575.

ENRIGHT, P. L. & SHERRILL, D. L. 1998. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med,* 158**,** 1384-7.

ENZINGER, P. C. & MAYER, R. J. 2003. Esophageal cancer. *N Engl J Med,* 349**,** 2241-52.

EVANS, W. J. & CAMPBELL, W. W. 1993. Sarcopenia and age-related changes in body composition and functional capacity. *J Nutr,* 123**,** 465-8.

FAYERS PM, A. N., BJORDAL K, GROENVOLD M, CURRAN D, BOTTOMLEY A, ON BEHALF OF THE EORTC QUALITY OF LIFE GROUP 2001. *The EORTC QLQ-C30 Scoring Manual.* 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer.

FEENEY, C., REYNOLDS, J. V. & HUSSEY, J. 2011. Preoperative physical activity levels and postoperative pulmonary complications post-esophagectomy. *Dis Esophagus,* 24**,** 489-94.

FEREDAY, J. & MUIR-COCHRANE, E. 2006. Demonstrating rigor using thematic analysis: A hybrid approach of inductive and deductive coding and theme development. *Int J Qual Methods,* 5**,** 80-92.

FERLAY J, SOERJOMATARAM, ERVIK M, DIKSHIT R, ESER S,MATHERS C, REBELO M, PARKIN DM, FORMAN D,BRAY, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 16/09/2015.

FERRI, L. E., LAW, S., WONG, K. H., KWOK, K. F. & WONG, J. 2006. The influence of technical complications on postoperative outcome and survival after esophagectomy. *Ann Surg Oncol,* 13**,** 557-64.

FESS, E. 1992. Grip Strength. In: CASANOVA, J. (ed.) *Clinical Assessment Recommendations.* 2nd ed. Chicago: American Society of Hand Therapists.

FINCH, E., BROOKS, D., STRATFORD, P.W., MAYO, N. 2002. Why Measurement Properties Are Important. In: FINCH, E., BROOKS, D., STRATFORD, P.W., MAYO, N. (ed.) *Physical Rehabilitation Outcome Measures: A Guide to Enhanced Clinical Decision Making.* 2nd ed. Hamilton Ontario: Lippincott Williams and Wilkins.

FISHER, A., WARDLE, J., BEEKEN, R. J., CROKER, H., WILLIAMS, K. & GRIMMETT, C. 2015. Perceived barriers and benefits to physical activity in colorectal cancer patients. *Support Care Cancer*. [epub ahead of print]

FORBES, C. C., BLANCHARD, C. M., MUMMERY, W. K. & COURNEYA, K. S. 2014. A comparison of physical activity correlates across breast, prostate and colorectal cancer survivors in Nova Scotia, Canada. *Support Care Cancer,* 22**,** 891-903.

FOX, N., HUNN, A., MATHERS, N. 2007. Sampling and sample size calculation. *The NIHR RDS for the East Midlands / Yorkshire & the Humber*

FREEDSON, P. S., MELANSON, E. & SIRARD, J. 1998. Calibration of the Computer Science and Applications, Inc. accelerometer. *Med Sci Sports Exerc,* 30**,** 777-81.

GARBER, C. E., BLISSMER, B., DESCHENES, M. R., FRANKLIN, B. A., LAMONTE, M. J., LEE, I. M., NIEMAN, D. C. & SWAIN, D. P. 2011. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc,* 43**,** 1334-59.

GEBSKI, V., BURMEISTER, B., SMITHERS, B. M., FOO, K., ZALCBERG, J. & SIMES, J. 2007. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol,* 8**,** 226-34.

GIVEN, L. M. 2008. *The Sage encyclopedia of qualitative research methods*, Sage Publications.

GJERSET, G. M., FOSSA, S. D., COURNEYA, K. S., SKOVLUND, E., JACOBSEN, A. B. & THORSEN, L. 2011. Interest and preferences for exercise counselling and programming among Norwegian cancer survivors. *Eur J Cancer Care (Engl),* 20**,** 96-105.

GOCKEL, I., EXNER, C. & JUNGINGER, T. 2005. Morbidity and mortality after esophagectomy for esophageal carcinoma: a risk analysis. *World J Surg Oncol,* 3**,** 37.

GRADAUSKAS, P., RUBIKAS, R. & SAFERIS, V. 2006. Changes in quality of life after esophageal resections for carcinoma. *Medicina (Kaunas, Lithuania),* 42**,** 187-194.

GRIMES, D. A. & SCHULZ, K. F. 2002. An overview of clinical research: the lay of the land. *Lancet,* 359**,** 57-61.

GUNTHER, C. M., BURGER, A., RICKERT, M., CRISPIN, A. & SCHULZ, C. U. 2008. Grip strength in healthy caucasian adults: reference values. *J Hand Surg Am,* 33**,** 558-65.

HALE, L. A., PAL, J. & BECKER, I. 2008. Measuring free-living physical activity in adults with and without neurologic dysfunction with a triaxial accelerometer. *Arch Phys Med Rehabil,* 89**,** 1765-71.

HARADA, K., IDA, S., BABA, Y., ISHIMOTO, T., KOSUMI, K., TOKUNAGA, R., IZUMI, D., OHUCHI, M., NAKAMURA, K., KIYOZUMI, Y., IMAMURA, Y., IWATSUKI, M., IWAGAMI, S., MIYAMOTO, Y., SAKAMOTO, Y., YOSHIDA, N., WATANABE, M. & BABA, H. 2015. Prognostic and clinical impact of sarcopenia in esophageal squamous cell carcinoma. Dis Esophagus. [epub agead of print] 30 June 2015 doi: 10.1111/dote.12381

HARKONEN, R., HARJU, R. & ALARANTA, H. 1993. Accuracy of the Jamar dynamometer. *J Hand Ther,* 6**,** 259-62.

HARRISON, S. L., GREENING, N. J., HOUCHEN-WOLLOFF, L., BANKART, J., MORGAN, M. D., STEINER, M. C. & SINGH, S. J. 2013. Age-specific normal values for the incremental shuttle walk test in a healthy British population. *J Cardiopulm Rehabil Prev,* 33**,** 309-13.

HAUSER, C., PATETT, C., VON SCHOENFELS, W., HEITS, N., SCHAFMAYER, C., MALCHOW, B., HAMPE, J., SCHNIEWIND, B., BECKER, T. & EGBERTS, J. H. 2014. Does neoadjuvant treatment before oncologic esophagectomy affect the postoperative quality of life? A prospective, longitudinal outcome study. *Dis Esophagus*. [epub ahead of print] 25 July 214. doi: 10.1111/dote.12257.

HAYNES, S. N., RICHARD, D.C.S., KUBANY, E.S. 1995. Content Validity in Psychological Assessment: A Functional Approach to Concepts and Methods. *Psychol Assessment,* 7**,** 238-247.

HEALY, G. N., CLARK, B. K., WINKLER, E. A., GARDINER, P. A., BROWN, W. J. & MATTHEWS, C. E. 2011. Measurement of adults' sedentary time in population-based studies. *Am J Prev Med,* 41**,** 216-27.

HEFFERON, K., MURPHY, H., MCLEOD, J., MUTRIE, N. & CAMPBELL, A. 2013. Understanding barriers to exercise implementation 5-year post-breast cancer diagnosis: a large-scale qualitative study. *Health Educ Res,* 28**,** 843-56.

HELLBOM, M., BERGELT, C., BERGENMAR, M., GIJSEN, B., LOGE, J. H., RAUTALAHTI, M., SMARADOTTIR, A. & JOHANSEN, C. 2011. Cancer rehabilitation: A Nordic and European perspective. *Acta Oncol,* 50**,** 179-86.

HEWITT, M., ROWLAND, J. H. & YANCIK, R. 2003. Cancer survivors in the United States: age, health, and disability. *J Gerontol A Biol Sci Med Sci,* 58**,** 82-91.

HEYWARD, V. H. 2010. *Advanced Fitness Assessment and Exercise Prescription*, 6th edn. Human Kinetics.

HIGGINS, J. P., THOMPSON, S. G., DEEKS, J. J. & ALTMAN, D. G. 2003. Measuring inconsistency in meta-analyses. *BMJ,* 327**,** 557-60.

HII, M. W., SMITHERS, B. M., GOTLEY, D. C., THOMAS, J. M., THOMSON, I., MARTIN, I. & BARBOUR, A. P. 2013. Impact of postoperative morbidity on long-term survival after oesophagectomy. *Br J Surg,* 100**,** 95-104.

HODGSON, T. 2006. Oesophageal cancer: Experiences of patients and their partners. *Br J Nurs,* 15**,** 1157-60.

HOFMAN, M., RYAN, J. L., FIGUEROA-MOSELEY, C. D., JEAN-PIERRE, P. & MORROW, G. R. 2007. Cancer-related fatigue: the scale of the problem. *Oncologist,* 12 Suppl 1**,** 4-10.

HONG, L., ZHANG, Y., ZHANG, H., YANG, J. & ZHAO, Q. 2013. The short-term outcome of three-field minimally invasive esophagectomy for siewert type i esophagogastric junctional adenocarcinoma. *Ann Thorac Surg,* 96**,** 1826-1831.

HOOPER, P., JUTAI, J. W., STRONG, G. & RUSSELL-MINDA, E. 2008. Age-related macular degeneration and low-vision rehabilitation: a systematic review. *Can J Ophthalmol,* 43**,** 180-7.

HOWLADER, N., NOONE, AM., KRAPCHO, M, GARCHELL, J., MILLER, D., ALTEKRUSE, SF., KOSARY, CL., YU, M., RUHL, J., TATALOVICH, Z.,MARIOTTO, A., LEWIS, DR., CHEN, HS., FEUER, EJ., CRONIN, KA. (eds). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on

November 2014 SEER data submission, posted to the SEER web site, April 2015.

HRUSCHKA, D. J., SCHWARTZ, D, COBB ST. JOHN, D., PICONE-DECARO, E., JENKINS, R.A., CAREY, J.W. 2004. Reliability in coding open-ended data: Lessons learned from HIV behavioral research. *Field Methods,* 16**,** 307-331.

HUANG, Q., ZHONG, J., YANG, T., LI, J., LUO, K., ZHENG, Y., YANG, H. & FU, J. 2015. Impacts of anastomotic complications on the health-related quality of life after esophagectomy. *J Surg Oncol,* 111**,** 365-70.

HUNTER, R. F., TULLY, M. A., DONNELLY, P., STEVENSON, M. & KEE, F. 2014. Knowledge of UK physical activity guidelines: implications for better targeted health promotion. *Prev Med,* 65**,** 33-9.

HUSSEY, J., BENNETT, K., DWYER, J. O., LANGFORD, S., BELL, C. & GORMLEY, J. 2009. Validation of the RT3 in the measurement of physical activity in children. *J Sci Med Sport,* 12**,** 130-3.

IDA, S., WATANABE, M., YOSHIDA, N., BABA, Y., UMEZAKI, N., HARADA, K., KARASHIMA, R., IMAMURA, Y., IWAGAMI, S. & BABA, H. 2015. Sarcopenia is a Predictor of Postoperative Respiratory Complications in Patients with Esophageal Cancer. *Ann Surg Oncol*. [epub ahead of print] 11 April 2015.

INOUE, J., ONO, R., MAKIURA, D., KASHIWA-MOTOYAMA, M., MIURA, Y., USAMI, M., NAKAMURA, T., IMANISHI, T. & KURODA, D. 2013. Prevention of postoperative pulmonary complications through intensive preoperative respiratory rehabilitation in patients with esophageal cancer. *Dis Esophagus,* 26**,** 68-74.

IRWIN, M. L., CRUMLEY, D., MCTIERNAN, A., BERNSTEIN, L., BAUMGARTNER, R., GILLILAND, F. D., KRISKA, A. & BALLARD-BARBASH, R. 2003. Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. *Cancer,* 97**,** 1746-57.

JACK, S., WEST, M. & GROCOTT, M. P. 2011. Perioperative exercise training in elderly subjects. *Best Pract Res Clin Anaesthesiol,* 25**,** 461-72.

JACK, S., WEST, M. A., RAW, D., MARWOOD, S., AMBLER, G., COPE, T. M., SHROTRI, M., STURGESS, R. P., CALVERLEY, P. M., OTTENSMEIER, C. H. & GROCOTT, M. P. 2014. The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery. *Eur J Surg Oncol*. 40 (10), 1313-20.

JAFFRIN, M. Y. 2009. Body composition determination by bioimpedance: an update. *Curr Opin Clin Nutr Metab Care,* 12**,** 482-6.

JAGER, K. J., STEL, V. S., WANNER, C., ZOCCALI, C. & DEKKER, F. W. 2007. The valuable contribution of observational studies to nephrology. *Kidney Int,* 72**,** 671-5.

JEBB, S. A., COLE, T. J., DOMAN, D., MURGATROYD, P. R. & PRENTICE, A. M. 2000. Evaluation of the novel Tanita body-fat analyser to measure body composition by comparison with a four-compartment model. *Br J Nutr,* 83**,** 115-22.

JONES, L. W. & COURNEYA, K. S. 2002. Exercise counseling and programming preferences of cancer survivors. *Cancer Pract,* 10**,** 208-15.

JONES, L. W., EVES, N. D., HAYKOWSKY, M., JOY, A. A. & DOUGLAS, P. S. 2008a. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol,* 9**,** 757-65.

JONES, L. W., EVES, N. D., PETERSON, B. L., GARST, J., CRAWFORD, J., WEST, M. J., MABE, S., HARPOLE, D., KRAUS, W. E. & DOUGLAS, P. S. 2008b. Safety and feasibility of aerobic

training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. *Cancer,* 113**,** 3430-9.

JONES, L. W., HORNSBY, W. E., GOETZINGER, A., FORBES, L. M., SHERRARD, E. L., QUIST, M., LANE, A. T., WEST, M., EVES, N. D., GRADISON, M., COAN, A., HERNDON, J. E. & ABERNETHY, A. P. 2012. Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. *Lung Cancer,* 76**,** 248-52.

JONES, L. W., PEDDLE, C. J., EVES, N. D., HAYKOWSKY, M. J., COURNEYA, K. S., MACKEY, J. R., JOY, A. A., KUMAR, V., WINTON, T. W. & REIMAN, T. 2007. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer,* 110**,** 590-8.

JURGENSEN, S. P., ANTUNES, L. C., TANNI, S. E., BANOV, M. C., LUCHETA, P. A., BUCCERONI, A. F., GODOY, I. & DOURADO, V. Z. 2011. The incremental shuttle walk test in older Brazilian adults. *Respiration,* 81**,** 223-8.

