

Preoperative exercise protocol to aid  
recovery (PREPARE) in radical  
cystectomy: a randomized controlled  
feasibility study

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by

Mr Srijit Banerjee

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# Abstract

## **Introduction:**

Radical cystectomy (RC) and urinary diversion is the gold standard treatment for both muscle-invasive urinary bladder cancer and for non-muscle invasive disease refractory to intravesical treatment. This is also one of the most complex urological procedures. Despite improvements in practice, technique and process of care, RC is still associated with significant complications, including death, with wide variability in reported postoperative morbidity and mortality rates ranging from 19% to 64% and 0.8% to 8.3%, respectively.

Cardiopulmonary Exercise Testing (CPET) is a non-invasive measurement of cardiopulmonary fitness. CPET variables such as anaerobic threshold (AT) and maximal oxygen consumption ( $VO_2$  max) have been demonstrated to be reliable predictors of postoperative morbidity, mortality and hospital length of stay (LOS) following major surgery and are helpful in risk stratifying patients. The foundations of enhanced recovery programmes (ERPs), also known as enhanced recovery after surgery or fast-track surgery, were laid down by Kehlet in the 1990s and have received widespread acceptance in various surgical specialities. The principles of these peri-operative strategies are to use a multidisciplinary approach to minimising morbidity. This revolves around a team approach, which includes surgeons, anaesthetists, nurses, physiotherapists, stoma therapists, dieticians and most importantly requires active participation from the patient and their family. The role of exercise training or 'prehabilitation' for optimising preoperative physiological function to counter catabolic effects of surgery has received little attention in patients undergoing radical cystectomy (RC). This randomised controlled feasibility study examines whether a short preoperative course of supervised exercise sessions is feasible, well tolerated and whether it can lead to an improvement in cardiopulmonary fitness in patients undergoing RC.

## **Methods:**

Over a 2 year period patients awaiting RC were randomised to either a control arm or an exercise intervention arm after initial CPET assessment. Patients in the exercise arm

were offered twice weekly supervised exercise sessions preoperatively for 4 weeks, whilst the control arm had standard care. Repeat assessment was performed in both groups at the end of 4 weeks. Feasibility outcomes such as recruitment rate, compliance and adverse events were recorded. Postoperative recovery including complications stratified as per Clavien classification and LOS were also recorded.

### **Results:**

112 eligible patients were approached of whom 60 were recruited to the study, with a recruitment rate of 53.5%. Mean age was 72 years (range 52-85 years). Nine (15%) patients did not complete repeat CPET testing. No adverse events were recorded during CPET testing or exercise sessions. Compliance with exercise sessions was satisfactory with patients attending for a median of 8 sessions. Dropout rate from the exercise sessions in the intervention arm was 23.3% (n=11). An analysis of covariance (ANCOVA) showed a statistically significant increase in mean VO<sub>2</sub> max in the intervention group when compared to the control group by +1.9ml/kg/min (0.87-3, 95% CI), (p=0.001). AT was also similarly increased by +0.33ml/kg/min (-0.68-1.3, 95% CI) (p=0.5). Mean preoperative VO<sub>2</sub> max was found to be significantly higher (p<0.001) in patients who had an uncomplicated recovery (22.04ml/kg/min) when compared to those with complications (Clavien grade I or above) (16.32ml/kg/min). Analysis using Spearman's rank correlation coefficient demonstrated a negative association between day of discharge from hospital and initial VO<sub>2</sub> max (p<0.001) indicating quicker postoperative recovery in patients with higher cardiorespiratory fitness levels.

Although not statistically significant there appears to be a trend with complication rates being higher in the control group (39.28%) compared to the exercise intervention arm (33.3%) (p=0.8)

### **Conclusion:**

CPET assessment and exercise training is safe and well tolerated. Patients comply with a supervised exercise regime and there is a measurable improvement in their cardiorespiratory fitness after 4 weeks. The data demonstrates that VO<sub>2</sub> max is a reliable predictor of outcomes following RC and can potentially be used to risk-stratify patients preoperatively. Although the study is not adequately powered to fully investigate the results of exercise training on postoperative outcomes, the results are promising, and

suggest the requirement for larger randomised controlled trials to elucidate the role of prehabilitation prior to surgery in this population.

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# Chapter 1: Introduction

## 1.1 Bladder cancer epidemiology:

Bladder cancer is the ninth most commonly diagnosed cancer worldwide, with more than 380,000 new cases each year and more than 150,000 deaths per year(1). In 2011, there were 10,399 new cases of bladder cancer diagnosed in the UK with 7,452 (72%) in men and 2,947 (28%) in women, giving a male: female ratio of around 2.5:1. The incidence rate shows that there are 24 new bladder cancer cases for every 100,000 males in the UK, and 9 for every 100,000 females(2).

## 1.2 Risk Factors for Bladder Cancer:

### 1.2.1 Age:

Age is now widely accepted as the greatest single risk factor for developing bladder cancer. While bladder cancer can occur at any age, it is generally a disease of middle-aged and elderly people. With the median age at diagnosis being 70 years, it is rare to find bladder cancer in those below the age of 50 years(3,4).

### 1.2.2 Gender:

Bladder cancer is the fourth most common cancer in UK in men after prostate, lung and colorectal cancers, accounting for 6.6% of all cancer cases(5). Men are nearly three times more likely to develop the disease than women. While men are at higher risk than women for developing bladder cancer, women tend to present with more advanced disease(3).

### 1.2.3 Tobacco smoking:

Approximately 40% of bladder cancer cases are attributable to cigarette smoking(6). Smoking cigarettes increases the relative risk of bladder cancer between 2 to 6 fold, depending on the overall duration of smoking and the number of cigarettes smoked per day(7). Cigarette smoke contains the carcinogens 4-aminobiphenyl (4ABP) and 2 naphthylamine. Slow hepatic acetylation (detoxification) of 4ABP by N-acetyltransferase and Glutathione S-transferase by induction of the cytochrome P-450 1 A2 demethylating enzyme appears to increase urothelial carcinogenic exposure (8). Smoking also leads to higher mortality rate from bladder cancer during long-term follow-up. There is a slow risk reduction (over 20 years) following cessation of smoking (9).

### 1.2.4 Occupational Exposure to chemicals:

Occupational exposure is an important risk factor for bladder cancer. Historically work-related cases accounted for 10% of bladder cancer (10,11). Individuals in occupations involving exposure to aniline dyes and aromatic amines such as rubber or cable manufacturing had an increased risk of bladder cancer, due to exposure to carcinogens commonly encountered in those industries, including  $\beta$ -naphthylamine and polycyclic aromatic hydrocarbons (12). There exists a latent period of 25 to 45 years between exposure and carcinogenesis (13).

### 1.2.5 Radiation Therapy:

Recent studies have shown an increase in incidence of bladder cancer in patients who have been treated with radiotherapy for other pelvic malignancy such as prostate and gynaecological malignancy (14,15). According to several studies external beam radiotherapy (EBRT) has been identified as an independent risk factor for secondary primary bladder cancer. The latency period between radiotherapy and developing

bladder cancer appears to vary between 3.07 years to 5.75 years although some other studies have reported a longer latency period of up to 30 years depending on the dose of pelvic radiation (16,17). As bladder cancer requires a long time to develop, patients treated with radiation at a young age are at highest risk and should be followed up closely.

### **1.2.6 Dietary factors:**

As bladder cancer is common in the Western world several dietary factors have been believed to be related to bladder cancer, however a link remains controversial. A recent meta-analysis reporting data on bladder cancer and diet supported the hypothesis that vegetable and fruit intake reduced the risk of bladder cancer(18).

### **1.2.7 Chronic urinary tract infection:**

Squamous cell cancer of the bladder is believed to be related to chronic irritation of the bladder such as due to chronic infection and long term catheterisation(19).

### **1.2.8 Bladder schistosomiasis:**

Bladder schistosomiasis (bilharziasis or liver fluke) is a common parasitic infection that affects sub-Saharan population. This has been established as a common cause for bladder cancer affecting people living in these countries. There appears to be a fivefold increase in risk in developing bladder cancer in patients who have been chronically exposed to this parasitic infection(20,21).

## **1.3 Diagnosis of bladder cancer**

### **1.3.1 Symptoms:**

The most common presenting symptom (85%) of bladder cancer is haematuria. Haematuria may be initial, throughout or terminal in the stream. It may also be macroscopic ( visible blood in the urine) or microscopic (non-visible blood in the urine, only detected with dipstick or urine microscopy) (22,23). Roughly one third (34%) of

patients aged more than 50 years and 10% aged less than 50 years with macroscopic haematuria seen in the clinic will be diagnosed with bladder cancer (24,25) .

Patients often have non-visible haematuria that was detected during routine screening by their general physicians. Less than 5% of those aged less than 50 years and 7-13% of those aged more than 50 years will have a urological malignancy in this group (26,27).

Some patients can complain of lower urinary tract symptoms such as urgency of urination and suprapubic pain along with microscopic or macroscopic haematuria. This is often referred to as “ malignant cystitis” (26).

More advanced cases of bladder cancer may present with symptoms of metastatic disease. These may include lower limb swelling due to lymphatic or venous obstruction, bone pain, weight loss, jaundice (due to liver metastasis) anorexia, confusion and renal failure secondary to ureteric obstruction (20).

### 1.3.2 Cystoscopy:

Diagnosis of bladder cancer is ultimately made by a combination of cystoscopy and histological evaluation of multiple bladder biopsies. Cystoscopy involves direct visualisation of the bladder using a flexible optical instrument called a cystoscope. This is often performed as an outpatient or office procedure under local anaesthetic and sterile precautions. Bladder cancer is often seen as an area of mucosal abnormality or a papillary or solid growth. A careful description of the cystoscopic findings (such as position of the tumour, size, appearance and number ) is necessary as it helps to guide the further management of the cancer and to risk stratify patients (20).

Although conventionally cystoscopy is performed using white light, recently there have been advances using blue light/ultraviolet light to detect a greater number of cancers. In this procedure before the cystoscopy a chemical (5-aminolaevulinic acid or hexaminolaevulinic acid) is instilled in the bladder of the patient via a catheter. Cystoscopy subsequently performed using blue light or ultraviolet light then not only

picks up the visible tumours, but also lesions in the mucosa which may have been missed by white light alone. Although the detection rate is slightly higher using this method, it can often lead to false positive results as well as adding extra cost implications (28–30).

### **1.3.3 Urine Cytology:**

Examination of voided urine to look for cancer cells (urine cytology) offers a useful adjunct to cystoscopy in picking up cancer of the bladder or urinary tract. It works on the principle that cancer cells are loosely adherent to the tumour and are often shed in the urine. Urine cytology however lacks the specificity of determining the site of the cancer (anywhere in the urinary tract starting from the kidneys through the ureters and into the bladder). This test also has low sensitivity for low-grade tumours (31–33). Most reported sensitivities for low-grade tumours are in the region of 30–60% (34). However the specificity is high for high grade tumours, in the region of 90% (35). Cytological interpretation is user dependent. The evaluation can be hampered by low cellular yield, urinary tract infections or intravesical installation of BCG. Current guidelines suggest using urine cytology as an adjunct to cystoscopy for diagnosis of bladder cancer, but its value as a first line test in haematuria clinic is limited (36).

### **1.3.4 Urinary markers:**

Several urinary marker tests have been investigated, regarding their diagnostic accuracy and possibility of complementing cystoscopy in the diagnosis of bladder cancer. Although several tests and combinations of markers have shown promising performance, their diagnostic accuracy cannot be considered sufficient to replace cystoscopy(37). Some tests which have been evaluated include fluorescence in situ hybridization (FISH), the nuclear matrix protein 22 (NMP22) and Urinary BC antigen (UBC) (38). The disadvantage of all these tests is their limitation to a simple positive or negative result as well as the fact that they are time-consuming to perform and expensive and as such they are unlikely to replace cystoscopy as a diagnostic test. A pooled analysis of predominantly cross-sectional studies yielded a sensitivity of 44% for cytology for all types of bladder cancer but higher sensitivity for immuno-cytology



(84%), fluorescence in situ hybridization (FISH) (76%), and nuclear matrix protein22 (NMP22) (68%) (39,40).

### 1.3.5 Imaging:

Bladder masses identified by diagnostic imaging such as ultrasound scan, intravenous urography, computed tomography (CT) or magnetic resonance imaging (MRI) should be confirmed with cystoscopy and histology. Imaging is much more useful in staging of the bladder cancer and identifying any hydronephrosis indicating ureteric obstruction.

Detecting extravesical extension of bladder cancer is an important feature of the bladder wall evaluation before radical cystectomy, as its presence negatively affects prognosis. Contrast-enhanced CT is reasonably accurate at this assessment and peri-vesical fat invasion on multi-detector row helical CT (MDCT) has been shown to have sensitivity and specificity of 89% and 95%, respectively (41).

Imaging helps to detect evidence of lymph node metastases in bladder cancer. MRI and CT diagnoses of positive LN are based on size criteria where nodes  $> 8$  mm or  $> 10$  mm are considered positive for round and oval nodes, respectively (42,43). Size criteria alone lack both sensitivity and specificity, because small metastatic nodes may be missed and enlarged benign nodes may be misclassified.

Imaging is also used in bladder cancer to evaluate the response of chemotherapy in advanced bladder cancer. A positive early response would provide support for continuing with chemotherapy, whereas disease progression would indicate the need for a change in therapy such as RC (44).

### 1.3.6 Transurethral Resection (TUR):

Transurethral resection of the tumour is both a diagnostic (as it provides histological samples) and therapeutic (as it removes the growth in superficial bladder cancer) tool. This is undertaken under general or spinal anaesthesia. The goal of TUR in Ta,T1 BC is to make the correct diagnosis and completely remove all visible lesions. It is a crucial procedure in the diagnosis and treatment of BC. TURBT should be performed systematically in individual steps. According to current EAU guidelines the following steps may be considered whilst performing TURBT:

- perform resection in one piece for small papillary tumours (< 1 cm), including a part from the underlying bladder wall.
- perform resection in fractions including the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area for tumours > 1 cm in diameter.
- take biopsies from abnormal-looking urothelium.
- biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder walls) are recommended when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance).
- take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.

The strategy of resection depends on the size of the lesion. Complete and correct TUR is essential to achieve a good prognosis. Sometimes separate biopsies or a second resection are undertaken for correct staging (45,46).

### 1.4 Staging and Grading:

Grading of bladder cancer indicates the aggressiveness of the tumour whereas staging denotes the extent of invasion of the cancer into the bladder wall and beyond. The most commonly adopted method of classification in staging is the Tumour Node Metastasis (TNM) classification. (table 1) (47).

**Table 1 : TNM classification of bladder cancer**

<p><b>T: Primary tumour</b>  TX Primary tumour cannot be assessed  T0 No evidence of primary tumour  Ta Non-invasive papillary carcinoma  Tis Carcinoma in situ: “flat tumour”  T1 Tumour invades subepithelial connective tissue  T2 Tumour invades muscle  T2a: Tumour invades superficial muscle (inner half)  T2b: Tumour invades deep muscle (outer half)  T3 Tumour invades perivesical tissue:  T3a: Microscopically  T3b: Macroscopically  T4 Tumour invades any of the following:  prostate, uterus, vagina, pelvic wall, abdominal wall  T4a: Tumour invades prostate, uterus, or vagina  T4b: Tumour invades pelvic wall or abdominal wall</p>
<p><b>N: Lymph nodes</b>  NX Regional lymph nodes cannot be assessed  N0 No regional lymph node metastasis  N1 Metastasis in a single lymph node &lt;2 cm in greatest dimension  N2 Metastasis in a single lymph node &gt;2 cm but not &gt;5 cm in greatest dimension, or multiple lymph nodes, none &gt;5 cm in greatest dimension  N3 Metastasis in a lymph node &gt;5 cm in greatest dimension</p>
<p><b>M: Distant metastasis</b>  MX Distant metastasis cannot be assessed  M0 No distant metastasis  M1 Distant metastasis</p>

Traditionally, bladder carcinomas have been graded according to the World Health Organization (WHO) 1973 grading of urothelial papilloma: well differentiated (G1), moderately differentiated (G2), or poorly differentiated (G3). In 2004, the WHO and the International Society of Urological Pathology (ISUP) published a new grading system that employs specific cytological and architectural criteria (48,49). The new WHO/ISUP classification differentiates between papillary urothelial neoplasms of low

malignant potential (PUNLMP) and low-grade and high-grade urothelial carcinomas. (table 2)

**Table 2: WHO grading of bladder cancer**

WHO 1973 <ul style="list-style-type: none"><li>• Urothelial papilloma</li><li>• Grade 1: well differentiated</li><li>• Grade 2: moderately differentiated</li><li>• Grade 3: poorly differentiated</li></ul>
WHO 2004 <ul style="list-style-type: none"><li>• Urothelial papilloma</li><li>• PUNLMP (papillary urothelial neoplasms of low malignant potential)</li><li>• Low-grade papillary urothelial carcinoma</li><li>• High-grade papillary urothelial carcinoma</li></ul>

## 1.5 Treatment of bladder cancer:

Bladder cancer is a heterogeneous disease, with 70% of patients presenting with non-muscle invasive (NMI or superficial tumours), which tend to recur but are generally not life threatening, and 30% presenting as muscle-invasive disease (MIBC) associated with a high risk of death from distant metastases (20).

### 1.5.1 Treatment of non-muscle invasive (NMI) bladder cancer:

The initial treatment for superficial (stages Ta, T1, or tumours in situ [Tis]), bladder cancer is transurethral resection of the bladder tumour. This resection should include muscularis propria, especially if the lamina propria is affected or the tumour is high grade. When the transurethral resection shows lamina propria invasion a repeat resection should be performed to rule out muscularis propria invasion. Moreover, the tumour is often under staged by initial resection. The likelihood that muscle-invasive

disease is detected by second resection of initially T1 tumour ranges from 4-25%, and it increases to 45% if there was no muscle in the initial resection (50).

50–70% of these NMI tumours will recur and approximately 10–20% will progress to muscularis propria invasive disease (T2–4) (51). The high rate of recurrence is the feature of bladder cancer that makes follow-up a crucial component in effective management. After transurethral resection of the tumour, patients should have cystoscopic follow up that needs to be tailored to the stage and grade of the tumour. To facilitate treatment recommendations, it is important to categorise patients into risk groups. Based on available prognostic factors and in particular data from the EORTC risk tables, the EAU Guidelines panel recommends stratification of patients into three risk groups for superficial bladder cancer i.e. low, intermediate and high risk (table 3) (52).

**Table 3 :Risk stratification of superficial BC**

<b>Risk group stratification</b>	<b>Characteristics</b>
Low-risk tumours	primary, solitary, Ta, G1 (PUNLMP, LG), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high-risk)
High-risk tumours	Any of the following: <ul style="list-style-type: none"> <li>•T1 tumour</li> <li>•G3 (HG) tumour</li> <li>•CIS</li> <li>•Multiple and recurrent and large (&gt;3cm) Ta G1G2 tumours (all conditions must be presented in this point)</li> </ul>

Upper tract imaging should be done, in selected patients, every 12–24 months to establish whether a transitional cell carcinoma is present in the renal collecting system

or ureters, because lifetime risk for the development of this upper tract tumour after a diagnosis of bladder cancer is about 5% (23).

Agents used for intravesical therapy are the immunomodulators such as BCG and interferon alpha, and chemo therapeutic agents such as mitomycin, doxorubicin, thiotepa and gemcitabine. Immediately after transurethral resection, one dose of intravesical chemotherapeutic agent is effective for the reduction of disease recurrence within the first 1–5 years after resection, the commonly used agent being mitomycin (46). Patients with high risk disease (multifocal Tis, high grade Ta or T1 tumours with associated Tis, and tumours that rapidly recur after transurethral tumour resection) should be regarded as candidates for further adjuvant courses of intravesical drug therapy. Such regimens generally consist of an induction course of BCG once every week for 6 weeks, and then, usually, intermittent maintenance cycles of one installation every week for 3 weeks. This 3-week course is repeated every 4–6 months for up to 2 years.(46,53). In the trials with BCG maintenance, there was a 32% reduction in the risk of recurrence. Two meta-analyses have demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression (54,55).

### **1.5.2 Treatment of muscle invasive bladder cancer with cystectomy:**

The standard treatment for bladder cancer invading the muscularis propria (either at presentation or when the disease progresses in spite of intravesical chemotherapy) is radical cystoprostatectomy for men and anterior exenteration including the bladder, urethra, uterus, and ventral vaginal wall for women. In men, a urethrectomy should be done when invasion of the prostatic stroma or concomitant Tis in the urethra is evident. After radical cystectomy, urinary diversion is performed in either a non-continent or continent fashion, using a segment of bowel. The simplest form is the non-continent ileal conduit. A continent urinary diversion can be either an orthotopic neobladder or an abdominal pouch. In both diversions a segment of bowel is made into a detubularised spherical form, with continence in the abdominal pouch relying on a catheterisable continent stoma and on the patient's striated urethral sphincter in the orthotopic neobladder (1,23).

## 1.6 Radical cystectomy; morbidity and mortality:

Radical cystectomy (RC) and urinary diversion is the gold standard treatment for muscle-invasive urinary bladder cancer as well as for non-muscle invasive disease that is refractory to intravesical treatment. This is also amongst the most extensive urological surgical procedures. Despite improvements in practice, technique and process of care, RC is still associated with significant complications, including death, with wide variability in reported postoperative morbidity and mortality rates ranging from 19% to 64% and 0.8% to 8.3%, respectively (56,57).