KATARIA, K., VERMA, G. R., MALHOTRA, A. & YADAV, R. 2012. Comparison of quality of life in patients undergoing transhiatal esophagectomy with or without chemotherapy. *Saudi J Gastroenterol,* 18**,** 195-200.

KEEGAN, N., CUFFE, S., CUNNINGHAM, M., RAVI, N., LEE, G., KENNEDY, M., GROGAN, W., O'NEILL, B., POWER, D. & LEONARD, G. 2014. ICORG 10-14: Neo-AEGIS: A randomized clinical trial of neoadjuvant and adjuvant chemotherapy (modified MAGIC regimen) versus neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the esophagus and esophagogastric junction. *J Clin Oncol,* 32**,** 5s (suppl; abstr TOS4145).

KELLY, L. A., MCMILLAN, D. G., ANDERSON, A., FIPPINGER, M., FILLERUP, G. & RIDER, J. 2013. Validity of actigraphs uniaxial and triaxial accelerometers for assessment of physical activity in adults in laboratory conditions. *BMC Med Phys,* 13**,** 5.

KENNELLY, J. Methodological approach to assessing the evidence. 2011. In: HANDLER A., KENNELLY, J., PEACOCK, N. (eds). *Reducing Racial/Ethnic Disparities in Reproductive and Perinatal Outcomes.* Springer.

KENNY, R. A., COEN, R. F., FREWEN, J., DONOGHUE, O. A., CRONIN, H. & SAVVA, G. M. 2013. Normative values of cognitive and physical function in older adults: findings from the Irish Longitudinal Study on Ageing. *J Am Geriatr Soc,* 61 Suppl 2**,** S279-90.

KIDANE, B., COUGHLIN, S., VOGT, K. & MALTHANER, R. 2015. Preoperative chemotherapy for resectable thoracic esophageal cancer. *Cochrane Database Syst Rev,* 5**,** CD001556.

KILGOUR, R. D., VIGANO, A., TRUTSCHNIGG, B., LUCAR, E., BOROD, M. & MORAIS, J. A. 2013. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Support Care Cancer,* 21**,** 3261-70.

KNOX, E. C., ESLIGER, D. W., BIDDLE, S. J. & SHERAR, L. B. 2013. Lack of knowledge of physical activity guidelines: can physical activity promotion campaigns do better? *BMJ Open,* 3**,** e003633.

KUSHI, L. H., DOYLE, C., MCCULLOUGH, M., ROCK, C. L., DEMARK-WAHNEFRIED, W., BANDERA, E. V., GAPSTUR, S., PATEL, A. V., ANDREWS, K. & GANSLER, T. 2012. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin,* 62**,** 30-67.

LAGERGREN, P., AVERY, K. N., HUGHES, R., BARHAM, C. P., ALDERSON, D., FALK, S. J. & BLAZEBY, J. M. 2007. Health-related quality of life among patients cured by surgery for

esophageal cancer. *Cancer,* 110**,** 686-93.

LAKOSKI, S. G., WILLIS, B. L., BARLOW, C. E., LEONARD, D., GAO, A., RADFORD, N. B., FARRELL, S. W., DOUGLAS, P. S., BERRY, J. D., DEFINA, L. F. & JONES, L. W. 2015. Midlife Cardiorespiratory Fitness, Incident Cancer, and Survival After Cancer in Men: The Cooper Center Longitudinal Study. *JAMA Oncol,* 1**,** 231-7.

LAMBERT, V. A. & LAMBERT, C. E. 2012. Qualitative Descriptive Research: An Acceptable Design. *Pac Rim Int J of Nurs Res,* 16**,** 2.

LARSSON, B., SVARDSUDD, K., WELIN, L., WILHELMSEN, L., BJORNTORP, P. & TIBBLIN, G. 1984. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *Br Med J (Clin Res Ed),* 288**,** 1401-4.

LAVIANO, A. & MEGUID, M. M. 1996. Nutritional issues in cancer management. *Nutrition,* 12**,** 358-71.

LAW, S., WONG, K. H., KWOK, K. F., CHU, K. M. & WONG, J. 2004. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. *Ann Surg,* 240**,** 791-800.

LEAHY, S., O'NEILL, C., SOHUN, R. & JAKEMAN, P. 2012. A comparison of dual energy X-ray absorptiometry and bioelectrical impedance analysis to measure total and segmental body composition in healthy young adults. *Eur J Appl Physiol,* 112**,** 589-95.

LEDERER, D. J., ARCASOY, S. M., WILT, J. S., D'OVIDIO, F., SONETT, J. R. & KAWUT, S. M. 2006. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med,* 174**,** 659-64.

LEIBMAN, S., SMITHERS, B. M., GOTLEY, D. C., MARTIN, I. & THOMAS, J. 2006. Minimally invasive esophagectomy: short- and long-term outcomes. *Surg Endosc,* 20**,** 428-33.

LEONG, D. P., TEO, K. K., RANGARAJAN, S., LOPEZ-JARAMILLO, P., AVEZUM, A., JR., ORLANDINI, A., SERON, P., AHMED, S. H., ROSENGREN, A., KELISHADI, R., RAHMAN, O., SWAMINATHAN, S., IQBAL, R., GUPTA, R., LEAR, S. A., OGUZ, A., YUSOFF, K., ZATONSKA, K., CHIFAMBA, J., IGUMBOR, E., MOHAN, V., ANJANA, R. M., GU, H., LI, W. & YUSUF, S. 2015. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet*.

LI, R. C., JASIEWICZ, J. M., MIDDLETON, J., CONDIE, P., BARRISKILL, A., HEBNES, H. & PURCELL, B. 2006. The development, validity, and reliability of a manual muscle testing device with integrated limb position sensors. *Arch Phys Med Rehabil,* 87**,** 411-7.

LIEDMAN, B., JOHNSSON, E., MERKE, C., RUTH, M. & LUNDELL, L. 2001. Preoperative adjuvant radiochemotherapy may increase the risk in patients undergoing thoracoabdominal esophageal resections. *Dig Surg,* 18**,** 169-75.

LIGIBEL, J. A., MEYERHARDT, J., PIERCE, J. P., NAJITA, J., SHOCKRO, L., CAMPBELL, N., NEWMAN, V. A., BARBIER, L., HACKER, E., WOOD, M., MARSHALL, J., PASKETT, E. & SHAPIRO, C. 2012. Impact of a telephone-based physical activity intervention upon exercise behaviors and fitness in cancer survivors enrolled in a cooperative group setting. *Breast Cancer Res Treat,* 132**,** 205-13.

LOPRINZI, P. D., LEE, H. & CARDINAL, B. J. 2013. Objectively measured physical activity among US cancer survivors: considerations by weight status. *J Cancer Surviv,* 7**,** 493-9.

LUC, G., DURAND, M., CHICHE, L. & COLLET, D. 2015. Major post-operative complications predict long-term survival after esophagectomy in patients with adenocarcinoma of

the esophagus. *World J Surg,* 39**,** 216-22.

LUKETICH, J. D., ALVELO-RIVERA, M., BUENAVENTURA, P. O., CHRISTIE, N. A., MCCAUGHAN, J. S., LITLE, V. R., SCHAUER, P. R., CLOSE, J. M. & FERNANDO, H. C. 2003. Minimally invasive esophagectomy: outcomes in 222 patients. *Ann Surg,* 238**,** 486-94; discussion 494-5.

LUND, M., VON DOBELN, G., NILSSON, M., WINTER, R., LUNDELL, L., TSAI, J. A. & KALMAN, S. 2015. Effects on heart function of neoadjuvant chemotherapy and chemoradiotherapy in patients with cancer in the esophagus or gastroesophageal junction inverted question mark a prospective cohort pilot study within a randomized clinical trial. *Radiat Oncol,* 10**,** 16.

LV, Y., ZHANG, J. & QIAO, L. 2014. Quality of life in patients with esophageal cancer receiving definitive chemoradiotherapy or esophagectomy. *Mol Clin Oncol,* 2**,** 870-874.

LYNCH, B. M., DUNSTAN, D. W., HEALY, G. N., WINKLER, E., EAKIN, E. & OWEN, N. 2010a. Objectively measured physical activity and sedentary time of breast cancer survivors, and associations with adiposity: findings from NHANES (2003-2006). *Cancer Causes Control,* 21**,** 283-8.

LYNCH, B. M., DUNSTAN, D. W., VALLANCE, J. K. & OWEN, N. 2013. Don't take cancer sitting down: a new survivorship research agenda. *Cancer,* 119**,** 1928-35.

LYNCH, B. M., DUNSTAN, D. W., WINKLER, E., HEALY, G. N., EAKIN, E. & OWEN, N. 2011. Objectively assessed physical activity, sedentary time and waist circumference among prostate cancer survivors: findings from the National Health and Nutrition Examination Survey (2003-2006). *Eur J Cancer Care (Engl),* 20**,** 514-9.

LYNCH, B. M., OWEN, N., HAWKES, A. L. & AITKEN, J. F. 2010b. Perceived barriers to physical activity for colorectal cancer survivors. *Support Care Cancer,* 18**,** 729-34.

MADDISON, R., NI MHURCHU, C., JIANG, Y., VANDER HOORN, S., RODGERS, A., LAWES, C. M. & RUSH, E. 2007. International Physical Activity Questionnaire (IPAQ) and New Zealand Physical Activity Questionnaire (NZPAQ): a doubly labelled water validation. *Int J Behav Nutr Phys Act,* 4**,** 62.

MAGILVY, J. K. & THOMAS, E. 2009. A first qualitative project: qualitative descriptive design for novice researchers. *J Spec Pediatr Nurs,* 14**,** 298-300.

MAHABIR, S., BAER, D. J., GIFFEN, C., CLEVIDENCE, B. A., CAMPBELL, W. S., TAYLOR, P. R. & HARTMAN, T. J. 2006. Comparison of energy expenditure estimates from 4 physical activity questionnaires with doubly labeled water estimates in postmenopausal women. *Am J Clin Nutr,* 84**,** 230-6.

MALMSTROM, M., IVARSSON, B., JOHANSSON, J. & KLEFSGARD, R. 2013. Long-term experiences after oesophagectomy/gastrectomy for cancer--a focus group study. *Int J Nurs Stud,* 50**,** 44-52.

MANN, C. J. 2003. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emerg Med J,* 20**,** 54-60.

MARTIN, L., LAGERGREN, J., LINDBLAD, M., ROUVELAS, I. & LAGERGREN, P. 2007. Malnutrition after oesophageal cancer surgery in Sweden. *Br J Surg,* 94**,** 1496-500.

MARTIN, L. & LAGERGREN, P. 2009. Long-term weight change after oesophageal cancer surgery. *Br J Surg,* 96**,** 1308-14.

MATHIOWETZ, V. 2002. Comparison of Rolyan and Jamar dynamometers for measuring grip strength. *Occup Ther Int,* 9**,** 201-9.

MATHIOWETZ, V., WEBER, K., VOLLAND, G. & KASHMAN, N. 1984. Reliability and validity of grip and pinch strength evaluations. *J Hand Surg Am,* 9**,** 222-6.

MAY, A. M., VAN WEERT, E., KORSTJENS, I., HOEKSTRA-WEEBERS, J. E., VAN DER SCHANS, C. P., ZONDERLAND, M. L., MESTERS, I., VAN DEN BORNE, B. & ROS, W. J. 2010. Monitoring training progress during exercise training in cancer survivors: a submaximal exercise test as an alternative for a maximal exercise test? *Arch Phys Med Rehabil,* 91**,** 351-7.

MCCORRY, N. K., DEMPSTER, M., CLARKE, C. & DOYLE, R. 2009. Adjusting to life after esophagectomy: the experience of survivors and carers. *Qual Health Res,* 19**,** 1485-94.

MCDOWELL, I. 2006. *Measuring health: a guide to rating scales and questionnaires,* New York, Oxford University Press.

MELANSON, E. L., JR. & FREEDSON, P. S. 1996. Physical activity assessment: a review of methods. *Crit Rev Food Sci Nutr,* 36**,** 385-96.

MELHADO, R. E., ALDERSON, D. & TUCKER, O. 2010. The changing face of esophageal cancer. *Cancers (Basel),* 2**,** 1379-404.

METZGER, R., BOLLSCHWEILER, E., VALLBOHMER, D., MAISH, M., DEMEESTER, T. R. & HOLSCHER, A. H. 2004. High volume centers for esophagectomy: what is the number needed to achieve low postoperative mortality? *Dis Esophagus,* 17**,** 310-4.

MILES, M. B. & HUBERMAN, A. B. 1994. *Qualitative Data Analysis An Expanded Sourcebook*, SAGE Publications

MILLS, M. E. & SULLIVAN, K. 2000. Patients with operable oesophageal cancer: their experience of information-giving in a regional thoracic unit. *J Clin Nurs,* 9**,** 236-46.

MILNE, J. & OBERLE, K. 2005. Enhancing rigor in qualitative description: a case study. *J Wound Ostomy Continence Nurs,* 32**,** 413-20.

MISHRA, S. I., SCHERER, R. W., GEIGLE, P. M., BERLANSTEIN, D. R., TOPALOGLU, O., GOTAY, C. C. & SNYDER, C. 2012a. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev,* 8**,** CD007566.

MISHRA, S. I., SCHERER, R. W., SNYDER, C., GEIGLE, P. M., BERLANSTEIN, D. R. & TOPALOGLU, O. 2012b. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev,* 8**,** CD008465.

MISSEL, M. & BIRKELUND, R. 2011. Living with incurable oesophageal cancer. A phenomenological hermeneutical interpretation of patient stories. *Eur J Oncol Nurs,* 15**,** 296-301.

MORGAN, K., MCGEE, H., WATSON, D., PERRY, I., BARRY, M., SHELLEY, E., HARRINGTON, J., MOLCHO, M., LAYTE, R., TULLY, N., VAN LENTE, E., WARD, M., LUTOMSKI, J., CONROY, R. & BRUGHA, R. 2008. SLÁN 2007: Survey of Lifestyle, Attitudes & Nutrition in Ireland. Main Report. Dublin: Department of Health and Children.

MOSHER, C. E., SLOANE, R., MOREY, M. C., SNYDER, D. C., COHEN, H. J., MILLER, P. E. & DEMARK-WAHNEFRIED, W. 2009. Associations between lifestyle factors and quality of life among older long-term breast, prostate, and colorectal cancer survivors. *Cancer,* 115**,** 4001-9.

MOURTZAKIS, M., PRADO, C. M., LIEFFERS, J. R., REIMAN, T., MCCARGAR, L. J. & BARACOS, V. E. 2008. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab,* 33**,** 997-1006.

MOYES, L. H., MCCAFFER, C. J., CARTER, R. C., FULLARTON, G. M., MACKAY, C. K. & FORSHAW, M. J. 2013. Cardiopulmonary exercise testing as a predictor of complications in oesophagogastric cancer surgery. *Ann R Coll Surg Engl,* 95**,** 125-30.

MULLINS, E. 2003. *Statistics for the Quality Control Chemistry Laboratory*, Royal Society of Chemistry.

MURRAY, P., WHITING, P., HUTCHINSON, S. P., ACKROYD, R., STODDARD, C. J. & BILLINGS, C. 2007. Preoperative shuttle walking testing and outcome after oesophagogastrectomy. *Br J Anaesth,* 99**,** 809-11.

NAFTEUX, P., MOONS, J., COOSEMANS, W., DECALUWE, H., DECKER, G., DE LEYN, P., VAN RAEMDONCK, D. & LERUT, T. 2011. Minimally invasive oesophagectomy: A valuable alternative to open oesophagectomy for the treatment of early oesophageal and gastro-oesophageal junction carcinoma. *Eur J Cardiothorac Surg,* 40**,** 1455-1464.

NEERGAARD, M. A., OLESEN, F., ANDERSEN, R. S. & SONDERGAARD, J. 2009. Qualitative description - the poor cousin of health research? *BMC Med Res Methodol,* 9**,** 52.

NEIL, S. E., GOTAY, C. C. & CAMPBELL, K. L. 2014. Physical activity levels of cancer survivors in Canada: findings from the Canadian Community Health Survey. *J Cancer Surviv,* 8**,** 143-9.

NEOVIUS, M., HEMMINGSSON, E., FREYSCHUSS, B. & UDDEN, J. 2006. Bioelectrical impedance underestimates total and truncal fatness in abdominally obese women. *Obesity (Silver Spring),* 14**,** 1731-8.

NESS, K. K., WALL, M. M., OAKES, J. M., ROBISON, L. L. & GURNEY, J. G. 2006. Physical performance limitations and participation restrictions among cancer survivors: a population-based study. *Ann Epidemiol,* 16**,** 197-205.

NOONAN, V. & DEAN, E. 2000. Submaximal exercise testing: clinical application and interpretation. *Phys Ther,* 80**,** 782-807.

NORMAN, K., STOBAUS, N., GONZALEZ, M. C., SCHULZKE, J. D. & PIRLICH, M. 2011. Hand grip strength: outcome predictor and marker of nutritional status. *Clin Nutr,* 30**,** 135-42.

NORMAN, K., STOBAUS, N., SMOLINER, C., ZOCHER, D., SCHEUFELE, R., VALENTINI, L., LOCHS, H. & PIRLICH, M. 2010. Determinants of hand grip strength, knee extension strength and functional status in cancer patients. *Clin Nutr,* 29**,** 586-91.

NOVICK, G. 2008. Is there a bias against telephone interviews in qualitative research? *Res Nurs Health,* 31**,** 391-8.

OHLSON, L. O., LARSSON, B., SVARDSUDD, K., WELIN, L., ERIKSSON, H., WILHELMSEN, L., BJORNTORP, P. & TIBBLIN, G. 1985. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes,* 34**,** 1055-8.

OLSSON, U., BERGBOM, I. & BOSAEUS, I. 2002. Patients' experiences of the recovery period 3 months after gastrointestinal cancer surgery. *Eur J Cancer Care (Engl),* 11**,** 51-60.

OPDENAKKER, R. 2006. Advantages and disadvantages of four interview techniques in qualitative research. *Forum Qual. Soc. Res*. 7 (4), art. 11.

OSOBA, D., RODRIGUES, G., MYLES, J., ZEE, B. & PATER, J. 1998. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol,* 16**,** 139-44.

OTTENBACHER, A. J., DAY, R. S., TAYLOR, W. C., SHARMA, S. V., SLOANE, R., SNYDER, D. C., KRAUS, W. E. & DEMARK-WAHNEFRIED, W. 2011. Exercise among breast and prostate

cancer survivors--what are their barriers? *J Cancer Surviv,* 5**,** 413-9.

PALINKAS, L. A., HORWITZ, S. M., GREEN, C. A., WISDOM, J. P., DUAN, N. & HOAGWOOD, K. 2015. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Adm Policy Ment Health,* 42**,** 533-44.

PALYS, T. 2008. *Purposive Sampling,* Thousand Oaks, CA, SAGE Publications, Inc.

PARAMESWARAN, R., BLAZEBY, J. M., HUGHES, R., MITCHELL, K., BERRISFORD, R. G. & WAJED, S. A. 2010. Health-related quality of life after minimally invasive oesophagectomy. *Br J Surg,* 97**,** 525-31.

PARAMESWARAN, R., MCNAIR, A., AVERY, K. N. L., BERRISFORD, R. G., WAJED, S. A., SPRANGERS, M. A. G. & BLAZEBY, J. M. 2008. The role of health-related quality of life outcomes in clinical decision making in surgery for esophageal cancer: A systematic review. *Ann Surg Oncol,* 15**,** 2372-2379.

PARREIRA, V. F., JANAUDIS-FERREIRA, T., EVANS, R. A., MATHUR, S., GOLDSTEIN, R. S. & BROOKS, D. 2014. Measurement properties of the incremental shuttle walk test. a systematic review. *Chest,* 145**,** 1357-69.

PARSONS, H. A., BARACOS, V. E., DHILLON, N., HONG, D. S. & KURZROCK, R. 2012. Body composition, symptoms, and survival in advanced cancer patients referred to a phase I service. *PLoS One,* 7**,** e29330.

PEEDELL, C. 2005. *Concise Clinical Oncology*, Elsevier.

PENNA, F., BUSQUETS, S., PIN, F., TOLEDO, M., BACCINO, F. M., LOPEZ-SORIANO, F. J., COSTELLI, P. & ARGILES, J. M. 2011. Combined approach to counteract experimental cancer cachexia: eicosapentaenoic acid and training exercise. *J Cachexia Sarcopenia Muscle,* 2**,** 95-104.

PERERA, S., MODY, S. H., WOODMAN, R. C. & STUDENSKI, S. A. 2006. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc,* 54**,** 743-9.

PESCATELLO, L.S. (ed) 2013. *ACSM's Guidelines for Exercise Testing and Prescription (9th edn),* Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins.

PETERSON, M. D. & GORDON, P. M. 2011. Resistance exercise for the aging adult: clinical implications and prescription guidelines. *Am J Med,* 124**,** 194-8.

PIETROBELLI, A., RUBIANO, F., ST-ONGE, M. P. & HEYMSFIELD, S. B. 2004. New bioimpedance analysis system: improved phenotyping with whole-body analysis. *Eur J Clin Nutr,* 58**,** 1479-84.

PLASQUI, G. & WESTERTERP, K. R. 2007. Physical activity assessment with accelerometers: an evaluation against doubly labeled water. *Obesity (Silver Spring),* 15**,** 2371-9.

POPE, C., ZIEBLAND, S. & MAYS, N. 2000. Qualitative research in health care. Analysing qualitative data. *BMJ,* 320**,** 114-6.

POWELL, S. M. & ROWLANDS, A. V. 2004. Intermonitor variability of the RT3 accelerometer during typical physical activities. *Med Sci Sports Exerc,* 36**,** 324-30.

PRADO, C. M., LIEFFERS, J. R., MCCARGAR, L. J., REIMAN, T., SAWYER, M. B., MARTIN, L. & BARACOS, V. E. 2008. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol,* 9**,** 629-35.

PROBST, V. S., HERNANDES, N. A., TEIXEIRA, D. C., FELCAR, J. M., MESQUITA, R. B.,

GONCALVES, C. G., HAYASHI, D., SINGH, S. & PITTA, F. 2012. Reference values for the incremental shuttle walking test. *Respir Med,* 106**,** 243-8.

PRUE, G., RANKIN, J., ALLEN, J., GRACEY, J. & CRAMP, F. 2006. Cancer-related fatigue: A critical appraisal. *Eur J Cancer,* 42**,** 846-63.

PUTHOFF, M. L. & SASKOWSKI, D. 2013. Reliability and responsiveness of gait speed, five times sit to stand, and hand grip strength for patients in cardiac rehabilitation. *Cardiopulm Phys Ther J,* 24**,** 31-7.

RAMAKRISHNAIAH, V. P. N., DASH, N. R., PAL, S., SAHNI, P. & KANTI, C. T. 2014. Quality of life after oesophagectomy in patients with carcinoma of oesophagus: A prospective study. *Indian J Cancer,* 51**,** 346-351.

RAWAT, S., KUMAR, G., PURI, A., SHARMA, M. K., KAKRIA, A. & KUMAR, P. 2011. Correlation of six-minute walk test, pulmonary function test and radiation pneumonitis in the management of carcinoma of oesophagus: A prospective pilot study. *J Radiother Pract,* 10**,** 191-199.

REYNOLDS, J. V., MCLAUGHLIN, R., MOORE, J., ROWLEY, S., RAVI, N. & BYRNE, P. J. 2006. Prospective evaluation of quality of life in patients with localized oesophageal cancer treated by multimodality therapy or surgery alone. *Br J Surg,* 93**,** 1084-90.

RIESENBERG, H. & LUBBE, A. S. 2010. In-patient rehabilitation of lung cancer patients--a prospective study. *Support Care Cancer,* 18**,** 877-82.

RILEY, M., MCPARLAND, J., STANFORD, C. F. & NICHOLLS, D. P. 1992. Oxygen consumption during corridor walk testing in chronic cardiac failure. *Eur Heart J,* 13**,** 789-93.

RIZK, N. P., BACH, P. B., SCHRAG, D., BAINS, M. S., TURNBULL, A. D., KARPEH, M., BRENNAN, M. F. & RUSCH, V. W. 2004. The impact of complications on outcomes after resection for esophageal and gastroesophageal junction carcinoma. *J Am Coll Surg,* 198**,** 42-50.

ROBERTS, H. C., DENISON, H. J., MARTIN, H. J., PATEL, H. P., SYDDALL, H., COOPER, C. & SAYER, A. A. 2011. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing,* 40**,** 423-9.

ROGERS, L. Q., MARKWELL, S., HOPKINS-PRICE, P., VICARI, S., COURNEYA, K. S., HOELZER, K. & VERHULST, S. 2011. Reduced barriers mediated physical activity maintenance among breast cancer survivors. *J Sport Exerc Psychol,* 33**,** 235-54.

ROLLAND, Y., CZERWINSKI, S., ABELLAN VAN KAN, G., MORLEY, J. E., CESARI, M., ONDER, G., WOO, J., BAUMGARTNER, R., PILLARD, F., BOIRIE, Y., CHUMLEA, W. M. & VELLAS, B. 2008. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. *J Nutr Health Aging,* 12**,** 433-50.

ROSS, R. M., MURTHY, J. N., WOLLAK, I. D. & JACKSON, A. S. 2010. The six minute walk test accurately estimates mean peak oxygen uptake. *BMC Pulm Med,* 10**,** 31.

ROWLANDS, A. V., THOMAS, P. W., ESTON, R. G. & TOPPING, R. 2004. Validation of the RT3 triaxial accelerometer for the assessment of physical activity. *Med Sci Sports Exerc,* 36**,** 518-24.

RUSH, E. C., VALENCIA, M. E. & PLANK, L. D. 2008. Validation of a 7-day physical activity diary against doubly-labelled water. *Ann Hum Biol,* 35**,** 416-21.

RUTEGARD, M., LAGERGREN, J., ROUVELAS, I., LINDBLAD, M., BLAZEBY, J. M. & LAGERGREN, P. 2008. Population-based study of surgical factors in relation to health-related quality of life after oesophageal cancer resection. *Br J Surg,* 95**,** 592-601.

RUTEGARD, M., LAGERGREN, P., ROUVELAS, I., MASON, R. & LAGERGREN, J. 2012. Surgical complications and long-term survival after esophagectomy for cancer in a nationwide Swedish cohort study. *Eur J Surg Oncol,* 38**,** 555-61.

SABISTON, C. M., BRUNET, J., VALLANCE, J. K. & METERISSIAN, S. 2014. Prospective examination of objectively assessed physical activity and sedentary time after breast cancer treatment: sitting on the crest of the teachable moment. *Cancer Epidemiol Biomarkers Prev,* 23**,** 1324-30.

SAFIEDDINE, N., XU, W., QUADRI, S. M., KNOX, J. J., HORNBY, J., SULMAN, J., WONG, R., GUINDI, M., KESHAVJEE, S. & DARLING, G. 2009. Health-related quality of life in esophageal cancer: effect of neoadjuvant chemoradiotherapy followed by surgical intervention. *J Thorac Cardiovasc Surg,* 137**,** 36-42.

SALDAÑA, J. 2012. *The coding manual for qualitative researchers*, Sage.

SAMSON, M. M., MEEUWSEN, I. B., CROWE, A., DESSENS, J. A., DUURSMA, S. A. & VERHAAR, H. J. 2000. Relationships between physical performance measures, age, height and body weight in healthy adults. *Age Ageing,* 29**,** 235-42.

SANCHEZ-JIMENEZ, A., CANTARERO-VILLANUEVA, I., DELGADO-GARCIA, G., MOLINA-BAREA, R., FERNANDEZ-LAO, C., GALIANO-CASTILLO, N. & ARROYO-MORALES, M. 2014. Physical impairments and quality of life of colorectal cancer survivors: a case-control study. *Eur J Cancer Care (Engl)*. 24, 642-49.

SANDELOWSKI, M. 2000. Whatever happened to qualitative description? *Res Nurs Health,* 23**,** 334-40.

SANTOS-LOZANO, A., TORRES-LUQUE, G., MARIN, P. J., RUIZ, J. R., LUCIA, A. & GARATACHEA, N. 2012. Intermonitor variability of GT3X accelerometer. *Int J Sports Med,* 33**,** 994-9.

SCARPA, M., SAADEH, L. M., FASOLO, A., ALFIERI, R., CAGOL, M., CAVALLIN, F., PINTO, E., ZANINOTTO, G., ANCONA, E. & CASTORO, C. 2013. Health-related quality of life in patients with oesophageal cancer: analysis at different steps of the treatment pathway. *J Gastrointest Surg,* 17**,** 421-33.