Kim et al in a recent series with a cohort of 50,625 patients who underwent RC found that the overall complication and mortality rates were 28.8% (14,584) and 2.1% (1081), respectively after surgery(58). The authors investigated the common causes of morbidity in this cohort and found 17% of the patients had postoperative digestive or bowel related complications (such as ileus, bowel injury and anastomotic leak etc.), while 4% had postoperative infections (including chest infection), 4% had cardiac complications, and 4% had wound complications. Although lower morbidity and (perioperative) mortality have been observed by surgeons and in hospitals with a higher caseload and therefore more experience, it still remains significantly high (59,60).

RC has come a long way since it was originally described in 1949 by Marshall and Whitmore who described the basic surgical principles of radical cystoprostatectomy (61). In 1987, following the neuroanatomic mapping of the pelvic plexus by Schlegel and Walsh, nerve-sparing cystectomy became a surgical option that allowed for preservation of sexual function. Over the years it has become evident that surgical approach (ie, open vs minimal access) does influence outcomes, complications and recovery rates. Minimally invasive surgery requires smaller incisions, reduces analgesic use, reduces bowel handling, and decreases blood loss (62). As such, laparoscopic RC may decrease postoperative complications, pain, and LOS compared with open surgery. However, it is unclear whether laparoscopic resection provides better outcomes than open surgeries (63). Robot-assisted surgical approaches are

increasingly utilized in urology but the exact benefit over open surgery remains unclear (63). Limited evidence suggests similarities in oncology and morbidity, with reduced blood loss and analgesic use, although operating times are significantly longer (64,65). Procedure-specific RCTs that incorporate cost analysis, recovery rates, and quality of life (QoL) outcomes are needed to assess the advantages of robotic assisted laparoscopy.

While the variability of peri-operative mortality may be explained by several factors, including patient characteristics (age and baseline medical conditions) disease characteristics (nodal involvement and lymphovascular invasion) and surgical technique (that is open or minimally invasive and conduit or orthotopic neobladder formation) the quality of postoperative care is equally important. In this respect, recognition of adverse events and a prompt management of these complications influence peri-operative mortality (66). ‘Failure to rescue’ is a term often coined for this patient group who died after a treatable post-operative complication (67). It is hypothesized that the ability of a hospital to successfully treat (rescue) a patient who suffers a complication is strongly related to the quality of care provided, whereas the occurrence of the complication is more closely related to the patient’s underlying risk (68).

## **1.7 Enhanced recovery and its role in radical cystectomy:**

The foundations of enhanced recovery programmes (ERPs), also known as enhanced recovery after surgery or fast-track surgery, were laid down by Kehlet in the 1990s (69). The principles of these peri-operative strategies are to use a multidisciplinary approach to minimising morbidity. This revolves around a team approach, which includes surgeons, anaesthetists, nurses, physiotherapists, stoma therapists, dieticians and, most importantly, requires active participation from the patient and family (70). They minimize physiological stress caused by surgery and promote recovery. Significant reductions in hospital stay have been shown without increased complications or readmissions (71,72). ERPs decrease ileus, prevent loss of lean body mass, reduce atelectasis, promote oxygenation and preserve cardiovascular response to exercise after surgery. ERPs have spread from colorectal surgery to other surgical specialities. Much



of the data from ERPs are from colorectal surgery however there is an increasing number of publications in the urological literature from UK centres describing this experience and adding on to an ever increasing evidence base (73,74).

Components of a typical ERP in Radical cystectomy as per McGrath et al are as follows: (75)

- Pre-assessment is used to inform participants, to highlight and overcome psychosocial barriers to early recovery or discharge, and to trigger medical optimization if required. Involvement of stoma nurses and oncology nurses to prepare patients for urostomy bags is crucial at this stage.
- Admission on the day of surgery and continuing clear fluids till up to 4 hours before surgery. Some centres prefer carbohydrate loading for a few days leading up to surgery. Traditional bowel preparation has been shown to confer no advantage in patients undergoing RC (76).
- Prevention of intraoperative hypothermia by careful temperature monitoring, use of “bear huggers” and warmed fluid infusion. This reduces sympathetic responses, cardiac arrhythmias and wound morbidity.
- High inspired oxygen level during the perioperative period increases intestinal oxygenation, reduces wound infection, and decreases postoperative nausea and vomiting.
- Goal-directed fluid therapy with oesophageal doppler allows precise fluid balance, and this reduces surgical complications and shortens length of hospital stay(77).
- Optimized pain relief allows early mobilization and opiate-sparing analgesia reduces nausea, vomiting and sedation. Epidural analgesia, is an important component of ERPs.
- Traditional management after surgery has involved resting the gastrointestinal tract until it regains its function. However, studies have confirmed the safety of

early postoperative feeding in elective colorectal surgery and such findings have been reported in patients undergoing RC.

- Early mobilisation and early feeding are also an important part of ERP.
- Minimally invasive surgery, such as laparoscopic and robotic assisted RC, where feasible is also helpful in enhancing recovery.

Patients undergoing radical cystectomy are a particularly applicable group for ERPs, as the procedure is still associated with significant morbidity and a prolonged inpatient stay by comparison with other operations. Implementation of an ERP for radical cystectomy in one UK centre reduced postoperative stay by 3 days, with no effect on morbidity or mortality (78).

The major focus of the ERP literature to date has been on peri and post-operative care. Improving the outcome for these participants, however, could begin long before the participant arrives at the preoperative assessment visit. A surgical procedure such as radical cystectomy is associated with a catabolic state, similar to prolonged endurance exercise and as such it is plausible that the outcome from surgery is more likely to be favourable if the patient has been “pre-conditioned” to undergo the stress of surgery.

## **1.8 Preoperative fitness as an independent predictor of outcome in Radical Cystectomy (RC):**

Clinicians often risk stratify patients before major surgery based on their age, weight and comorbidities to attempt to predict their post-operative morbidity and mortality. Methods (such as ASA grading) although commonly used have its limitations including largely being a subjective assessment of the patient's fitness for surgery(79). Cardiopulmonary exercise testing (CPET) is a clinical tool used to objectively measure the performance of the cardiorespiratory system and assess an individual's functional capacity (fitness level). CPET is a graded exercise challenge which, through non-invasive measurements of gas exchange through analysis of exhaled air, ECG trace

observation, and analysis of heart rate, blood pressure, and peripheral oxygen saturation, allows the cardiovascular and respiratory systems to be studied under the controlled 'stress' of exercise (80). Although alternative methods of assessment of cardiorespiratory fitness such as 6 min walk, shuttle walking and stair climbing have been proposed, CPET provides the most objective assessment of fitness(80,81). Various CPET assessment parameters are commonly used, including VO<sub>2</sub> max (VO<sub>2</sub> max), AT (anaerobic threshold), V<sub>E</sub>/V<sub>O<sub>2</sub></sub> and V<sub>E</sub>/V<sub>CO<sub>2</sub></sub> (ventilatory equivalent of oxygen and carbon dioxide respectively).

Almost two decades ago, Older and colleagues identified an association between low functional capacity determined by CPET, and poor patient outcome following non-cardiopulmonary surgery (82). In their study they demonstrated that a low AT was associated with an increased mortality rate in elderly patients following surgery. In general, patients with an AT <11 ml/kg/min had a higher rate of cardiovascular mortality (18%) than those with an AT >11 ml/kg/min (0.8% p <0.001) (83). Assessing 843 patients undergoing major colorectal surgery, radical nephrectomy and cystectomy, Wilson et al. concluded that in this patient cohort (aged >55 years), an AT of 11 ml/kg/min or less and a V<sub>E</sub>/VCO<sub>2</sub> of 34 or more had a sensitivity of 88% and a specificity of 47% for hospital mortality (84). Based on this, and subsequent published literature, CPET-derived variables have been increasingly adopted as objective measures of fitness prior to surgery, particularly within the National Health Service (NHS) in the UK. This information is used to inform operative decisions, choice of perioperative management and to discuss risk with patients (85). In a recent literature review, in data spanning 2275 patients over 12 studies, Grocott et al demonstrated that CPET variables are reliably associated with outcome measures such as LOS and morbidity and mortality following major surgery. CPET also has utility in identifying the high-risk surgical patient. However, the optimal predictor of high risk appears to differ between surgery types, with AT shown to be the best indicator of higher risk patients for major intra-abdominal surgery and VO<sub>2</sub> max associated with outcome following upper GI surgery (80).

Radical cystectomy (RC) with pelvic lymph node dissection and ileal conduit or orthotopic bladder reconstruction remains the 'gold standard' surgical treatment for muscle-invasive bladder cancer (86). However, RC is associated with high rates of

morbidity (19–64%) and mortality (0.8-8.3%) (87–91). The average length of stay across the UK after radical cystectomy is 14-17 days (92). A recent study of 82 patients undergoing radical cystectomy for bladder cancer demonstrated impaired preoperative cardiopulmonary reserve was related to major morbidity, prolonged LOS (length of stay) and increased use of critical care resource after RC(93). They concluded that anaerobic threshold (AT) remained as the only significant independent predictor variable for the presence or absence of major postoperative complications (odds ratio 0.74, 95% CI 0.57–0.97; P = 0.03). When the optimal predictive value of AT of 12 mL/min/kg was used as a fitness marker, there was a significant relationship between fitness and LOS (median LOS: ‘unfit’ 22 days vs ‘fit’ 16 days; HR 0.47, 95% CI 0.28–0.80; p= 0.006).

Based on these studies it appears that CPET variables can help to risk stratify patients undergoing radical cystectomy. Preoperative recognition of patients with a reduced preoperative AT, would firstly warn clinicians of the need to be vigilant in a high-risk population. Secondly, it would improve rationalisation of limited critical care resources and allow the institution appropriate postoperative care pathways to promote expedient recognition and treatment of complications when they occur, conforming to the ‘failure to rescue’ principle. It is also plausible that preoperative exercise could improve CPET variables in this group of patients.