SCHLANSKY, B., DIMARINO, A. J., JR., LOREN, D., INFANTOLINO, A., KOWALSKI, T. & COHEN, S. 2006. A survey of oesophageal cancer: pathology, stage and clinical presentation. *Aliment Pharmacol Ther,* 23**,** 587-93.

SCHMIDT, K., VOGT, L., THIEL, C., JAGER, E. & BANZER, W. 2013. Validity of the six-minute walk test in cancer patients. *Int J Sports Med,* 34**,** 631-6.

SCHMITZ, K. H., COURNEYA, K. S., MATTHEWS, C., DEMARK-WAHNEFRIED, W., GALVAO, D. A., PINTO, B. M., IRWIN, M. L., WOLIN, K. Y., SEGAL, R. J., LUCIA, A., SCHNEIDER, C. M., VON GRUENIGEN, V. E. & SCHWARTZ, A. L. 2010. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc,* 42**,** 1409-26.

SCHNEIDER, L., HARTWIG, W., AULMANN, S., LENZEN, C., STROBEL, O., FRITZ, S., HACKERT, T., KELLER, M., BUCHLER, M. W. & WERNER, J. 2010. Quality of life after emergency vs. elective esophagectomy with cervical reconstruction. *Scand J Surg,* 99**,** 3-8.

SHEN, H., WANG, J., LI, W., YI, W. & WANG, W. 2015. Assessment of health-related quality of life of patients with esophageal squamous cell carcinoma following esophagectomy using EORTC quality of life questionnaires. *Mol Clin Oncol,* 3**,** 133-138.

SHEPHARD, R. J., ALLEN, C., BENADE, A. J., DAVIES, C. T., DI PRAMPERO, P. E., HEDMAN, R., MERRIMAN, J. E., MYHRE, K. & SIMMONS, R. 1968. The maximum oxygen intake. An

international reference standard of cardiorespiratory fitness. *Bull World Health Organ,* 38**,** 757-64.

SIEWERT, J. R., STEIN, H. J., FEITH, M., BRUECHER, B. L., BARTELS, H. & FINK, U. 2001. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. *Ann Surg,* 234**,** 360-7; discussion 368-9.

SILVER, J. K. & BAIMA, J. 2013. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *Am J Phys Med Rehabil,* 92**,** 715-27.

SILVER, J. K., BAIMA, J. & MAYER, R. S. 2013. Impairment-driven cancer rehabilitation: an essential component of quality care and survivorship. *CA Cancer J Clin,* 63**,** 295-317.

SILVERMAN, S. R., SCHERTZ, L. A., YUEN, H. K., LOWMAN, J. D. & BICKEL, C. S. 2012. Systematic review of the methodological quality and outcome measures utilized in exercise interventions for adults with spinal cord injury. *Spinal Cord,* 50**,** 718-27.

SINGH, F., NEWTON, R. U., GALVAO, D. A., SPRY, N. & BAKER, M. K. 2013. A systematic review of pre-surgical exercise intervention studies with cancer patients. *Surg Oncol,* 22**,** 92-104.

SINGH, S. J., MORGAN, M. D., HARDMAN, A. E., ROWE, C. & BARDSLEY, P. A. 1994. Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. *Eur Respir J,* 7**,** 2016-20.

SINGH, S. J., MORGAN, M. D., SCOTT, S., WALTERS, D. & HARDMAN, A. E. 1992. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax,* 47**,** 1019-24.

SNYDER, L. B. 2007. Health communication campaigns and their impact on behavior. *J Nutr Educ Behav,* 39**,** S32-40.

SOLHEIM, T. S. & LAIRD, B. J. 2012. Evidence base for multimodal therapy in cachexia. *Curr Opin Support Palliat Care,* 6**,** 424-31.

SPRUIT, M. A., SILLEN, M. J., GROENEN, M. T., WOUTERS, E. F. & FRANSSEN, F. M. 2013. New normative values for handgrip strength: results from the UK Biobank. *J Am Med Dir Assoc,* 14**,** 775 e5-11.

STARK, T., WALKER, B., PHILLIPS, J. K., FEJER, R. & BECK, R. 2011. Hand-held dynamometry correlation with the gold standard isokinetic dynamometry: a systematic review. *PM R,* 3**,** 472-9.

STEIN, H. J. & SIEWERT, J. R. 2004. Improved prognosis of resected esophageal cancer. *World J Surg,* 28**,** 520-5.

STEIN, H. J., VON RAHDEN, B. H. & SIEWERT, J. R. 2005. Survival after oesophagectomy for cancer of the oesophagus. *Langenbecks Arch Surg,* 390**,** 280-5.

STEL, V. S., JAGER, K. J., ZOCCALI, C., WANNER, C. & DEKKER, F. W. 2007. The randomized clinical trial: an unbeatable standard in clinical research? *Kidney Int,* 72**,** 539-42.

STOKES, E. 2011. *Rehabilitation Outcome Measures* Edinburgh, Churchill Livingstone.

STRASSER, F. 2008. Diagnostic criteria of cachexia and their assessment: decreased muscle strength and fatigue. *Curr Opin Clin Nutr Metab Care,* 11**,** 417-21.

STRUTHERS, R., ERASMUS, P., HOLMES, K., WARMAN, P., COLLINGWOOD, A. & SNEYD, J. R. 2008. Assessing fitness for surgery: a comparison of questionnaire, incremental shuttle

walk, and cardiopulmonary exercise testing in general surgical patients. *Br J Anaesth,* 101**,** 774-80.

SUMUKADAS, D., LAIDLAW, S. & WITHAM, M. D. 2008. Using the RT3 accelerometer to measure everyday activity in functionally impaired older people. *Aging Clin Exp Res,* 20**,** 15-8.

SURESH, K. & CHANDRASHEKARA, S. 2012. Sample size estimation and power analysis for clinical research studies. *J Hum Reprod Sci,* 5**,** 7-13.

TAGUCHI, S., OSUGI, H., HIGASHINO, M., TOKUHARA, T., TAKADA, N., TAKEMURA, M., LEE, S. & KINOSHITA, H. 2003. Comparison of three-field esophagectomy for esophageal cancer incorporating open or thoracoscopic thoracotomy. *Surg Endosc,* 17**,** 1445-50.

TAN, B. H., BRAMMER, K., RANDHAWA, N., WELCH, N. T., PARSONS, S. L., JAMES, E. J. & CATTON, J. A. 2015. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. *Eur J Surg Oncol,* 41**,** 333-8.

TATEMATSU, N., EZOE, Y., TANAKA, E., MUTO, M., SAKAI, Y. & TSUBOYAMA, T. 2013a. Impact of neoadjuvant chemotherapy on physical fitness, physical activity, and health-related quality of life of patients with resectable esophageal cancer. *Am J Clin Oncol,* 36**,** 53-6.

TATEMATSU, N., HASEGAWA, S., TANAKA, E., SAKAI, Y. & TSUBOYAMA, T. 2013b. Impact of oesophagectomy on physical fitness and health-related quality of life in patients with oesophageal cancer. *Eur J Cancer Care (Engl),* 22**,** 308-13.

TEMEL, J. S., GREER, J. A., GOLDBERG, S., VOGEL, P. D., SULLIVAN, M., PIRL, W. F., LYNCH, T. J., CHRISTIANI, D. C. & SMITH, M. R. 2009. A structured exercise program for patients with advanced non-small cell lung cancer. *J Thorac Oncol,* 4**,** 595-601.

TEOH, A. Y., YAN CHIU, P. W., WONG, T. C., LIU, S. Y., HUNG WONG, S. K. & NG, E. K. 2011. Functional performance and quality of life in patients with squamous esophageal carcinoma receiving surgery or chemoradiation: results from a randomized trial. *Ann Surg,* 253**,** 1-5.

THRIFT, A. P. & WHITEMAN, D. C. 2012. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. *Ann Oncol,* 23**,** 3155-62.

TOPP, R., DITMYER, M., KING, K., DOHERTY, K. & HORNYAK, J., 3RD 2002. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. *AACN Clin Issues,* 13**,** 263-76.

TRAMPISCH, U. S., FRANKE, J., JEDAMZIK, N., HINRICHS, T. & PLATEN, P. 2012. Optimal Jamar dynamometer handle position to assess maximal isometric hand grip strength in epidemiological studies. *J Hand Surg Am,* 37**,** 2368-73.

TROIANO, R. P., BERRIGAN, D., DODD, K. W., MASSE, L. C., TILERT, T. & MCDOWELL, M. 2007. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc,* 40**,** 181-8.

TROOSTERS, T., GOSSELINK, R. & DECRAMER, M. 1999. Six minute walking distance in healthy elderly subjects. *Eur Respir J,* 14**,** 270-4.

TRUTSCHNIGG, B., KILGOUR, R. D., REINGLAS, J., ROSENTHALL, L., HORNBY, L., MORAIS, J. A. & VIGANO, A. 2008. Precision and reliability of strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs. bioimpedance analysis) measurements in advanced cancer patients. *Appl Physiol Nutr Metab,* 33**,** 1232-9.

TSOUTSOU, P. G. & KOUKOURAKIS, M. I. 2006. Radiation pneumonitis and fibrosis:

mechanisms underlying its pathogenesis and implications for future research. *Int J Radiat Oncol Biol Phys,* 66**,** 1281-93.

VALKENET, K., TRAPPENBURG, J. C., GOSSELINK, R., SOSEF, M. N., WILLMS, J., ROSMAN, C., PIETERS, H., SCHEEPERS, J. J., DE HEUS, S. C., REYNOLDS, J. V., GUINAN, E., RUURDA, J. P., RODRIGO, E. H., NAFTEUX, P., FONTAINE, M., KOUWENHOVEN, E. A., KERKEMEYER, M., VAN DER PEET, D. L., HANIA, S. W., VAN HILLEGERSBERG, R. & BACKX, F. J. 2014. Preoperative inspiratory muscle training to prevent postoperative pulmonary complications in patients undergoing esophageal resection (PREPARE study): study protocol for a randomized controlled trial. *Trials,* 15**,** 144

VAN DER KOOY, K. & SEIDELL, J. C. 1993. Techniques for the measurement of visceral fat: a practical guide. *Int J Obes Relat Metab Disord,* 17**,** 187-96.

VAN KNIPPENBERG, F. C. E., OUT, J. J., TILANUS, H. W., MUD, H. J., HOP, W. C. J. & VERHAGE, F. 1992. Quality of life in patients with resected oesophageal cancer. *Soc Sci Med,* 35**,** 139-145.

VAN MEERTEN, E., VAN DER GAAST, A., LOOMAN, C. W., TILANUS, H. W., MULLER, K. & ESSINK-BOT, M. L. 2008. Quality of life during neoadjuvant treatment and after surgery for resectable esophageal carcinoma. *Int J Radiat Oncol Biol Phys,* 71**,** 160-6.

VAN REMOORTEL, H., RASTE, Y., LOUVARIS, Z., GIAVEDONI, S., BURTIN, C., LANGER, D., WILSON, F., RABINOVICH, R., VOGIATZIS, I., HOPKINSON, N. S. & TROOSTERS, T. 2012. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PLoS One,* 7**,** e39198.

VANCE, V., MOURTZAKIS, M., MCCARGAR, L. & HANNING, R. 2011. Weight gain in breast cancer survivors: prevalence, pattern and health consequences. *Obes Rev,* 12**,** 282-94.

VAUGHAN, T. L., DAVIS, S., KRISTAL, A. & THOMAS, D. B. 1995. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev,* 4**,** 85-92.

VERSCHUUR, E. M., STEYERBERG, E. W., KUIPERS, E. J., ESSINK-BOT, M. L., TRAN, K. T., VAN DER GAAST, A., TILANUS, H. W. & SIERSEMA, P. D. 2006. Experiences and expectations of patients after oesophageal cancer surgery: an explorative study. *Eur J Cancer Care (Engl),* 15**,** 324-32.

VIKLUND, P., LINDBLAD, M. & LAGERGREN, J. 2005. Influence of surgery-related factors on quality of life after esophageal or cardia cancer resection. *World J Surg,* 29**,** 841-8.

VIKLUND, P., LINDBLAD, M., LU, M., YE, W., JOHANSSON, J. & LAGERGREN, J. 2006. Risk factors for complications after esophageal cancer resection: a prospective population-based study in Sweden. *Ann Surg,* 243**,** 204-11.

VOLGYI, E., TYLAVSKY, F. A., LYYTIKAINEN, A., SUOMINEN, H., ALEN, M. & CHENG, S. 2008. Assessing body composition with DXA and bioimpedance: effects of obesity, physical activity, and age. *Obesity (Silver Spring),* 16**,** 700-5.

VOLKOVA, M. & RUSSELL, R., 3RD 2011. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. *Curr Cardiol Rev,* 7**,** 214-20.

WAGNER, D. R. & HEYWARD, V. H. 1999. Techniques of body composition assessment: a review of laboratory and field methods. *Res Q Exerc Sport,* 70**,** 135-49.

WAINWRIGHT, D., DONOVAN, J. L., KAVADAS, V., CRAMER, H. & BLAZEBY, J. M. 2007. Remapping the body: Learning to eat again after surgery for esophageal cancer. *Qual Health Res,* 17**,** 759-771.

WANG, H., FENG, M., TAN, L. & WANG, Q. 2010. Comparison of the short-term quality of life in patients with esophageal cancer after subtotal esophagectomy via video-assisted thoracoscopic or open surgery. *Dis Esophagus,* 23**,** 408-14.

WANG, H., SHEN, Y., FENG, M., ZHANG, Y., JIANG, W., XU, S., TAN, L. & WANG, Q. 2015. Outcomes, quality of life, and survival after esophagectomy for squamous cell carcinoma: A propensity score-matched comparison of operative approaches. *J Thorac Cardiovasc Surg*. 149, 1006-15.

WANG, H., TAN, L., FENG, M., ZHANG, Y. & WANG, Q. 2011. Comparison of the short-term health-related quality of life in patients with esophageal cancer with different routes of gastric tube reconstruction after minimally invasive esophagectomy. *Qual Life Res,* 20**,** 179-189.

WATT, E. & WHYTE, F. 2003. The experience of dysphagia and its effect on the quality of life of patients with oesophageal cancer. *Eur J Cancer Care (Engl),* 12**,** 183-93.

WEAVER, K. E., FORSYTHE, L. P., REEVE, B. B., ALFANO, C. M., RODRIGUEZ, J. L., SABATINO, S. A., HAWKINS, N. A. & ROWLAND, J. H. 2012. Mental and physical health-related quality of life among U.S. cancer survivors: population estimates from the 2010 National Health Interview Survey. *Cancer Epidemiol Biomarkers Prev,* 21**,** 2108-17.

WELLS, J. C. & FEWTRELL, M. S. 2006. Measuring body composition. *Arch Dis Child,* 91**,** 612-7.

WERLE, S., GOLDHAHN, J., DRERUP, S., SIMMEN, B. R., SPROTT, H. & HERREN, D. B. 2009. Age- and gender-specific normative data of grip and pinch strength in a healthy adult Swiss population. *J Hand Surg Eur Vol,* 34**,** 76-84.

WEST, M. A., LOUGHNEY, L., LYTHGOE, D., BARBEN, C. P., SRIPADAM, R., KEMP, G. J., GROCOTT, M. P. & JACK, S. 2015. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *Br J Anaesth,* 114**,** 244-51.

WESTERTERP, K. R. 2009. Assessment of physical activity: a critical appraisal. *Eur J Appl Physiol,* 105**,** 823-8.

WORLD HEALTH ORGANIZATION, 2000. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser,* 894**,** i-xii, 1-253.

WORLD HEALTH ORGANIZATION, 2011. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation. Geneva.

WILLIAMS, K., STEPTOE, A. & WARDLE, J. 2013. Is a cancer diagnosis a trigger for health behaviour change? Findings from a prospective, population-based study. *Br J Cancer,* 108**,** 2407-12.

WIN, T., JACKSON, A., GROVES, A. M., SHARPLES, L. D., CHARMAN, S. C. & LAROCHE, C. M. 2006. Comparison of shuttle walk with measured peak oxygen consumption in patients with operable lung cancer. *Thorax,* 61**,** 57-60.

YIP, C., GOH, V., DAVIES, A., GOSSAGE, J., MITCHELL-HAY, R., HYNES, O., MAISEY, N., ROSS, P., GAYA, A., LANDAU, D. B., COOK, G. J., GRIFFIN, N. & MASON, R. 2014. Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer. *Eur Radiol,* 24**,** 998-1005.

YORKE, A. M., CURTIS, A. B., SHOEMAKER, M. & VANGSNES, E. 2015. Grip Strength Values Stratified by Age, Gender, and Chronic Disease Status in Adults Aged 50 Years and Older. *J Geriatr Phys Ther*. 38 (3), 115-21.

ZENG, J. & LIU, J. S. 2012. Quality of life after three kinds of esophagectomy for cancer. *World J*

Gastroenterol, 18**,** 5106-13.

ZIEREN, H. U., JACOBI, C. A., ZIEREN, J. & MULLER, J. M. 1996. Quality of life following resection of oesophageal carcinoma. *Br J Surg.,* 83**,** 1772-1775.

Appendices

Appendix I: Search strategies for the systematic review

EMBASE

1	(esophag* NEAR/3 (cancer OR neoplasm* OR adenocarcinoma* OR carcinoma*)):ab,ti
2	(oesophag* NEAR/3 (cancer OR neoplasm* OR adenocarcinoma* OR carcinoma*)):ab,ti
3	'esophagus cancer'/exp OR 'esophagus tumor'/exp OR 'esophageal adenocarcinoma'/exp OR 'esophagus carcinoma'/exp
4	1 OR 2 OR 3
5	esophagectom*:ab,ti OR esophagogastroplast*:ab,ti OR esophagogastrectom*:ab,ti
6	oesophagectom*:ab,ti OR oesophagogastroplast*:ab,ti OR oesophagogastrectom*:ab,ti
7	(esophag* NEAR/3 (surgery OR resection*)):ab,ti
8	(oesophag* NEAR/3 (surgery OR resection*)):ab,ti
9	chemotherapy:ab,ti OR radiotherapy:ab,ti OR 'radiation therapy':ab,ti OR ‘combined modality therapy’:ab,ti OR ‘multimodal therapy’:ab,ti OR chemoradiotherapy:ab,ti OR ‘cancer radiation’:ab,ti OR ‘tumor irradiation’:ab,ti
10	'esophagus resection'/exp OR 'esophagus surgery'/exp OR ‘chemotherapy'/exp OR 'radiotherapy'/exp OR 'multimodality cancer therapy'/exp
11	5 OR 6 OR 7 OR 8 OR 9 OR 10
12	'quality of life assessment'/exp OR 'quality of life'/exp OR 'health status'/exp OR 'physical activity, capacity and performance'/exp OR 'accelerometry'/exp OR 'cardiorespiratory fitness'/exp OR 'strength'/exp
13	(physical NEAR/3 (function* OR activity OR fitness OR capacity OR performance OR test)):ab,ti
14	fitness:ab,ti OR strength:ab,ti OR exercise:ab,ti OR ‘quality of life’:ab,ti OR ‘functional status’:ab,ti
15	4 AND 11
16	12 OR 13 OR 14
17	15 AND 16

PubMed

1	esophageal cancer[tiab] OR oesophageal cancer[tiab] OR esophageal neoplasm*[tiab] OR oesophageal neoplasm*[tiab] OR esophageal adenocarcinoma*[tiab] OR oesophageal adenocarcinoma*[tiab] OR esophageal carcinoma*[tiab] OR oesophageal carcinoma*[tiab]
2	"Esophageal Neoplasms"[Mesh]
3	1 OR 2
4	esophageal surgery[tiab] OR oesophageal surgery[tiab] OR esophageal resection[tiab] OR oesophageal resection[tiab] OR esophagectom*[tiab] OR oesophagectom*[tiab] OR esophagogastroplast*[tiab] OR oesophagogastroplast*[tiab] OR esophagogastrectom*[tiab] OR oesophagogastrectom*[tiab]
5	"Esophagectomy"[Mesh] OR "Esophagoplasty"[Mesh]
6	"Chemoradiotherapy"[Mesh] OR "Combined Modality Therapy"[Mesh] OR "Radiotherapy"[Mesh] OR "Chemotherapy, Adjuvant"[Mesh] OR "Consolidation Chemotherapy"[Mesh] OR "Induction Chemotherapy"[Mesh] OR "Maintenance Chemotherapy"[Mesh]
7	chemotherap*[tiab] OR radiotherap*[tiab] OR radiation therap*[tiab] OR cancer radiation[tiab] OR multimodal therapy[tiab] OR chemoradiotherapy[tiab] OR combined modality therapy[tiab] OR cancer radiation[tiab] OR tumor irradiation[tiab]
8	4 OR 5 OR 6 OR 7
9	"Physical Fitness"[Mesh] OR "Quality of Life"[Mesh] OR "Motor Activity"[Mesh] OR "Health Status"[Mesh] OR "Muscle Strength"[Mesh] OR "Exercise Tolerance"[Mesh] OR "Exercise Test"[Mesh] OR "Exercise"[Mesh] OR "Accelerometry"[Mesh] OR "Muscle Strength Dynamometer"[Mesh]
10	Physical Fitness[tiab] OR Quality of Life[tiab] OR physical activity[tiab] OR physical capacity[tiab] OR physical performance[tiab] OR physical function*[tiab] OR strength[tiab] OR exercise[tiab] OR functional status[tiab]
11	9 OR 10
12	3 AND 8 AND 11

CINAHL

1	TI (esophag* N3 (cancer OR neoplasm* OR adenocarcinoma* OR carcinoma*)) OR AB (esophag* N3 (cancer OR neoplasm* OR adenocarcinoma* OR carcinoma*))
2	TI (oesophag* N3(cancer OR neoplasm* OR adenocarcinoma* OR carcinoma*)) OR AB (oesophag* N3(cancer OR neoplasm* OR adenocarcinoma* OR carcinoma*))
3	MH "Esophageal Neoplasms"
4	1 OR 2 OR 3
5	TI (esophagectom* OR esophagogastroplast* OR esophagogastrectom* OR oesophagectom* OR oesophagogastroplast* OR oesophagogastrectom*) OR AB (esophagectom* OR esophagogastroplast* OR esophagogastrectom* OR oesophagectom* OR oesophagogastroplast* OR oesophagogastrectom*)
6	TI (((esophag* OR oesophag*) N3 (surgery OR resection))) OR AB (((esophag* OR oesophag*) N3 (surgery OR resection)))
7	(MH "Esophagoplasty") OR (MH "Esophageal Neoplasms/SU")
8	TI (chemotherapy OR radiotherapy OR 'radiation therapy' OR ‘cancer radiation’ OR ‘tumor irradiation’ OR ‘combined modality therapy’ OR ‘multimodal therapy’) OR AB (chemotherapy OR radiotherapy OR 'radiation therapy' OR ‘cancer radiation’ OR ‘tumor irradiation’ OR ‘combined modality therapy’ OR ‘multimodal therapy’)
9	(MH "Antineoplastic Agents, Combined") OR (MH "Chemotherapy, Cancer") OR (MH "Chemotherapy, Adjuvant") OR (MH "Neoadjuvant Therapy") OR (MH "Radiotherapy") OR (MH "Combined Modality Therapy")
10	5 OR 6 OR 7 OR 8 OR 9
11	(MH "Physical Fitness") OR (MH "Exercise") OR (MH "Exercise Test") OR (MH "Exercise Test, Muscular") OR (MH "Quality of Life") OR (MH "Motor Activity") OR (MH "Activities of Daily Living") OR (MH "Physical Activity") OR (MH "Exercise Tolerance") OR (MH "Health Status") OR (MH "Muscle Strength") OR (MH "Accelerometry")
12	TI (Physical N3 (Fitness OR activity OR capacity OR performance OR function OR test*)) OR (Physical N3 (Fitness OR activity OR capacity OR performance OR function OR test*))
13	TI (strength OR exercise OR ‘quality of life’ OR ‘functional status’) OR AB (strength OR exercise OR ‘quality of life’ OR ‘functional status’)
14	11 OR 12 OR 13
15	4 AND 10 AND 14

SCOPUS

1	TITLE-ABS (esophag* W/3 cancer)
2	TITLE-ABS (esophag* W/3 neoplasm*)
3	TITLE-ABS (esophag* W/3 adenocarcinoma*)
4	TITLE-ABS (esophag* W/3 carcinoma*)
5	TITLE-ABS (oesophag* W/3 cancer)
6	TITLE-ABS (oesophag* W/3 neoplasm*)
7	TITLE-ABS (oesophag* W/3 adenocarcinoma*)
8	TITLE-ABS (oesophag* W/3 carcinoma*)
9	#1 OR #2 OR #3 OR #4 OR #5 or #6 OR #7 OR #8
10	TITLE-ABS (esophagectom* OR esophagogastroplast* OR esophagogastrectom*)
11	TITLE-ABS (oesophagectom* OR oesophagogastroplast* OR oesophagogastrectom*)
12	TITLE-ABS (esophag* W/3 surgery)
13	TITLE-ABS (esophag* W/3 resection)
14	TITLE-ABS (chemotherapy OR radiotherapy OR “radiation therapy” OR chemoradiotherapy OR “multimodal therapy” OR “combined modality therapy” OR “cancer radiation” OR “tumor irradiation”)
15	#10 OR #11 OR #12 OR #13 OR #14
16	TITLE-ABS (physical* W/3 function)
17	TITLE-ABS (physical* W/3 activity)
18	TITLE-ABS (physical* W/3 fitness)
19	TITLE-ABS (physical* W/3 capacity)
20	TITLE-ABS (physical* W/3 performance)
21	TITLE-ABS (physical* W/3 test)
22	TITLE-ABS (“quality of life” OR fitness OR strength OR exercise OR ”functional status”)
23	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24	#9 AND #15 AND #23

PsycINFO

1	TI (esophag* N3 (cancer OR neoplasm* OR adenocarcinoma* OR carcinoma*)) OR AB (esophag* N3 (cancer OR neoplasm* OR adenocarcinoma* OR carcinoma*))
2	TI (oesophag* N3(cancer OR neoplasm* OR adenocarcinoma* OR carcinoma*)) OR AB (oesophag* N3(cancer OR neoplasm* OR adenocarcinoma* OR carcinoma*))
3	((DE "Neoplasms") OR (DE "Oncology")) AND (DE "Esophagus")
4	1 OR 2 OR 3
5	TI (esophagectom* OR esophagogastroplast* OR esophagogastrectom* OR oesophagectom* OR oesophagogastroplast* OR oesophagogastrectom*) OR AB (esophagectom* OR esophagogastroplast* OR esophagogastrectom* OR oesophagectom* OR oesophagogastroplast* OR oesophagogastrectom*)
6	TI (((esophag* OR oesophag*) N3 (surgery OR resection))) OR AB (((esophag* OR oesophag*) N3 (surgery OR resection)))
7	DE "Surgery"
8	TI (chemotherapy OR radiotherapy OR 'radiation therapy' OR ‘cancer radiation’ OR ‘tumor irradiation’ OR ‘combined modality therapy’ OR ‘multimodal therapy’) OR AB (chemotherapy OR radiotherapy OR 'radiation therapy' OR ‘cancer radiation’ OR ‘tumor irradiation’ OR ‘combined modality therapy’ OR ‘multimodal therapy’)
9	(DE "Chemotherapy") OR (DE "Radiation Therapy") OR (DE "Multimodal Treatment Approach")
10	5 OR 6 OR 7 OR 8 OR 9
11	(DE "Physical Fitness") OR (DE "Physical Strength") OR (DE "Physical Activity") OR (DE "Physical Examination") OR (DE "Physical Mobility") OR (DE "Aerobic Exercise") OR (DE "Exercise") OR DE ("Quality of Life") OR (DE "Activities of Daily Living")
12	TI (Physical N3 (Fitness OR activity OR capacity OR performance OR function OR test*)) OR (Physical N3 (Fitness OR activity OR capacity OR performance OR function OR test*))
13	TI (strength OR exercise OR ‘quality of life' OR ‘functional status’) OR AB (strength OR exercise OR ‘quality of life' OR ‘functional status’)
14	11 OR 12 OR 13
15	4 AND 10 AND 14

Appendix II: Downs & Black Checklist for Measuring Study Quality

Appendix

Checklist for measuring study quality

Reporting

1. *Is the hypothesis/aim/objective of the study clearly described?*

yes	1
no	0

2. *Are the main outcomes to be measured clearly described in the Introduction or Methods section?*
If the main outcomes are first mentioned in the Results section, the question should be answered no.

yes	1
no	0

3. *Are the characteristics of the patients included in the study clearly described ?*
In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

yes	1
no	0

4. *Are the interventions of interest clearly described?*
Treatments and placebo (where relevant) that are to be compared should be clearly described.

yes	1
no	0

5. *Are the distributions of principal confounders in each group of subjects to be compared clearly described?*
A list of principal confounders is provided.

yes	2
partially	1
no	0

6. *Are the main findings of the study clearly described?*
Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).

yes	1
no	0

7. *Does the study provide estimates of the random variability in the data for the main outcomes?*
In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

yes	1
no	0

8. *Have all important adverse events that may be a consequence of the intervention been reported?*
This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

yes	1
no	0

9. *Have the characteristics of patients lost to follow-up been described?*
This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

yes	1
no	0

10. *Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*

yes	1
no	0

External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*
The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant

population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

yes	1
no	0
unable to determine	0

12. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?*
The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

yes	1
no	0
unable to determine	0

13. *Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?*
For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

yes	1
no	0
unable to determine	0

Internal validity - bias

14. *Was an attempt made to blind study subjects to the intervention they have received ?*
For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

yes	1
no	0
unable to determine	0

15. *Was an attempt made to blind those measuring the main outcomes of the intervention?*

yes	1
no	0
unable to determine	0

16. *If any of the results of the study were based on "data dredging", was this made clear?*
Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

yes	1
no	0
unable to determine	0

17. *In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?*
Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

yes	1
no	0
unable to determine	0

18. *Were the statistical tests used to assess the main outcomes appropriate?*
The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

yes	1
no	0
unable to determine	0

19. *Was compliance with the intervention/s reliable?*
Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

yes	1
no	0
unable to determine	0

20. *Were the main outcome measures used accurate (valid and reliable)?*

For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

yes	1
no	0
unable to determine	0

Internal validity - confounding (selection bias)

21. *Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?*
For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.

yes	1
no	0
unable to determine	0

22. *Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?*
For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

yes	1
no	0
unable to determine	0

23. *Were study subjects randomised to intervention groups?*
Studies which state that subjects wererandomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.

yes	1
no	0
unable to determine	0

24. *Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*
All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

yes	1
no	0
unable to determine	0

25. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*
This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

yes	1
no	0
unable to determine	0

26. *Were losses of patients to follow-up taken into account?*
If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

yes	1
no	0
unable to determine	0

Power

27. *Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?*
Sample sizes have been calculated to detect a difference of x% and y%.