## 1.9 Role of ‘Prehabilitation’ in the context of radical cystectomy:

Interventions to improve post-surgical recovery have usually been intra and postoperative, which for high-risk populations might be too late (94). The preoperative period might be a better time to engage patients in enhancing physical fitness, that is often referred as , ‘prehabilitation’ (95,96). Pre-surgical exercise interventions are feasible, safe, improve function, and quality of life, but little is known of their effects on physical fitness measured by cardiopulmonary exercise testing (CPET) (97,98). Identifying prehabilitation programmes to optimize preoperative fitness is therefore a priority. O’Doherty et al in their systematic review of 10 studies analysed the role of ‘prehabilitation’. They commented based on their review that although there is a lot of variations in the type of exercise prescribed in the preoperative period, preoperative

aerobic exercise training seems to be generally effective in improving physical fitness in patients awaiting intra-cavity surgery and appear to be feasible and safe (98). There does not appear to be any consensus however on the optimal duration and intensity or the type of exercise that should be prescribed as part of 'prehabilitation'. It appears plausible that benign conditions merit longer duration of preoperative optimisation where as in malignant conditions a balance has to be struck between the benefits of preoperative exercise versus the risk of cancer progression. A period of 4-6 weeks appears to be effective and safe based on several studies (99–101).

Till date there is no evidence on the role of prehabilitation or preoperative exercise in patients undergoing RC.

## Chapter 2: Methods and study design

### 2.1 Aims of the study

PrEPARe (Preoperative Exercise Protocol to Aid Recovery) for Radical Cystectomy was a feasibility study to explore the role of preoperative fitness, as determined by CPET, in contributing to an enhanced recovery following radical cystectomy. The aims of the study were:

- To explore the feasibility outcomes to form the basis of a larger RCT. The principal aim was to look at recruitment rate, reasons for non-recruitment, attrition and dropout rates. It was also designed to see if patients who agreed to participate would tolerate and comply with a preoperative programme of aerobic exercise interval training before cystectomy.
- A secondary aim was to explore any possible improvement in exercise tolerance and cardio-respiratory fitness after a short period of aerobic exercise regimen before major cancer surgery in an elderly group of people.
- Preliminary data were collected to explore any possible trends in enhancing recovery and improving post-operative outcome measures after RC as a result of preoperative exercise. This would help in sample size calculations for a future large scale definitive RCT.

## 2.2 Study Protocol

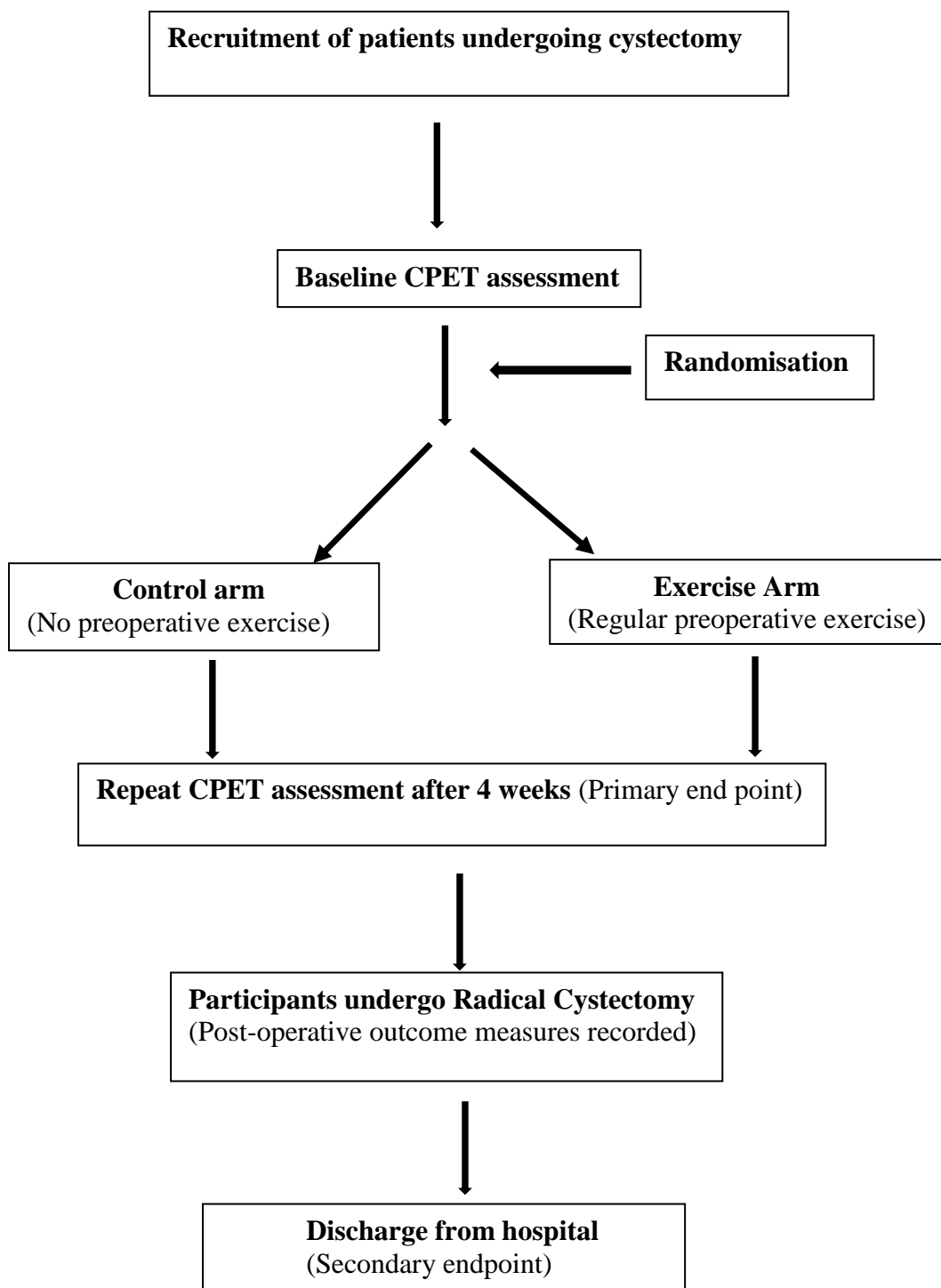
- Ethics approval was obtained from the East of England regional ethics committee (ref no.11/EE/0127).
- Following ethics approval 60 patients were recruited to this study. Patients who had been listed for radical cystectomy (RC) for bladder cancer from the urology specialist multidisciplinary team meeting at the Norfolk and Norwich University Hospital, were identified as prospective participants. As this was a feasibility study there was no formal sample size calculation but we aimed to recruit 60 patients (30 in each group), in accordance with recommendations for feasibility studies as laid down by COSORT (102,103).
- After the patients had their initial consultation with their respective consultant urologist and were made aware of the decision to offer them radical cystectomy, they were approached by the chief investigator (SB) and were informed about the study. They were supplied with the patient information sheet and participants were given at least 24 hours to think about the information supplied and clarify any doubts before they decided whether or not they wanted to participate in the study. If they declined to take part the reason for nonparticipation was also ascertained.
- Once they agreed the participants underwent a baseline CPET assessment. The participants were then subsequently randomised to receive either a four week intensive exercise training according to a preset exercise protocol (exercise arm) or the standard treatment (control arm).
- **Randomisation** was carried out using a pre-generated sequence, generated using N-Query software, (30 patients in each arm) which was kept with a secretary who was not part of the trial (to ensure blinding). After initial assessment she was informed of the participants' initials and sequence and group allocation were obtained. When participants were approached for recruitment it was made clear to them that the role of the study (PREPARE for

cystectomy) was to investigate the possible relationship between preoperative fitness and post-operative outcome and also the ability to improve fitness in a short time span in patients due to undergo major surgery. It was also made clear that, as far as the investigators were aware, trial participants would not be knowingly advantaged or disadvantaged in anyway by either being in the control or exercise arm.

- At the completion of the four week period participants from both group underwent further CPET assessment to assess whether there were any differences in the CPET parameters. The participants then subsequently underwent radical cystectomy as treatment for their bladder cancer.
- Post operatively these patients were monitored and their post-operative course charted, including time of discharge from HDU, need for inotropic support, time to opening bowel, tolerating diet, mobilising and length of stay in hospital (LOS). The complications in the post-operative period were recorded according to the Clavien classification.



## 2.2.1 Flow chart of the study protocol



*Figure 1: Study protocol*

## 2.2.2 Exercise protocol

Participants who were randomised to the exercise arm were invited to attend an exercise physiology laboratory at the University of East Anglia for supervised exercise sessions comprising 60 min of aerobic exercise based on their background fitness level as determined by the CPET analysis (intensity of 70-80% of maximum heart rate achieved in the incremental cycle ergometry test). They were invited for these sessions twice a week for four weeks.

### **A typical exercise session would consist of the following**

#### **Warm Up:**

A typical warmup of 5-10 min comprised of freehand exercise of patients' choice such as jogging at one place / paced walking in the exercise physiology lab.

#### **Cycle ergometry exercise:**

Sessions comprised aerobic exercise interval training on a cycle ergometer (Monark 824E; Varberg, Sweden). This is a static cycle/ bike where the intensity/effort of cycling is increased by sequential adding of weights to the flywheel in batches of 500gms. The aim was 6 x 5 min intervals at 70-80% of maximum heart rate (achieved in the incremental cycle ergometry test or CPET). Each interval was followed by a 2.5 min rest period. A typical exercise session lasted for an hour. Following a 5-10 minute warm-up against low resistance, patients performed 6 x 5 min intervals at a target perceived exertion of 13-15 ('somewhat hard' to 'hard'), with 2.5 min interpolated rest periods. They were instructed to maintain a steady pedalling cadence (pedal rate) of 50-60 rev/min on the exercise bike during the aerobic intervals and the exercise programme was progressed by gradually adding more load to the flywheel to maintain the target perceived exertion.

Heart rate and ratings of perceived exertion according to Borg RPE scale (fig.2), were recorded in the final minute of each interval. Rate of perceived exertion or RPE is a simple measure, or scale denoting exercise intensity or physical strain (104). The RPE functions as a perceptual range from extremely light exercise to extremely hard

exercise. The scale numbers from 6 to 20 and often corresponds to a heart rate of 60 to 200 beats per minute. Descriptors are given to feelings of intensity at each number (very light, somewhat hard, hard, very hard, etc.). Exercise intensity was progressed at an appropriate rate for each individual's level of exertion.

**Cool Down:** A typical cool down period of 5-10 min was allowed after the cycling exercise. Patients were instructed to gradually slow down their pedaling rate till complete stoppage.



**Figure 2: Borg RPE scale**



**Figure 3: Patient undergoing CPET**



**Figure 4: participants during a typical exercise session**

### Standard care and control group:

The participants who were randomised to the control group were advised to carry on with their lifestyles in the “usual” way. They were neither encouraged nor discouraged to take on self-directed exercise, however if any participant in the control group did undertake any physical exercise (which was not routine for them) then that was recorded.

Post –operatively after cystectomy, participants from both the exercise and control group had same levels of care which included planned admission to the same HDU for the immediate post-operative period and step down ward, patients were looked after by the same group of nurses and doctors who would have been otherwise involved in their care. The doctors and nurses looking after the participants were blinded to their group allocation.