	Size of *smallest* intervention group	
A	$<n_1$	0
B	n_1–n_2	1
C	n_3–n_4	2
D	n_5–n_6	3
E	n_7–n_8	4
F	n_9+	5

Appendix III: Quality assessment of studies included in the meta-analyses using Downs & Black Checklist for Measuring Study Quality (Q1-15)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
Chang et al., (2014)	1	1	1	1	2	1	1	1	1	1	0	1	1	1	1
Barbour et al., (2008)	1	1	1	1	2	1	1	1	1	0	1	0	1	0	0
Hong et al., (2013)	1	1	1	1	2	1	1	1	0	1	1	0	1	0	0
van Meertan et al., (2008)	1	1	1	1	2	1	1	1	1	0	0	1	0	0	0
Ramakrishnaiagh et al., (2014)	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0
Parameswaran et al., (2009)	1	1	1	1	2	1	1	1	1	0	1	1	1	0	0
Nafteux et al., (2011)	1	1	1	1	2	1	1	1	0	1	1	0	1	0	0
Wang et al., (2010)	1	1	1	1	2	1	1	1	0	0	0	0	0	0	0
Wang et al., (2011)	1	1	1	1	2	1	1	1	0	0	0	0	0	0	0
Wang et al., (2015)	1	1	1	1	2	1	1	1	1	1	1	1	0	0	0
Lv et al., (2014)	1	1	1	1	2	1	1	0	1	1	0	0	1	0	0
Liebman et al., (2006)	1	1	1	1	2	0	0	1	1	0	1	1	0	0	0
Teoh et al., (2011)	1	1	1	1	2	0	1	0	0	1	1	0	1	0	0
Lagergren et al., (2007)	1	1	1	1	2	0	0	1	1	0	1	1	1	0	0
Avery et al., (2007)	1	1	1	1	2	1	1	1	1	1	1	1	1	0	0
Reynolds et al., (2006)	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0

Quality assessment of studies included in the meta-analyses using Downs & Black Checklist for Measuring Study Quality (Q16-27)

Study	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	Q24	Q25	Q26	Q27	Total	Quality
Chang et al., (2014)	1	1	1	0	1	1	1	0	0	0	1	0	21	Good
Barbour et al., (2008)	1	1	1	0	1	1	1	0	0	0	1	0	19	Fair
Hong et al., (2013)	0	1	1	0	1	1	1	1	0	1	0	0	19	Fair
van Meertan et al., (2008)	1	1	1	0	1	0	1	0	0	0	1	0	17	Fair
Ramakrishnaiagh et al., (2014)	1	1	1	0	1	1	1	0	0	0	0	0	18	Fair
Parameswaran et al., (2009)	1	1	1	0	1	1	1	0	0	0	1	0	20	Good
Nafteux et al., (2011)	1	1	1	0	1	1	1	0	0	0	0	0	18	Fair
Wang et al., (2010)	1	1	1	0	1	0	0	0	0	1	1	0	15	Fair
Wang et al., (2011)	1	1	1	0	1	0	0	0	0	1	1	0	15	Fair
Wang et al., (2015)	1	1	1	0	1	1	1	0	0	1	1	0	21	Good
Lv et al., (2014)	1	1	1	0	1	1	1	0	0	1	1	0	19	Fair
Liebman et al., (2006)	1	1	1	0	1	1	1	0	0	0	1	0	17	Fair
Teoh et al., (2011)	0	1	1	0	1	1	1	1	0	1	0	0	17	Fair
Lagergren et al., (2007)	1	1	1	0	1	1	1	0	0	1	1	0	19	Fair
Avery et al., (2007)	0	1	1	0	1	1	1	0	0	1	1	0	21	Good
Reynolds et al., (2006)	0	1	1	0	1	1	1	0	0	0	1	0	18	Fair

Appendix IV: Modified Borg Dyspnoea Scale

Rating of exertion	**Description**
Nothing at all	0
Extremely slight	0.5
Very slight	1
Slight	2
Moderate	3
Somewhat severe	4
Severe	5
	6
Very severe	7
	8
Extremely Severe	9
Maximal	10

Reference: BORG, G. A. 1982. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc,* 14**,** 377-81.

Appendix V: Physical Activity Readiness Questionnaire

Physical Activity Readiness
Questionnaire - PAR-Q
(revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

→

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

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continued on other side...

Appendix VI: Standard operating procedure for safety during exercise testing

Prior to Exercise Test

Assess for exclusion criteria for exercise testing.

Participant not to complete the exercise test if any of the following apply:

- A neurological or musculoskeletal condition limiting independent mobility.
- Medically unsuitable to complete an exercise test.
- Known absolute contraindications to exercise testing and exercise training as per the American College of Sports Medicine guidelines (Pescatello, 2013):
  - ☐ Recent significant change in the resting ECG suggesting significant ischemia, recent myocardial infarction (within 2 days) or other acute cardiac event.
  - ☐ Unstable angina.
  - ☐ Uncontrolled cardiac dysrhythmias causing symtoms or haemodynamic compromise.
  - ☐ Symptomatic severe aortic stenosis.
  - ☐ Uncontrolled symptomatic heart failure.
  - ☐ Acute pulmonary embolus or pulmonary infarction.
  - ☐ Acute myocarditis or pericarditis.
  - ☐ Suspected or known dissecting aneurysm.
  - ☐ Acute systemic infection, accompanied by fever, body aches, or swollen lymph glands.

Complete Physical Activity Readiness Questionnaire (PAR-Q)

If participant responds “yes” to any questions obtain further details and determine suitability for completing test.

Measure resting heart rate and blood pressure prior to exercise testing.

If resting blood pressure is consistently higher than 144/94 on the day of testing, do not compete fitness test and advise participant to inform their G.P at their next appointment.

During Exercise Test

Observe participant during test to assess for any termination criteria.

Test to be immediately stopped if any following occur:

- Any chest pain that is suspicious of angina.
- Intolerable dyspnoea.
- Evolving light headedness or dizziness.
- Leg pain or fatigue to limit further exercise.
- Evolving mental confusion or lack of coordination.
- Diaphoresis.
- Pale or ashen appearance.
- Any other clinically warranted reason.

After Exercise Test

Ensure that each participant reports feeling well and his/her heart rate has returned to resting values before the leaving the centre.

Appendix VII: Accelerometer participant information leaflets & exercise diaries

RT3

RT3 accelerometer

Thank you for agreeing to wear an RT3 activity monitor this week. This monitor is similar to a pedometer and will record the amount and the intensity of physical activity you undertake during the period that you wear it.

During the measurement period you will need to wear the accelerometer **on the band of your trousers during waking hours**.

How to start your activity monitor

1. Remove the sellotape and the see through clip.
2. Press the big button on the front surface of the monitor once to start. You may hear a small beep when you press this to indicate that it has been switched on. Otherwise look at the screen on the top surface of the monitor. When the monitor is active the dots between the numbers will flash.
3. Clip the RT3 activity monitor onto your trousers or skirt at the right hip on the front of your body. Buttons should face outwards.
4. The RT3 activity monitor is now working. You are not required to press the buttons again during the week. Do not worry if you press one of the buttons accidentally. This will not affect the recording of your activity data.

RT3 Diary

1. You are asked to record the time you put your activity monitor on in the morning and the time you take it off when going to bed at night.
2. You should also record any other times during the day that you remove your activity monitor and when you put it on again. Reasons to remove your activity monitor include:
    a) Going for a shower/bath
    b) Going for a swim
    c) Going for a sleep in bed during the day (wear your monitor if taking a rest on the couch)
3. Please record what activities you complete when not wearing your monitor.

- Start wearing your monitor first thing in the morning when you get up, even if you choose not to get dressed into your day clothes at that point (e.g if you wear your dressing gown in the morning- clip the monitor onto your dressing gown belt).

- Wear your monitor until you go to bed at night. A good tip is to place your monitor on your locker when you go to bed so you can see it first thing in the morning.

- At the end of the week please return the activity monitor and diary to us in the stamped addressed envelope provided.

Please remember not to change your activities- our aim is to get an idea of your 'normal' activity patterns over the monitoring period.

Start Date: _____ Name:_____

	Time monitor on	Time Monitor off	Activities completed when not wearing monitor
Day: _____ Date: _____			
Day: _____ Date: _____			
Day: _____ Date: _____			
Day: _____ Date: _____			
Day: _____ Date: _____			
Day: _____ Date: _____			
Day: _____ Date: _____			

Thank you very much for recording your physical activity.

ActiGraph

Participant Information Leaflet

ActiGraph Activity Monitor

Thank you for agreeing to wear the ActiGraph Activity Monitor. The ActiGraph measures your physical activity levels and provides us with information on the about of time you spend engaging in different intensities of activity. The following information leaflet addresses some frequently asked questions. Should you have any queries please contact the Physiotherapy Postgraduate and Research Room at the Trinity Centre for Health Sciences, St. James's Hospital on 01-8963613.

1. How many days do I wear the monitor?

You are requested to wear the activity monitor for one week (7 days) during waking hours.

2. Do I wear the monitor to bed?

No. You put the monitor on first thing in the morning and take it off last thing at night. You are requested to record the time you put the monitor on in the morning and the time you take if off at night in the activity diary provided.

3. Do I wear the monitor in the shower?

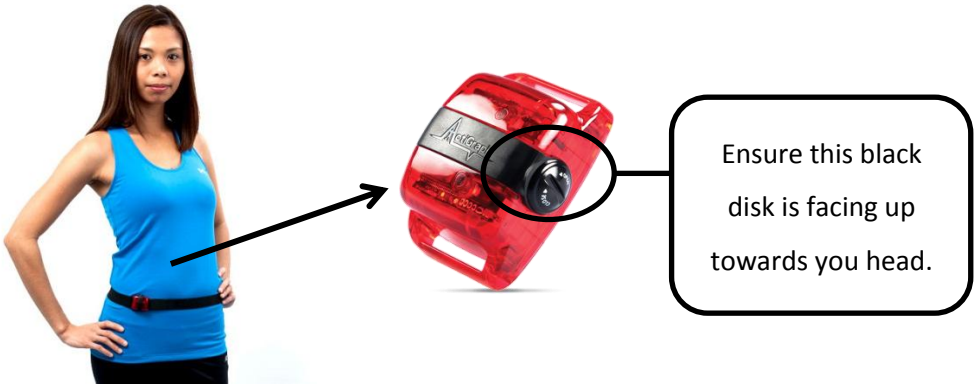
No. You should remove the monitor during any water-based activity such as showering, bathing or swimming. You are requested to record these activities, including the times your take the monitor on and off in the activity diary provided.

4. Do I need to press any button to start / finish the monitor?

No. The monitor is set-up by the researcher leading your study. You do not have to press any button to activate or stop the monitor.

5. Where on my body is the monitor worn?

The monitor is connected to a flexible strap with a clip. The strap should be worn like a belt around your waist with the monitor sitting at hip level on the right side of your body (see picture). Ensure the black disk on the side of the monitor is pointing towards your head. The strap should not be too tight or too loose. You can adjust the strap size if necessary. You may wear the monitor under or over your clothes.



6. Do I need to charge the monitor during the week?

No. Do not plug the monitor into any power source or connect to any USB cable during the week and this may wipe the data collected.

7. I forgot to wear the monitor – what should I do?

If you forget to wear the activity monitor on a particular day don't worry. Please write down clearly in the activity diary which day you forgot to wear the monitor and just carry on wearing it as normal the following day.

8. What should I do when I finish wearing the activity monitor?

When you finish wearing the monitor please return it to us in the stamped addressed envelope provided. Please return the monitor to us as soon as possible to ensure that the battery does not die before we receive it.

Try not to change your activity levels while wearing the monitor as our aim is to get an idea of <u>normal</u> activity patterns

Thank you very much for recording your physical activity

Physical Activity Diary

You are requested to wear your ActiGraph Activity Monitor during **all waking hours**. You will have to remove the activity monitor when you are going to bed or during water-based activities such as showering or swimming. Please record the time you put the activity monitor and the time you take it off in the following activity diary. If you forget to wear the monitor for a day please record this clearly in the activity diary. This record will help us to analyse your physical activity data as accurately as possible.

Should you have any queries please contact the Physiotherapy Postgraduate and Research Room at the Trinity Centre for Health Sciences, St. James's Hospital on 01-xxxxxxx. The following example outlines the details required.

Example:

On Date	On Time	Off Date	Off Time	Activity completed while not wearing the monitor
04.10.2013	*8.20am*	*04.10.2013*	*7.10pm*	*Shower*
04.10.2013	*7.30pm*	*04.10.2013*	*10.30pm*	*Sleeping in bed*
05.10.2013	*8.10am*	*05.10.2013*	*10.50pm*	*Sleeping in bed*

Modifiers of Functional Performance During Treatment for Esophageal Cancer

Participants Name/Study ID: _____

On Date	On Time	Off Date	Off Time	Activity completed while not wearing the monitor

Thank you for taking the time to record your physical activity.

Appendix VIII: EORTC-QLQ-C30 & OES-18

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ – OES18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Could you eat solid food?	1	2	3	4
32.	Could you eat liquidised or soft food?	1	2	3	4
33.	Could you drink liquids?	1	2	3	4
34.	Have you had trouble with swallowing your saliva?	1	2	3	4
35.	Have you choked when swallowing?	1	2	3	4
36.	Have you had trouble enjoying your meals?	1	2	3	4
37.	Have you felt full up too quickly?	1	2	3	4
38.	Have you had trouble with eating?	1	2	3	4
39.	Have you had trouble with eating in front of other people?	1	2	3	4
40.	Have you had a dry mouth?	1	2	3	4
41.	Have you had problems with your sense of taste?	1	2	3	4
42	Have you had trouble with coughing?	1	2	3	4
43.	Have you had trouble with talking?	1	2	3	4
44.	Have you had acid indigestion or heartburn?	1	2	3	4
45.	Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
46.	Have you had pain when you eat?	1	2	3	4
47.	Have you had pain in your chest?	1	2	3	4
48.	Have you had pain in your stomach?	1	2	3	4

Appendix IX: Scoring Procedure for the EORTC QLQ-C30 Version 3.0

As outlined in the EORTC QLQ-C30 Scoring Manual:

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual (3rd Edition).*

Published by: European Organisation for Research and Treatment of Cancer, Brussels, 2001.

Scoring principle for all scales:

1. Estimate the average of the items that contribute to the scale: raw score (RS)
2. Use a linear transformation to standardise the raw score so that scores range from 0 to 100.

*Higher scores represent a higher ("better") level of functioning or a higher ("worse") level of symptoms.

Formulas

Calculation of the raw score (RS)	$RS = (I_1 + I_2 ... I_n)/n$ I = scale item n = total number of items
Linear Transformations	Functional Scales Score = {1- [(RS - 1)/range]} x 100 Symptom Scales Score = {(*RS* -1) *range*} - 100 Global health status/QOL Score = {(*RS* - 1) *range*} - 100 range = is the difference between the maximum possible value of RS and the minimum possible value.

Scales and Corresponding Items

Scale	Abbreviation	Item Numbers
Global health status/QOL	QL2	
Functional Scales		
Physical functioning	PF2	1 - 5
Role functioning	RF2	6, 7
Emotional functioning	EF	21 - 24
Cognitive functioning	CF	20, 25
Social functioning	SF	26, 27
Symptom Scales/Items		10, 12, 18
Fatigue	FA	
Nausea & vomiting	NV	14, 15
Pain	PA	9, 19
Dyspnoea	DY	8
Insomnia	SL	11
Appetite loss	AP	13
Constipation	CO	16
Diarrhoea	DI	17
Financial difficulties	FI	28

Appendix X: Codebooks for Study 2 and Study 4 (short versions)

Study 2

Categories	Codes
Activity & Exercise	Active person Active throughout life Moderately active person Not active person Activity limitations/restrictions No or min activity limitations Exercising currently
Barriers to Exercise	Ageing Afraid/reluctant Lack of interest Lazy Less food intake Physical side effects Reduced stamina Weather Weight loss BW not a concern on terms of PA No barriers to exercise
Emotions	Depression, worry, anxiety, stress Happy with progress, feeling fortunate " Forget about it"
Exercise Knowledge & Understanding	Advice re activity, exercise Can't recall any specific advice Enough information No specific exercise advice, more needed Exercise is beneficial Exercise not beneficial Exercise query benefits Guidelines-no knowledge Guidelines-vague
Facilitators to exercise	Attitude Build up Eating properly Frustrated inactive, get moving, get back to normal Goal setting Habit Weather Misc
Food & Eating	Eating changes Eating normal Eating problems Rest after eating
Lifestyle Changes	Daily rest Healthier eating Lifestyle changed

	Lifestyle not changed Needs more sleep Occupation changes Pacing, Planning, Slower Restrictive Lifestyle
Physical Changes	Decreased fitness Decreased stamina Decreased strength No treatment side effects PA levels changed Physical side effects, changes
Recovery	Back to normal Not back to normal “New normal” DC-not able for much Don’t expect to be 100% Enough information Harder-old Harder-young Recovery not going to plan Sicker than expected Spouse helpful Time back to normal Treatment type, success Prolonged recovery Role/importance of inpatient physio
Rehab	Journeys different Peer support Rehab beneficial, needed Rehab interest Rehab no interest “Take part if thought it would help” Components Education/info beneficial HEP Hospital class After treatment During treatment
Weight	BWstable, normal Have lost weight from max WL negative WL positive

Study 4

Categories	Codes
Activity & Exercise	Active during life Active person Exercise is beneficial Guidelines-no knowledge Guidelines-vague knowledge Barriers to exercise • Reduced food intake • Told to take it easy • Weather • Weight • BW not a concern in terms of PA • No barriers to exercise Facilitators to exercise • Attitude • Cutting grass • Eating normally • Habit • Walking dogs • Wanting to maintain fitness • Weather
Treatment Experiences	Activity limitations, restrictions Activity slowly built back up Back to, almost back to normal activity levels Completing normal household tasks Currently exercising Decreased PA, stamina, energy Education/information/support beneficial Emotions/attitude 'Feeling good' Maintained lifestyle/PA levels 'Minding myself' No activity limitations No problems/side effects during neoadjuvant treatment Not working Side effects only after rx finished Side effects/problems during treatment Time back to 'normal' after treatment Weight changes Weight stable 'Wiped out' after treatment
Food & Eating	Eating changes Eating a lot just to maintain weight Eating normal Eating problems
Prehabilitation	'Do my own thing' Exc intervention post rx

	‘Take part if I thought it would help’ Able for it Beneficial Peer support HEP Hospital class Interest Timing Not able/Unsure whether able

Appendix XI: Study 1 invitation letter, participant information leaflet and consent form

Trinity Centre for Health Sciences,
St James's Hospital,
James's Street,
Dublin 8.

Dear Mr/Ms.

I am a physiotherapist carrying out postgraduate research with Professor Reynolds in Trinity College Dublin and St. James's Hospital. I am writing to invite you to take part in a study we are currently undertaking which aims to document the physical fitness and functioning of people who are at least six months after oesophageal surgery. One of the aims of the study is to determine if there is a need for specific physical rehabilitation in the months after oesophageal resection.

In order to determine the fitness and functioning of this cohort, participants in this study will be asked have the following measurements carried out:

- Body Composition; weight, height, BMI and muscle mass
- Physical Activity Levels
- Exercise Capacity
- Hand Grip Strength
- Quality of Life & Fatigue Questionnaire

A brief description of what is involved in each assessment is detailed in the attached participant information leaflet.

If you elect to take part you would need to attend the Trinity Centre for Health Sciences, in the grounds of St. James's Hospital, for one appointment lasting approximately an hour and a half. This appointment can be made for a time that is most convenient for you. Arrangements can be made to have the appointment on the same day as other appointments you may have in the hospital in the upcoming

months. Travel fares can be refunded if required.

If you are interested in taking part in this study you can post back the enclosed form in the stamped addressed envelope, indicating your preferred contact number. A phone call can then be made to ask you some brief screening questions to determine eligibility and to arrange an appointment. Alternatively you can ring me directly to express interest and make an appointment.

Gathering of this data will give us a better picture of the physical functioning of patients after oesophageal surgery. This will highlight if there is a need to provide physical rehabilitation in the months after surgery.

Participation in this study will give you valuable information regarding your strength and fitness levels. In addition, you will be invited to ask any questions you may have regarding physical activity and exercise guidelines.

If you have any questions about the study or would like to make an appointment to take part please do not hesitate to contact me on 01-xxxxxxxx or xxx@tcd.ie.

I look forward to hearing from you.

Kind regards,

_____

Jenny Gannon

Research Physiotherapist

PARTICIPANT INFORMATION LEAFLET

Title: Physical functioning after oesophageal surgery

What is this study about?

The aim of this study is to gather data on the physical status of patients at least six months after oesophageal surgery.

It has been shown that short and long term health related quality of life is affected after oesophagectomy. Compared to normal values patients after oesophagectomy have been shown to score lower for physical function, vitality and general health perception. The majority of studies determine physical functioning solely through the use of questionnaires. There is very little information on fitness, strength and the amount of physical activity in patients after oesophagectomy. We are interested in these measures to see if there is a need to help patients increase their fitness and activity levels which could be done through a post-operative rehabilitation programme.

The objective of this study is to obtain a physical profile of patients from six months after oesophageal surgery.

Who is being asked to participate?

Patients who had an oesophagectomy and received treatment at St. James's Hospital and are at least 6 months post surgery are being offered the opportunity to participate in this study. Your surgeon is happy that I contact you and has provided medical approval for you to complete the assessments involved in this study.

What do I have to do?

You would be required to attend the Trinity Centre for Health Sciences, which is located on the grounds of St. James's Hospital, for one appointment during which your assessment will take place. The assessment will last approximately an hour and a half.

What assessments are involved?

1. Body Composition

You will be asked to stand on a machine called a body composition analyser. This machine will calculate your body mass index, which is an equation used to estimate the ideal weight for your height. In addition, the machine will provide details on your percentage body fat, your muscle mass and your total body water. You do not feel anything while the measures are being taken. It takes 30 seconds to complete the measurements.

In addition, we will measure your waist circumference. This will measure the amount of weight you store on your stomach which may have important implications for your health.

2. Physical Activity

To measure your physical activity levels, you will be given an activity monitor to wear when you leave the centre. This monitor, call the RT3 accelerometer, is the same size as a small mobile phone. You will be asked to wear it on the band of your trousers for one week. You will be provided with a stamped addressed envelope to post the monitor back to the study investigator. You will be required to fill out an activity diary for the duration of the week that you are wearing the accelerometer.

3. Aerobic Fitness

Your fitness will be assessed by carrying out an incremental shuttle walking test. This is a performance based test that measures fitness levels. The distance walked is measured in metres. The longer the distance that is walked the better the performance. To complete this test you will be required to walk between two cones in time to a set of auditory beeps played on a CD. Initially, the walking speed is very slow, but each minute the required walking speed progressively increases. You will be required to walk for as long as you can until you are either too breathless or can no longer keep up with the beeps at which time the test ends. The test will last no longer than 12 minutes.

4. Muscle Strength

Grip strength has been shown to be good predictor of overall strength and health. Your hand grip strength will be measured using a dynamometer. This is a very simple test where you will be required to squeeze the dynamometer as hard as you can three times. The average score will be recorded and compared to normative data.

5. Quality of Life & Fatigue

You will be asked to fill out the EORTC-QLQ questionnaire during the appointment. This questionnaire may already be familiar to you and it asks a series of questions relating to quality of life and fatigue symptoms associated with your illness.

What are the benefits to me?

You will receive feedback regarding all the assessments completed during the study from a chartered physiotherapist. In addition, you will be invited to ask any questions

you may have regarding physical activity and exercise guidelines.

What are the risks?

We do not anticipate adverse effects during the assessments. Occasionally, people can feel dizzy or breathless when doing an exercise test. However, because the exercise test is carefully graded, the risks of this happening are minimal. You will be required to complete a medical screening questionnaire prior to participation to assess suitability. The assessment will be conducted by a qualified physiotherapist with experience in all of the assessments outlined above. If any concerns are expressed, you will have the opportunity to be followed up by referral to the Physiotherapy Department or appropriate medical team for review. The practitioners involved in this study have current medical indemnity cover.

Will my information be confidential?

Your identity and data will remain confidential. Your name will not be published and will not be disclosed to anyone outside of the hospital.

Compensation

The postgraduate research student who is conducting the assessment is a chartered physiotherapist and is covered by the Trinity College Dublin insurance scheme. Nothing in this document restricts or curtails your rights.

What if I change my mind?

If you volunteer to participate in this study, you may stop at any time. If you decide not to participate, or if you stop, you will not be penalised and will not give up any benefits which you had before entering the study.

Stopping the study

Your doctor or the investigator in this study may stop your participation at any time without your consent.

Permission

This study has received Hospital Research Ethics committee approval.

I have more questions, who will I ask?

You can get more information or answers to your questions about the study, your participation in the study, and your rights from Jenny Gannon (Study Investigator & Physiotherapist) who can be telephoned at (01) xxxxxx (9am to 5pm Monday to Friday).

CONSENT FORM

Title of research study: Physical functioning after oesophageal surgery.

This study and this consent form have been explained to me. The investigator has answered all my questions to my satisfaction.

I believe I understand what will happen if I agree to be part of this study. I will carry out all assessments related to this study including body composition measurements, hand grip strength dynamometry, a fitness test and completion of a health, quality of life questionnaire. In addition, I will undertake activity monitoring and the maintenance of an exercise dairy for a week following the study.

I understand my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care being affected. I agree to allow the investigator in this study to access my medical chart in order to record information relating to the type of illness I have, the treatment/procedures I received and other relevant data from my postoperative course to be used as study outcomes.

I consent to the publication of data from this study and understand that my identity will remain confidential. I agree to the use of data collected in this study to be used in future studies without the need for giving consent again.

I have read, or have read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights.

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date:

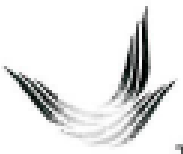
Date on which the participant was first furnished with this form:

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Investigator's signature: **Date**:

Appendix XII: Letters of ethics approval for Study 1 & Study 2

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR ORDERING PURPOSES



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SJH/AMNCH Research Ethics Committee Secretariat
Ursula Ryan Ph: 4142342 email: Ursula.Ryan@amnch.ie
Secretariat Fax: 4142371

Ms. Jenny Gannon
Discipline of Physiotherapy
School of Medicine
Trinity Centre for Health Sciences
St. James's Hospital
James Street
Dublin 8

March 20th 2012

Re: Preoperative exercise Training & Post Operative Outcomes post Oesophagectomy.

Please quote this reference in any follow up to this letter: 2012/09/19

Dear Jenny,

Thank you for your letter dated February 23rd 2012 and enclosures in which you request ethical approval of an amendment to the above referenced study.