### 2.2.3 Exclusion and inclusion criteria

The patients eligible for the study were identified from the uro-oncology multidisciplinary meeting at the Norfolk and Norwich University Hospital NHS Foundation Trust. This hospital is a tertiary referral centre in the East of England and has a wide catchment area including local district general hospitals namely James Paget Hospital, Queen Elizabeth Hospital, Ipswich Hospital and West Suffolk hospital. The Norfolk and Norwich University hospital covers an estimated total population of 1.2 million people.

#### Inclusion criteria:

- Those patients who were listed for radical cystectomy for treatment of bladder cancer were eligible for recruitment to the study. The decision whether or not to offer radical cystectomy to a patient after staging investigations for bladder cancer were completed, was taken at the weekly multidisciplinary meeting in the urology department at the Norfolk and Norwich Hospital. Usually radical cystectomy is offered to patients who have organ confined muscle invasive bladder cancer or high risk non muscle invasive bladder cancer (HRNMIBC) refractory to intravesical treatment and are fit for the intervention.
- Patients who underwent neo-adjuvant chemotherapy before radical cystectomy were also eligible for the study. Patients who underwent neo-adjuvant chemotherapy only entered the trial at least two weeks after completion of their chemotherapy regimen.
- Patients are often offered different surgical approaches such as laparoscopic or open cystectomy as well as different methods of urinary diversion such as standard ileal conduit formation or orthotopic neobladder formation. Patients' eligibility to participate in this trial was not limited by the choice of surgery that they were offered.

## Exclusion Criteria:

- Patients who were offered urinary diversion (such as standard ideal conduit) for benign disease (such as interstitial cystitis or painful bladder syndrome) were excluded from the study.

## 2.3 Outcome measures recorded

### 2.3.1 Feasibility parameters:

The main aim of this study was to assess feasibility of preoperative exercise training in patients undergoing radical cystectomy for bladder cancer. As such feasibility parameters such as recruitment rate and factors influencing recruitment, willingness to be randomised, and adherence of the participants in terms of exercise protocol, adverse events during CPET assessment or during exercise sessions and attrition during the trial were recorded. This would help to inform the design of a future RCT with the aim of exploring the role of preoperative exercise in enhancing recovery after radical cystectomy.

### 2.3.2 Preoperative outcome measures:

#### CPET assessment

CPET is a graded exercise challenge which, through non-invasive measurements of gas exchange at the mouth, ECG trace observation, and analysis of heart rate, blood pressure, and peripheral oxygen saturation, allows the cardiovascular and respiratory systems to be studied under the controlled 'stress' of exercise. This allows inspection of the integrated oxygen delivery system when the demand for oxygen is high and the system is required to function near to its maximum capacity. Despite requiring a



moderate to high level of exertion, CPET is well tolerated by patients and is safe to conduct on most patient cohorts (80).

Before the start of CPET assessment a detailed medical history of the patient was obtained. Height, weight and resting blood pressure were also recorded.

CPET was conducted on an electronically-braked cycle ergometer (Excalibur Sport, Lode ® Netherlands). Initial rest phase (approximately 2 min) was employed to establish baseline values, followed by an unloaded cycling (0 W) phase to allow the patient to become familiar with the cycling motion and to reduce the influence of the lag present between increased work rate (WR) and the oxygen uptake ( $\text{VO}_2$ ) response. Following this, the incremental exercise phase began. A ramp protocol (20 watt /min, unless the patient was very unfit in which case a slightly lower intensity of 10 watts /min) was used, during which the set WR was increased linearly with time, with a corresponding increase in the intensity of the exercise. Participants were encouraged to continue cycling (at least at 50 rev/min speed) to volitional exhaustion or until a plateau in oxygen consumption was observed. Heart rate and 12 lead ECG were recorded continuously by electrocardiogram (Cardioperfect<sup>®</sup>, Welch Allyn USA) and perceived exertion (Borg RPE Scale) were assessed at 2 min intervals.

Upon test completion, a recovery period of low intensity exercise was performed to encourage maintenance of venous return, thus reducing the risk of brisk blood pressure reduction and associated light-headedness. The patient was observed throughout recovery until physiological variables, including heart rate, blood pressure, ventilation, and oxygen saturation, were close to baseline levels and any exercise induced ECG changes had resolved. All CPET assessments were carried out under medical supervision with at least two staff members being present in the exercise physiology lab at all times till the completion of the test. Protocol dictated that the test should be stopped if the patient experienced any adverse symptoms (e.g. chest pain, dizziness, or severe breathlessness) or if the physiological data indicated a potential adverse event (e.g. ECG abnormalities, substantial blood pressure changes). A complete list of contraindications is listed in the protocol ( appendix 2)

Initially the following parameters were measured both in the control and exercise (intervention) arm at the physiology lab.

- Maximal oxygen consumption ( $\text{VO}_2$  max)
- Minute ventilation
- Anaerobic threshold
- $\text{VO}_2$  / power slope
- $\text{O}_2$  pulse

After the 4-week intervention these parameters were calculated again to assess if there had been any change. The control arm also underwent a similar test at the end of the 4-week period to control for order or practice effect. A detailed description of these parameters measured is as follows:

### **Maximal oxygen consumption ( $\text{VO}_2$ max) / peak $\text{VO}_2$**

$\text{VO}_2$  max or peak  $\text{VO}_2$  (maximal oxygen consumption or aerobic capacity) is the maximum capacity of an individual's body to transport and use oxygen during incremental exercise, which reflects the physical fitness of the individual (105). Accurately measuring  $\text{VO}_2$  max involves a physical effort sufficient in duration and intensity to fully tax the aerobic energy system. In general, clinical and athletic testing, this usually involves a graded exercise test (either on a treadmill or on a cycle ergometer) in which exercise intensity is progressively increased while measuring ventilation and oxygen and carbon dioxide concentration of the inhaled and exhaled air.  $\text{VO}_2$  max is reached when oxygen consumption remains at steady state despite an increase in workload (106,107).

Maximum Oxygen uptake ( $\text{VO}_2$  max), reflecting the upper limit of the body's aerobic functioning, is the most widely used parameter characterizing the effective integration of the central nervous, cardiopulmonary, and metabolic systems. Its quantification (typically by using a cycle ergometer or treadmill) requires oxygen uptake ( $\text{VO}_2$ ) to reach a value such that further increases in work rate result in no further (or trivially

small) increases in  $\text{VO}_2$  (i.e., a “plateau” is attained). Such a  $\text{VO}_2$  plateau has been viewed as the best criterion for establishing  $\text{VO}_2$  max. Although in elite athletes  $\text{VO}_2$  max is attainable in the non-trained common subjects (which would include elderly cancer sufferers) often a “system-limited” peak oxygen uptake (peak  $\text{VO}_2$ ) value, rather than a  $\text{VO}_2$  max, is reported.

However, the advent of continuous work rate tests, where the work rate is increased every 1 to 3 min (which is the method of determining peak  $\text{VO}_2$  in the current study), largely replaced the progressive, constant-load format (108). Concern had been expressed whether the  $\text{VO}_2$  max attained from these tests was as high as those from the “traditional” discontinuous protocol. However, a number of groups found no difference in  $\text{VO}_2$  max between incremental (i.e., progressively increasing work rate every 2 min) and discontinuous (where discrete square waves of different work rates are separated by periods of rest) constant work rate treadmill tests (109,110). Available evidence suggests that “end-exercise” plateaus in  $\text{VO}_2$  may only be evident in as little as ~50% of the incremental treadmill tests (110,111). In the published literature often the values of Peak  $\text{VO}_2$  and  $\text{VO}_2$  max are used interchangeably as evidence has pointed out that provided the subject has given maximal effort these two values are often same (112). We have used the term Peak  $\text{VO}_2$  and  $\text{VO}_2$  max interchangeably to indicate maximal oxygen consumption at steady maximal work rate.

## Minute ventilation

Minute ventilation (respiratory minute volume, or flow of gas) is the volume of air inhaled (inhaled minute volume) or exhaled (exhaled minute volume) from a person's lungs in one minute. Minute volume is calculated by taking the tidal volume (volume of air per breath) and multiplying it by the respiratory rate (the number of breaths per minute). The higher the minute volume the more carbon dioxide ( $\text{CO}_2$ ) the person is releasing. It is an important parameter the anesthetists' measure while the patients are on ventilator either during or after surgery (113).

## Anaerobic threshold (AT):

AT is the point above which the muscles derive their energy mainly from anaerobic rather than aerobic sources during exercise. The body can only operate above this threshold for a short period of time, such as when sprinting, before lactic acid builds up in the muscles.(114) When performing graded exercise, the anaerobic threshold (AT) is an estimate of the onset of metabolic acidosis due to an oxygen supply: demand imbalance. Numerically it is presented as the rate of oxygen consumption ( $\text{VO}_2$ ) at which lactic acid starts to accumulate. This is seldom invasively measured but is usually taken as the time at which the patient starts to exhale increasing amounts of carbon dioxide to compensate for a buildup of lactic acid and resulting metabolic acidosis. The AT occurs at about 50–60% of  $\text{VO}_2$  max in normal individuals but has a range of 30–80%. It is a well-defined physiological point that can be measured in most patients. A low pre-operative AT has been shown to correlate with postoperative mortality (115). Although there is no clear agreement on the best single predictor of outcome, thresholds of peak oxygen consumption ( $\text{VO}_2$  peak / $\text{VO}_2$  max) of 15 ml /kg/min and an oxygen consumption at the anaerobic threshold (AT) of 11 ml/kg/ min have been shown to discriminate between higher and lower risk patients in non-cardiac surgery (80). There are different methods of calculating AT ,we used the Wasserman method (116). This was derived using the ventilatory slope (and is characterized by a disproportionate increase in  $V_E/\text{VO}_2$  without an increase in  $V_E/\text{VCO}_2$  values. 2 independent assessors (JS and GC) looked at individual gas exchange data to arrive at a consensus value for AT for each participant.

## Oxygen pulse:

This parameter approximately equates to stroke volume and may reflect cardiovascular disease or ventilator constraint. It is measured as  $\text{VO}_2$  /Heart Rate.

## **VO<sub>2</sub> / power slope:**

This represents the relationship between oxygen uptake and work rate (in watts). It is reduced in any condition that reduces blood flow to the periphery and is not affected by obesity.

### **2.3.3 Post-operative outcome measures:**

#### **Time spent in HDU**

Initially after cystectomy all patients in our unit are transferred to the high dependency unit (HDU) for the first post-operative night. This is done to facilitate one-to-one monitoring of the patient and pick up any early signs of deterioration. Once the patient has stabilised he or she is returned to the general ward. Time spent in HDU is a good indicator of initial post-operative recovery (117,118).

#### **Need for inotropic support**

Some patients after cystectomy need inotropic support to maintain their blood pressure, common examples being noradrenaline and epinephrine. Very often the amount of inotropic support needed, if at all, depends on the physiological reserve to withstand major surgical intervention and the amount of blood loss (119,120).