The Chairman, on behalf of the Research Ethics Committee, has reviewed this proposed amendment and has given ethical approval to the amendment. He has requested that the Patient Information Sheet & Consent Forms are amended in accordance with the changes to your study.

Yours sincerely

Ms. Ursula Ryan
Secretary, SJH/AMNCH Research Ethics Committee

SJH/AMNCH Research Ethics Committee

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

Ms. Jenny Gannon
Post Graduate Research Student
Physiotherapy Department
St. James's Hospital
James's Street
Dublin 8

10th April 2014

RE: Amendment to extend the study "Preoperative Exercise and Post-Operative Outcomes post Oesophagectomy/Gastrectomy"

Reference REC: 2011/12/12 Chairman Action and 2012/09/19 / 2014/02/List 6/2014/04/Chairman

(Please quote REC reference and EudraCT number on all correspondence)

Dear Jenny,

Thank you for your correspondence and I apologies for the confusion. It is clear that the Committee did not have all the documentation when this proposal was considered.

The Chairman on behalf of the Research Ethic Committee has reviewed and approved the above study. We now take into consideration that a Patient Information Leaflet /Consent form specifically for Controls is available. We also note that appropriate consent for accessing medical records will be in place.

Yours sincerely

Dr. Paul Crotty
Chairman
SJH/AMNCH Research Ethics Committee

Appendix XIII: Study 2 invitation letter, participant information leaflet and consent form

Trinity Centre for Health Sciences,
St James's Hospital,
James's Street,
Dublin 8.

Dear Mr/Ms.

Thank you very much for your previous participation in our study. With your help we have gathered some very useful information on physical functioning in the months and years after oesophageal cancer surgery. As I explained on the phone we are now hoping to gather further information on patient experiences and perspectives through a more structured discussion about topics such as activity levels, barriers to exercise and rehabilitation programmes.

I have enclosed a participant information leaflet which explains this additional study and what would be required to participate.

Take some time to read through the leaflet and think about whether you might be interested in participating. I will give you a call in the next few weeks to discuss this further and if you are interested in taking part we can schedule an appointment or a phone call for the interview then.

If you have any queries or would like further information please do not hesitate to contact me.

Thank you again for your time.

Kind regards,

_____

Jenny Gannon
Research Physiotherapist

PARTICIPANT INFORMATION LEAFLET

Title: Patient perspectives on functional recovery and physical activity levels following oesophagectomy

What is this study about?

The aim of this study is to talk to patients about their experience of regaining function and normal activity levels in the months and years following surgery for oesophageal cancer.

Ongoing investigations by our research group are looking into physical outcomes such as strength, fitness and activity levels in people following oesophageal cancer. This has revealed a number of ongoing concerns which may be potential barriers to participation in physical activity and functional recovery after surgery.

Our experience to date has highlighted the need for a more formal approach to investigate these concerns. It is hoped that a structured discussion between investigators and patients about some of these concerns may gather useful information from patient experiences which we cannot measure with physical tests. Health care professionals have a lot to learn from patient perspectives. The information gained from this study will give us a greater understanding of patients experiences.

Who is being asked to participate?

Patients who had an oesophagectomy and received treatment at St. James's Hospital and are at least 6 months post surgery are being offered the opportunity to participate in this study.

What do I have to do?

The interview with the lead investigator of this study (Jenny Gannon) can take place either over the phone or in person in the Trinity Centre for Health Sciences, located on the grounds of St. James's Hospital.

This will be a discussion during which the following four topics will be explored:

- Your general health since your cancer diagnosis.
- Discussion about your previous and current activity levels.
- What you might consider as potential barriers to recommended activity levels and exercise.
- Your views on the development of a rehabilitation programme for oesophageal cancer survivors.

You can say as much or as little as you like regarding each topic and there are no right or wrong answers. We are just interested in your opinion on these topics.

The interview should take no longer than 30 minutes. You may attend on your own or with a friend or family member.

The interview will be recorded and transcribed but all responses will be kept anonymous.

What are the benefits to me?

This interview will give you the opportunity to ask any questions you may have regarding physical activity and exercise guidelines.

What are the risks?

As this study consists of an interview only we do not anticipate there to be any risks involved.

Will my information be confidential?

Your identity and data will remain confidential. Your name will not be published and will not be disclosed to anyone outside of the hospital.

Compensation

The postgraduate research student who is conducting the assessment is a chartered

physiotherapist and is covered by the Trinity College Dublin insurance scheme. Nothing in this document restricts or curtails your rights.

What if I change my mind?

If you volunteer to participate in this study, you may stop at any time. If you decide not to participate, or if you stop, you will not be penalised and will not give up any benefits which you had before entering the study.

Stopping the study

Your doctor or the investigator in this study may stop your participation at any time without your consent.

Permission

This study has received Hospital Research Ethics committee approval.

I have more questions, who will I ask?

You can get more information or answers to your questions about the study, your participation in the study, and your rights from Jenny Gannon (Study Investigator & Physiotherapist) who can be telephoned at (01) xxxxxxx (9am to 5pm Monday to Friday).

CONSENT FORM

Title of research study:

Patient perspectives on functional recovery and physical activity levels following oesophagectomy

This study and this consent form have been explained to me. The investigator has answered all my questions to my satisfaction.

I believe I understand what will happen if I agree to be part of this study. I will complete a recorded interview with the lead investigator of this study to discuss various topics related to physical activity and functional recovery from oesophageal cancer surgery.

I understand my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care being affected. I agree to allow the investigator in this study to access my medical chart in order to record general socio-demographic details and information relating to the type of illness I have, the treatment/procedures I received and other and relevant data from my postoperative course to be used as study outcomes.

I consent to the publication of data from this study and understand that my identity will remain confidential. I agree to the use of data collected in this study to be used in future studies without the need for giving consent again.

I have read, or have read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights.

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date:

Date on which the participant was first furnished with this form:

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Investigator's signature:

Date:

Appendix XIV: Interview Schedule – Study 2

	General health & physical functioning	
1.	Since your operation/the completion of your treatment how has it been for you recovering your health, your strength and your fitness?	
	• Do you feel back to normal? How long did this take?	
	• Do you feel there are any differences in your lifestyle pre and post diagnosis?	
	• Are there certain activities that you would not undertake now having had cancer and the treatment?	
	Physical activity levels	
2.	The next thing we are going to talk about is physical activity... There are guidelines available regarding the amount of physical activity that is recommended for health benefits. Do you know how much activity is recommended for health benefits? What would be your impression of your own activity levels?	
	• Would you consider yourself an active person currently?	
	• How do your daily PA levels compare to what they were pre-diagnosis?	
	• What advice were you given regarding physical activity during and after your treatment?	
	• Do you think exercise and increased activity would benefit you? How? (*Benefits of exercise*)	
	Barriers to activity/exercise	
3.	Could you describe any barriers in your life which may have an impact on your PA levels?	
	• If you have experienced body weight changes do you think this had an impact? (*Weather?*) (*Decreased food intake*?)	
	• Side effects of treatment? Early/Late	

	• Did you find that family members did/do more for you?	
	• Are/were you unsure about how much you were “allowed” to do after your cancer treatment? Are there certain things that you thought/think you should not do after your cancer treatment?	
	• Are you restricted in any tasks/activities?	
	Rehabilitation	
4.	It has been suggested that a rehabilitation programme (brief explanation) may be of benefit to people who are treated for oesophageal cancer. As clinicians trying to develop a programme of this nature the input of patients is extremely helpful... Is a rehabilitation programme something that you would have been/would be interested in? If no, why not? If yes, what do you think a rehabilitation programme should consist of?	
	• At what time do you think it would be most appropriate/helpful to implement a rehabilitation programme?	
	• Would you attend a rehabilitation programme/exercise class?	
	• At any point during your cancer treatment and recovery would you have liked more information and advice regarding activity and exercise? • When? What? Do you think you would have been in a position to take this advice on board and implement it? What would have helped you to do this?	

That’s all the topics covered so unless there is anything you want to add we can finish there. Thank you.

Appendix XV: Letters of ethics approval for Study 3 & Study 4

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
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SJH/AMNCH Research Ethics Committee
David Willow david.willow@amnch.ie
Secretariat Phone: (01) 414 2342

Dr. Emer Guinan
Discipline of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
Dublin 8

13th February 2014

RE: Pre-operative inspiratory muscle training to prevent post-operative pneumonia in patients undergoing oesophageal resection

Reference REC: 2014/01/list 1 / 2014/02/list 6

(please quote references in all correspondence)

Dear Dr. Guinan,

With thanks for the amendments made to the Patient Information and Consent forms and explanation as per your letter of 29/01/2014.

On behalf of the Research Ethics Committee I can confirm that the study is approved to proceed.

Yours sincerely,

David Willow
Secretary
SJH/AMNCH Research Ethics Committee

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
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Ms. Emer Guinan
Research Fellow
Discipline of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
Dublin 8

20th November 2014

Re: Rehabilitation Strategies Following Oesophageal Cancer

REC Reference : 2014-11 Chairman's Action (2) *(please quote references and title on all correspondence)*

Dear Ms Guinan,

Thank you for your correspondence in which you requested ethical approval for the above study.

The Chairman, on behalf of the SJH/AMNCH Research Ethics Committee has reviewed your submission and has given ethical approval.

Full ethical approval is now in place for this study.

Yours sincerely

Claire Hartin Secretary,
SJH/AMNCH Research Ethics Committee

Appendix XVI: Participant information leaflet and consent form for Study 3 & Study 4

Modifiers of Functional Performance during Treatment for Esophageal Cancer

Participant Information Leaflet

Functional performance describes the ability to carry out normal activities such as walking or household tasks. Treatments for cancer of the oesophagus (food-pipe) such as chemotherapy, radiotherapy or surgery may alter normal functional performance. At St. James's hospital we are interested in measuring the change that may occur in functional performance during oesophageal cancer treatment. This information will help us to understand the problems experienced by patients and plan rehabilitation strategies. The following study will identify factors which influence the ability to function normally during treatment for oesophageal cancer.

Interventions such as inspiratory muscle training which is being prescribed in the PREPARE trial, may improve the ability to regain functional performance following surgery. The following study is being run in conjunction with the PREPARE trial. This information leaflet refers only to assessments which are additional to the PREPARE trial. All other details regarding your rights and data confidentiality are outlined in the PREPARE trial information leaflet.

What measurements are involved?

The following selection of assessments will be completed. Many of these measures are carried out as part of your routine medical care and will be completed during your routine hospital visits. The first assessment will be completed at the time of your diagnosis.

- **A walking test**
    - You will be asked to walk along a marked path on the hospital corridor for 6 minutes. You can walk at your own comfortable speed and will be able to rest during this time if you require.

- **Muscle strength**
    - We measure hand grip strength using a hand-held measurement device.

- **Physical activity**
    - We complete a physical activity questionnaire during your appointment and provide you with an activity monitor to wear at home for one week. We will also take some time to discuss with you how easy or difficult it is for you to be active and ask you to identify reasons may affect your ability to be active. Your activity levels will also be recorded during the first five days following your surgery. Activity will be measured by the activity monitor which will be worn on your waist. Your activity patterns will be recorded by your treating physiotherapist and nurse.

- **Body composition**
    - We will measure your height, body weight and BMI.

What are the risks?

We do not anticipate adverse effects during the assessments. You may feel a little tired after the walking test however we expect that you will recover quickly. No serious adverse events are anticipated.

I have more questions, who will I ask?

For more information or answers to your questions about the study, your participation in the study, and your rights from Emer Guinan (Lead Investigator & Physiotherapist) who can be telephoned at (01) xxxxxxx (9am to 5pm Monday to Friday).

Modifiers of Functional Performance during Treatment for Esophageal Cancer

Consent Form

This study and this consent form have been explained to me. The investigator has answered all my questions to my satisfaction.

I believe I understand what will happen if I agree to be part of this study. I understand my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care being affected. I consent to the publication of data from this study and understand that my identity will remain confidential. I consent to the processing of my data collected as part of this study.

I agree to allow the investigator in this study to access my medical chart in order to record information that might be relevant to the study.

0 yes

0 no

I consent to my physical activity and physical performance measures being stored at an institutional database at Trinity College Dublin for use in future research.

0 yes

0 no

I agree to the use of data collected in this study to be used in future studies without the need for giving consent again.

0 yes

0 no

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights

Subject name: .....

Date of Birth: .....

Signature: Date :

Statement of investigator's responsibility

I have explained the nature, purpose, procedures, benefits, risks of or alternatives to this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Name investigator (or representative): .....

Signature: Date:

Appendix XVII: Interview Schedule – Study 4

	PA levels	
1.	The first thing we are going to talk about is physical activity... There are guidelines available regarding the amount of physical activity that is recommended for health benefits. Are these guidelines something you would be aware of? Do you know how much activity is recommended for health benefits?	
	• What would be your impression of your own activity levels? Would you consider yourself an active person currently?	
	• How do your daily PA levels compare to what they were before you were diagnosed?	
	• Would you have been an active person throughout your life? Has that changed? Why?	
	The effect of diagnosis and treatment on PA levels	
2.	You have just completed your chemotherapy and/or radiotherapy treatment... Looking back over the past few weeks how would you describe your energy and activity levels?	
	• Have you experienced any side effects from the treatment which have impacted on your exercise and activity levels and /or your strength?	
	• Have you experienced any significant body composition changes? Has this had an impact on your energy/exercise/PA levels?	
	• Are you experiencing any functional limitations at present? Are you limited functionally in any way? Is there anything that you would like to do that you are not able to?	
	• Apart from what we have already mentioned can you describe any barriers to exercise and PA you are currently experiencing? Are you as active as you would like to be?	
	• Do you think being more active at this time would be beneficial to you?	

	Prehabilitation	
3.	It has been suggested that a prehabilitation programme (brief explanation) may be of benefit to people who are awaiting surgery for oesophageal cancer. As clinicians trying to develop a programme of this nature the input of patients is extremely helpful... Do you think you would have been willing/able to complete an exercise programme over the past few weeks/presently?	
	• Do you think something like this would be beneficial before your surgery?	
	• In terms of an exercise programme what would be your preferences in terms of: ➢ Home based/hospital based (Do you think you would comply with a HEP? Would you be willing to travel/come in for extra appointments?) ➢ Individual/group? ➢ Type: Aerobic/resistance/respiratory training/combination? ➢ Combined with input from other health care professionals e.g dietician, O.T, nurse, doctor..?	

That's all the topics covered so unless there is anything you want to add we can finish there. Thank you.