#### **Chest infection and post-operative ileus:**

Chest infection and post-operative ileus are the two most common post-operative complications after cystectomy and any other major abdomino-pelvic surgery (121,122). The presence or absence of these complications, often dictate the length of post-operative stay in the hospital. We recorded prospectively if the patients had any of these post-operative complications.

## Clavien –Dindo complications:

Classification of post-operative surgical complications can be challenging. Any deviation from the normal post-operative recovery is regarded as a complication. Clavien et al first published a system in which complications were systematically graded, and that is the basis of the *Clavien system* (123). In 2004, Dindo et al reevaluated and modified their own criteria to increase its accuracy and applicability in the surgical community (124). This method of classification of surgical complications has been widely accepted and validated in the domain of urological surgery(125–127). Several authors while reporting their respective series of experience with radical cystectomy have used this method to list their complications (128–130). A brief description of this method of classification is given in the table (table 4) below. In the current cohort of participants any such deviation from usual post-operative recovery was recorded.

**Table 4: Clavien-Dindo Classification of surgical complications**

<b>Grades</b>	<b>Definition</b>
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	Intervention not under general anesthesia
Grade III-b:	Intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management.
Grade IV-a:	Single organ dysfunction (including dialysis)
Grade IV-b:	Multi-organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

### Length of hospital stay (LOS):

Time spent in the hospital after surgery is often used as a tool to measure post-operative recovery(131) . Although various factors such as the help available at home, patients' confidence with managing urostomy bags, catheters and drainage bags might also influence when the patient is discharged from hospital after cystectomy.

### **2.3.4 Qualitative outcome measures:**

There are many definitions of a focus group in the literature. Some authors define a focus group as a group of persons who are invited by researchers to share their personal experience while participating in a group discussion (132). The authors further state that focus groups are a form of group interviewing that involves a number of people at the same time, with emphasis on the questions and responses between the researcher and interviewees. Other authors define focus groups as one who relies on the conversation and interaction within the group based on the topic introduced by the researcher. Focus groups have been documented to be an excellent method for data collection throughout the literature (133–135). Focus groups also tend to be useful in obtaining information on collective views, and deeper discussion of various viewpoints on a specific topic. They are also extremely useful in facilitating discussions of participants' experiences and values. Discussions are generally very rich.

#### **Focus group meetings:**

Thirteen participants from the intervention group were purposefully sampled to participate in a total of 3 focus group meetings (at the end of the intervention and at least 6-8 weeks following surgery) based on their specific consent. All focus groups were conducted by Miss Kelly Semper (qualitative research analyst, University of East Anglia) and took place in private seminar rooms located at the Norwich and Norfolk University Hospital. For analysis purposes the focus groups meetings were audio recorded and this was also made clear to all participants on all information sheets prior to consenting.

These focus groups aimed to gauge feedback on the intervention such as feasibility and enjoyment from the view point of participants. These focus groups were also aimed to:



- Consider which elements of the protocol were perceived as being most and least helpful.
- Explore the participants' perception of the effect that they think the exercise has had on their well-being and quality of life after surgery
- Uncover any potential barriers or problems associated with the exercise protocol
- Explore how this protocol could be refined and enhanced for use in larger scale interventions.

Broad thematic analysis was used to elucidate experiences and views. The data was used to thematically sort and chart key themes and experiences.

## 2.4 Statistical analysis

### Quantitative analysis

Data collection and analysis was computed using SPSS ( SPSS Inc, IBM) .The data was tested for normality of distribution ( using Kolmogorov-Smirnov test) .CPET data such as VO2 max and AT were found to be normally distributed as was demographic data and hence parametric tests were applied ( ANCOVA to compare variation in between groups) . Chi -Square test was done to compare categorical data. Post-operative stay in the HDU and length of stay in hospital were not normally distributed and hence non parametric tests were used.

The significance level adopted was  $P < 0.05$ . Data is presented as the mean  $\pm$  standard deviation.

## Qualitative analysis:

Thematic analysis is a method for identifying, analysing and reporting patterns within the data through careful reading and rereading of the data (136). This offers a flexible approach to analysing the data with the potential of gaining a rich and detailed account of patients' experiences. Braun & Clarke (2006) propose 6 steps in thematic analysis;

- 1) Familiarizing oneself with the data by transcribing the data, reading and re-reading the data, noting down initial ideas.
- 2) Generating initial codes
- 3) Searching for themes;
- 4) Reviewing themes: generating a 'map' of the analysis;
- 5) Defining and naming themes;
- 6) Producing the report: - the final opportunity for analysis

These basic steps were utilised when analysing the focus group meeting data and deriving emergent themes.

# Chapter 3: Results

## 3.1 Feasibility Outcomes

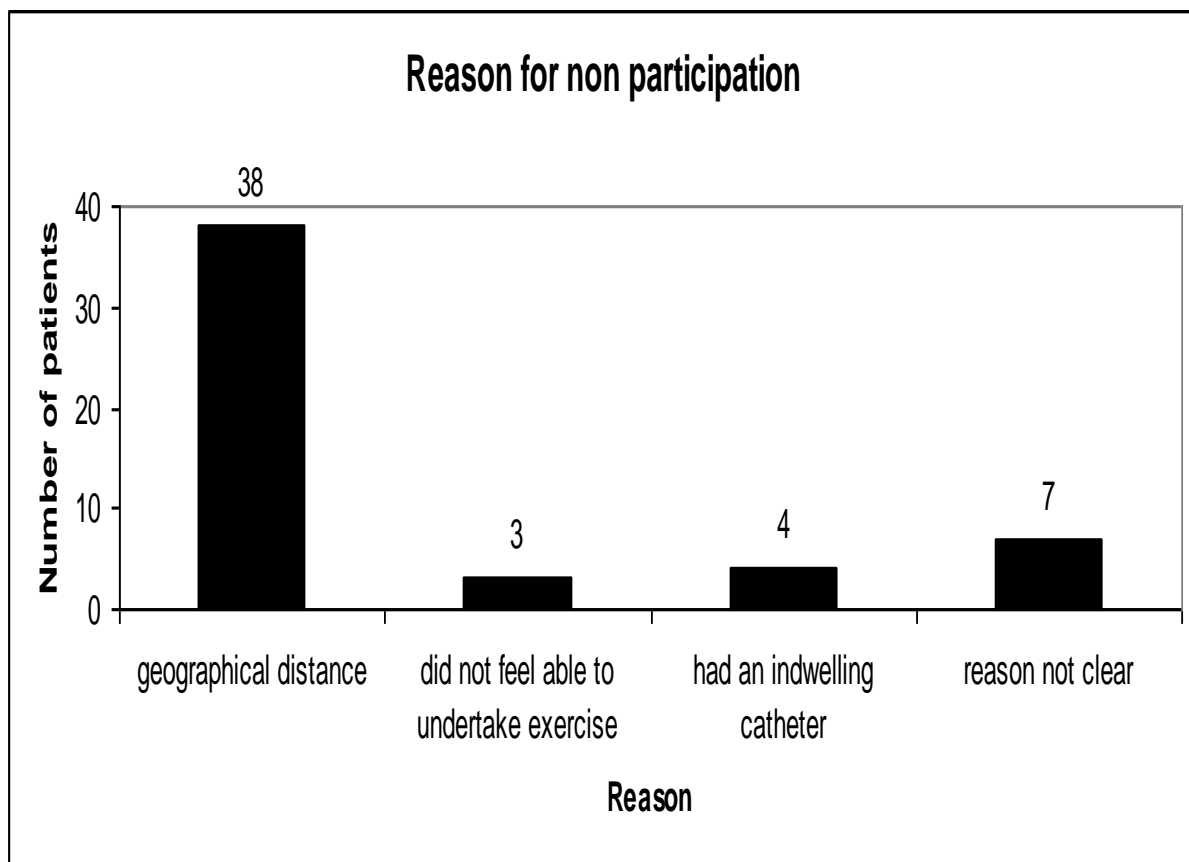
### 3.1.1. Recruitment rate

112 eligible patients were approached to take part in the study between 01/07/2012 and 01/07/2014. Of these, 53.5% (n= 60) patients agreed to participate and were recruited to the study.

### 3.1.2 Reason for non-recruitment

The Norfolk and Norwich University Hospital covers a wide geographical catchment area as it is a tertiary referral centre for the East of England for major urological surgery. The main reason for non-recruitment was distance the patients would have to travel from their home to the UEA exercise physiology laboratory. Although the patients who were in the control group had to travel twice (once for the initial assessment and again for the final assessment), the patients who were in the exercise arm had to make twice-weekly trips to the laboratory every week for four weeks. As randomisation took place after baseline assessments were complete, the participants were not aware of group allocation. As such, all participants had to be willing to make multiple visits before randomisation. Most of the patients who declined participation in the study were from neighbouring areas such as Suffolk, and had to travel a considerable distance to take part in the trial. 73 % (n=38) of patients who refused to take part did so due to travel difficulties (fig. 5).

A small number of people (n=3) who refused to take part did so because they felt they would be unable to undertake CPET assessment or comply with the exercise regime. A further four patients (7.6%) refused to take part as they had an indwelling urethral catheter or a nephrostomy which they thought might prevent them from undertaking physical activity. Seven patients (13.4%) did not specify their reasons for non-participation.



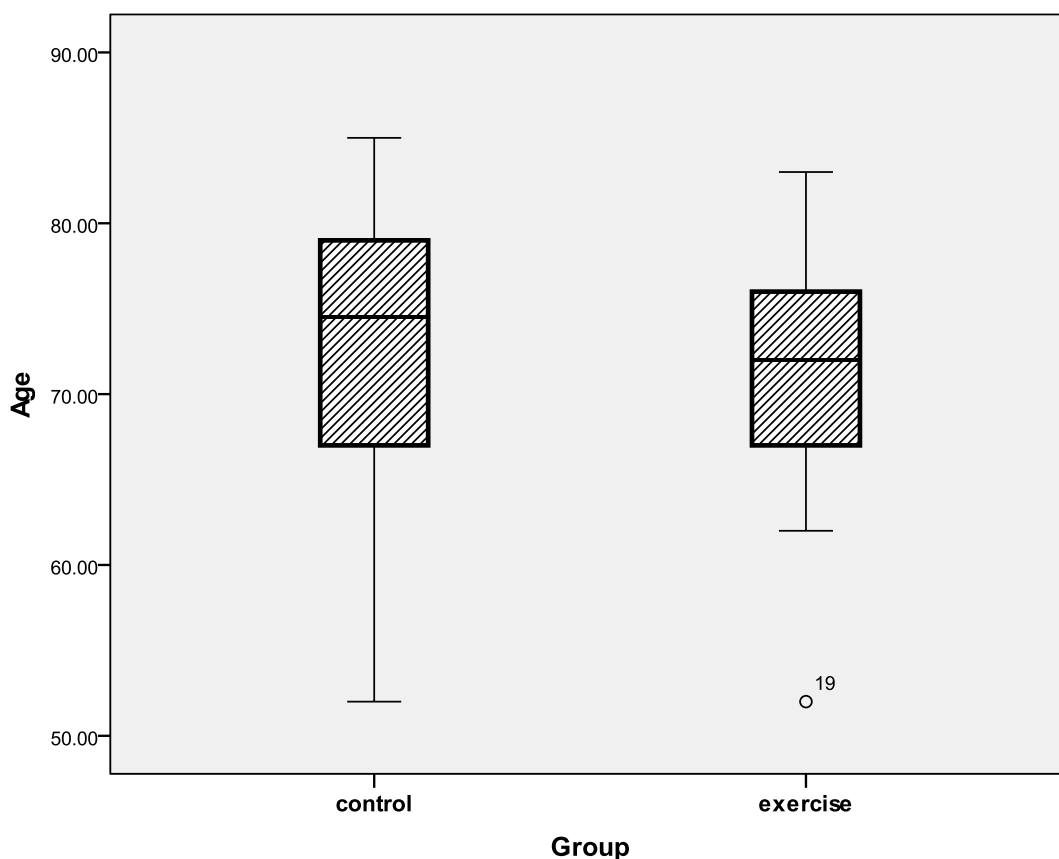
**Figure 5: reason for non-participation**

### 3.1.3 Compliance with randomisation:

All recruited participants were willing to be randomised into either of the two groups, and no one withdrew consent following randomisation. However, two participants in control group did not comply, participating in self-directed exercise after being randomised.

### 3.1.4 Patient demographics:

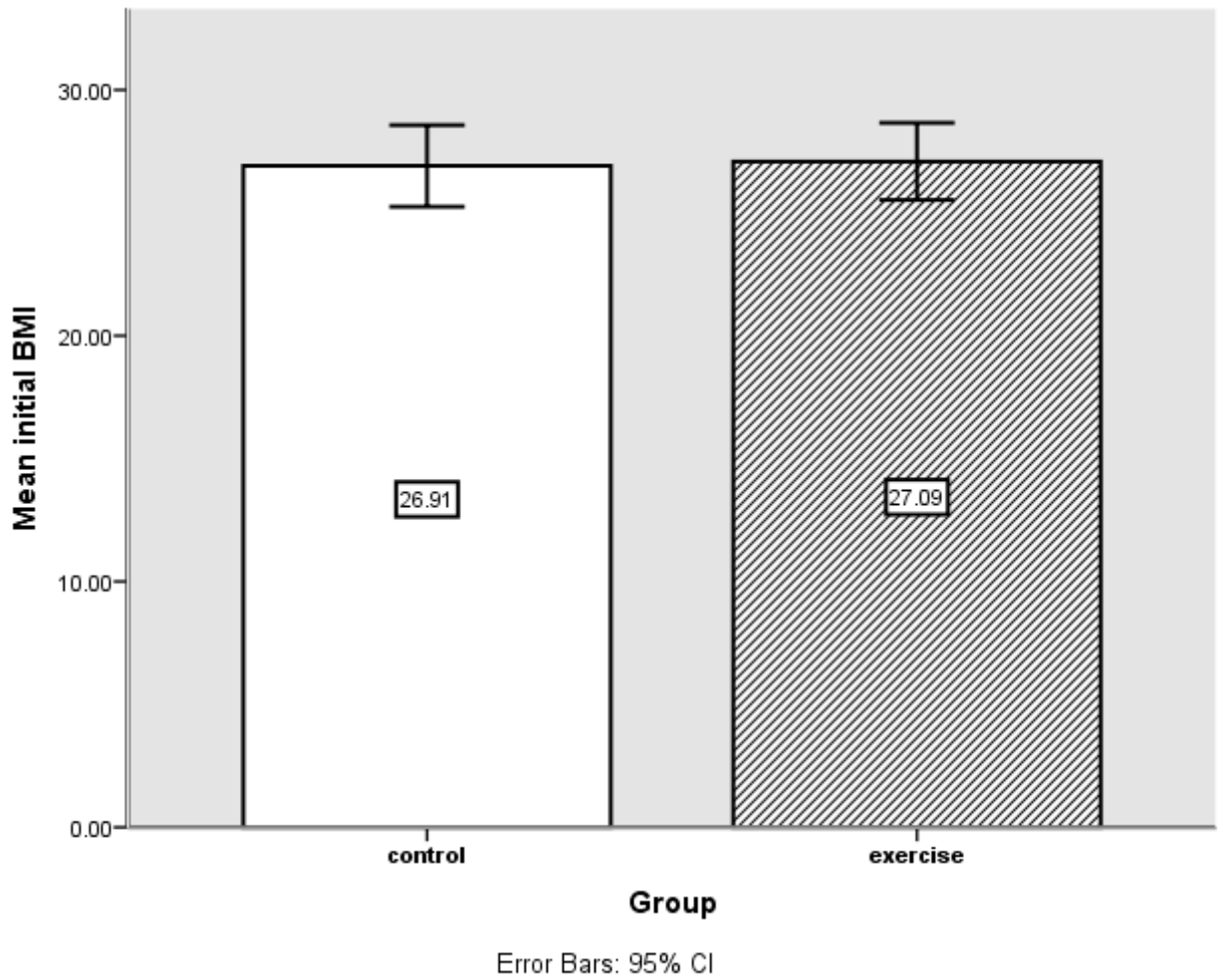
Of the 60 patients recruited to the study, 53 (88.3%) were male and 7 (11.7%) female. The mean age of the participants was 72 years (range 52-85 years). The mean age of the participants in control group was 72.5 ( $\pm$  8.4) years and in the exercise group 71.6 ( $\pm$  6.7) years. The groups were matched for age and normally distributed (fig 6).



**Figure 6: Age distribution in Control and Exercise group**

\*participant no 19 was an outlier in age distribution

Initial BMI distribution was similar across both exercise and control groups. The mean BMI in the control group was 26.9 ( $\pm 4.4$ ) and in the exercise group was 27.09( $\pm 4.2$ ) (fig 7).



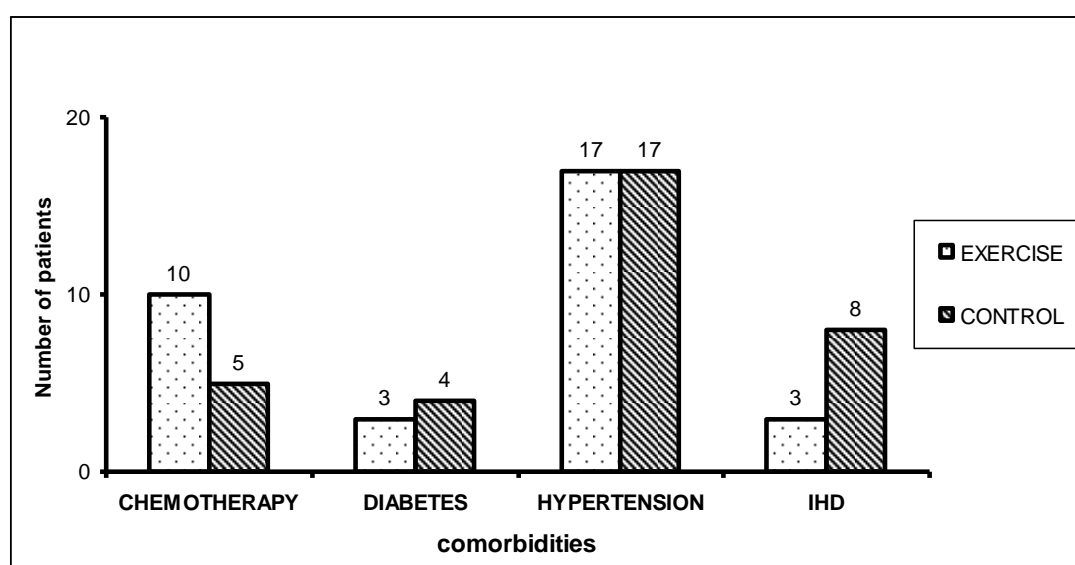
**Figure 7: BMI distribution between groups**

### 3.1.5 Associated comorbidities:

There was a substantial presence of comorbidities within the study population, with hypertension (56.6%), ischemic heart disease (IHD) (18.3%) and Type II diabetes (11.6%) being the most frequent. The distribution of comorbidities between groups was similar. An equal number of patients in both groups had hypertension (n = 17). Three patients in the exercise group and four patients in the control group suffered from Type II diabetes. Fewer patients in the exercise group than the control group had a history of IHD (n = 3 and n = 8, respectively; fig 8).

60 % (n=15) of eligible patients in the trial had neoadjuvant (i.e. preoperative) chemotherapy. These patients were recruited at least 2 weeks after completing the last cycle of chemotherapy. Of these, ten patients in the exercise group and five patients in the control group had received chemotherapy. Of the 60 patients listed for cystectomy and recruited to the trial, 34 (56.6 %) had bladder cancer refractory to BCG treatment, 25 (41.67%) had muscle invasive disease at presentation and one patient had squamous cell cancer (SCC) of the bladder.

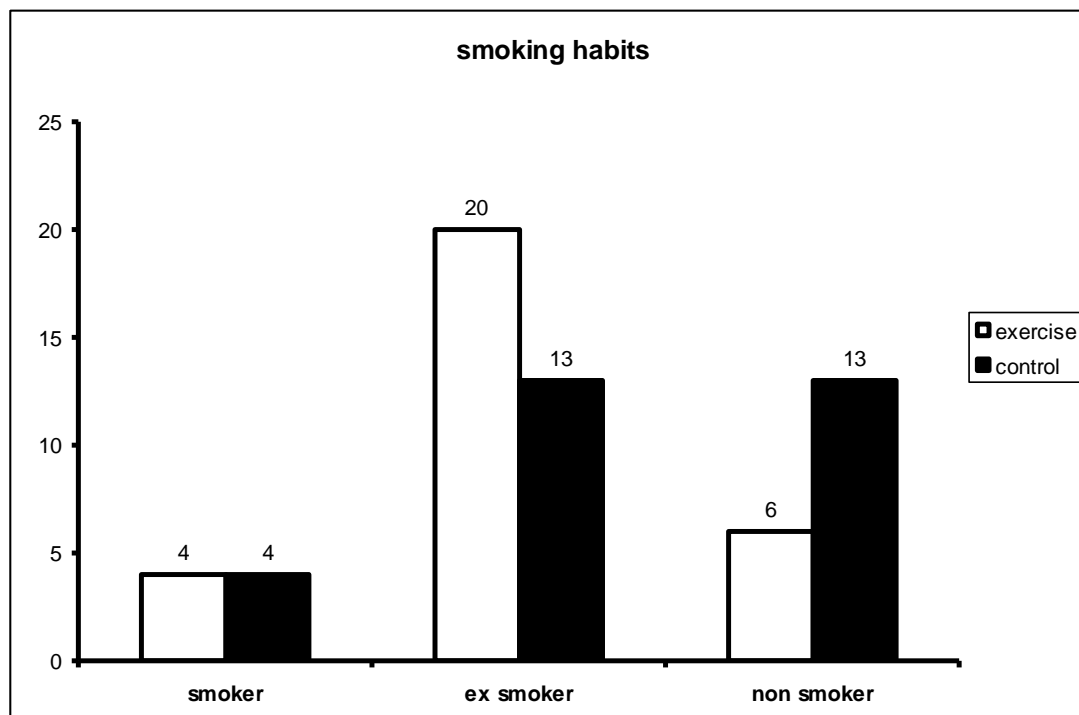
The prevalence of these comorbidities in the study population was similar to that found in the general population (137–141).



**Figure 8: Prevalence of comorbidities**

### 3.1.6 Smoking habit:

68.3% (n = 41) of patients were either current or ex-smokers. In both the exercise and control groups there were four current smokers, and 20 and 13 ex-smokers, respectively. Amongst the non-smokers 6 were randomised to exercise and 13 allocated to control (fig 9).



**Figure 9: Smoking habits**



On comparison both the control and exercise groups were matched for demographics such as age, comorbidities, BMI, smoking habits and CPET parameters such as VO<sub>2</sub> max, AT, minute volume and Oxygen pulse at baseline assessment after randomisation (table 5).

**Table 5: Matching of control and exercise groups at baseline**

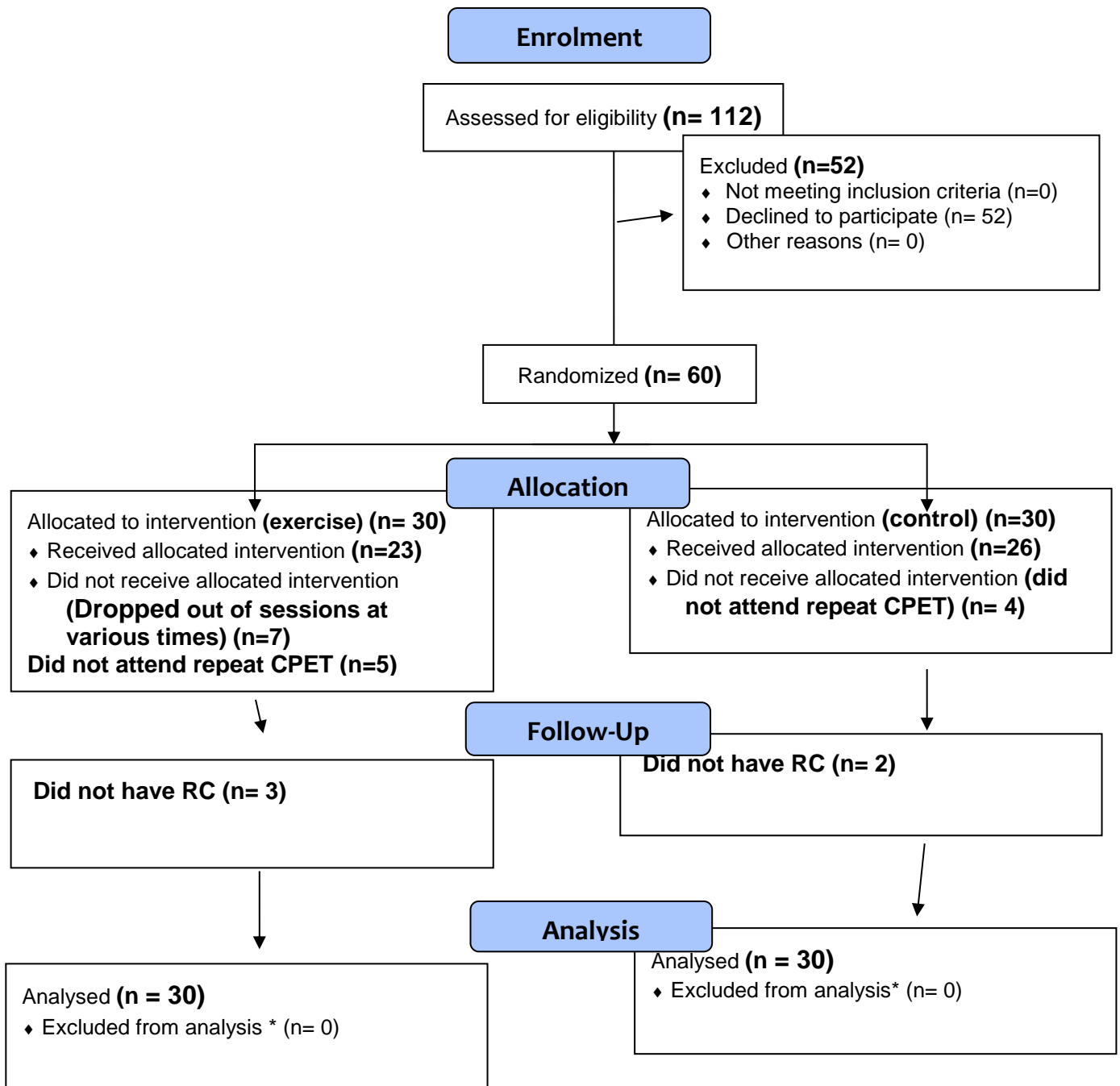
	Control	Exercise	p value
<b>demographics</b>			
Mean Age	72.5 (± 8.4) years	71.6 (± 6.7) years	0.65
Mean BMI	26.9 (±4.4)	27.09(±4.2).	0.87
Hypertension(n=)	17	17	1
Diabetes(n=)	4	3	0.68
IHD(n=)	8	3	0.09
Smoker(ex and current)(n=)	17	24	0.05
<b>CPET parameters</b>			
VO <sub>2</sub> max	20.53 (±6.9) ml/kg/min	19.01(± 4.58) ml/kg/min	0.32
AT	10.06 ( ± 2.7 ) ml/kg/min	9.01 ( ± 2.5 ) ml/kg/min	0.13
Minute Volume (VE)	65.8 (± 20.82) L/min	71.35( ± 22.64 ) L/min	0.33
Oxygen Pulse	10.9(± 2.7) ml/beat	11.1 (± 2.6) ml/beat	0.68

### 3.1.7 Attrition /dropouts during trial:

The overall compliance of the study participants was very good. After initial CPET assessment, 60 participants were randomised into equal groups. In the control arm 25/30 participants completed both CPET assessments, which was similar in the exercise group (26/30) (fig 10).

In the control arm, 28 patients had surgery and 2 patients elected for radiotherapy after randomisation. In the exercise arm, 27 patients had surgery and 3 elected for radiotherapy. Of these 5 patients in total, three elected for radiotherapy by personal choice, and 2 were deemed unfit by a consultant anaesthetist (one had PE and the other patient had pleural effusion). Post-operative data for these five patients was therefore not available. The patients who attended the initial CPET assessment but not the final assessment consented for post-operative data to be collected.

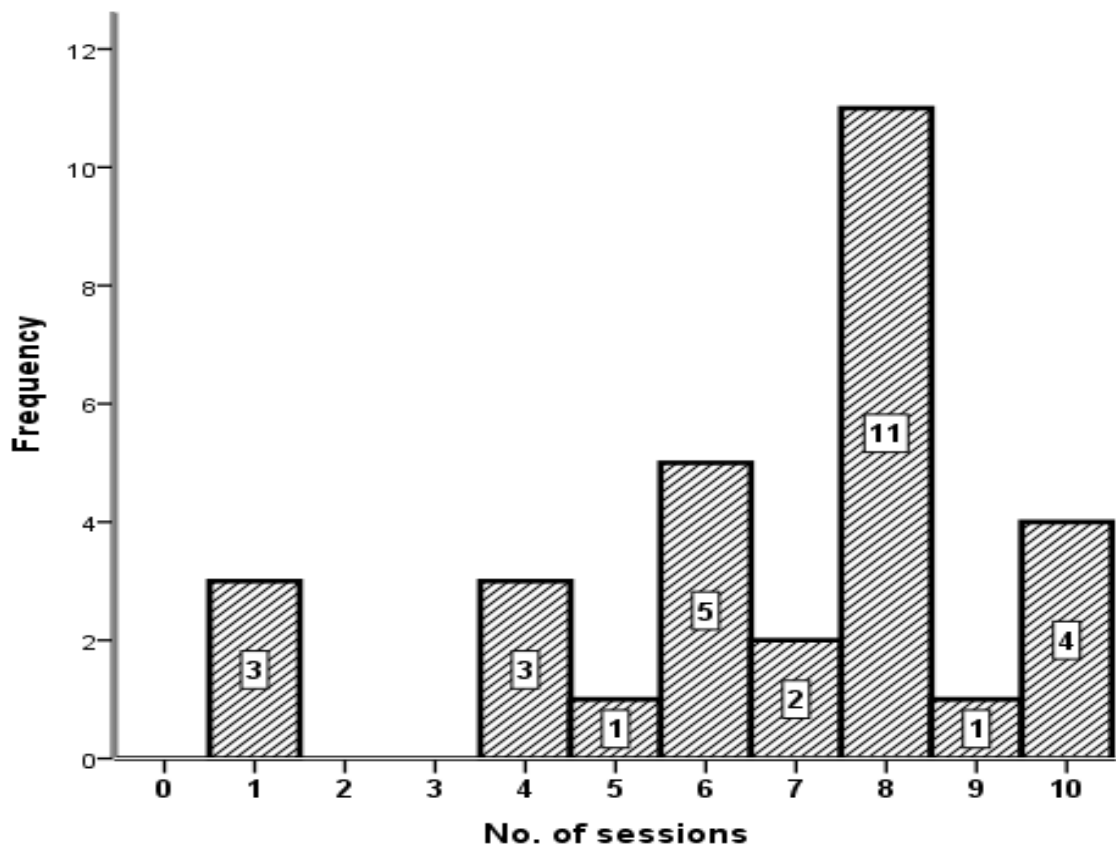
**Figure 10: Consort flow chart**



\* As this was a feasibility trial in spite of protocol deviation all participants' CPET data were analysed

### 3.1.8 Compliance with exercise:

Adherence to the exercise protocol was very good. The median number of sessions attended by patients in the exercise arm was 8, which was the prescribed regimen as per the protocol. In four patients surgery was delayed by longer than 4 weeks (because of unavailable dates for cystectomy) but these patients were very keen to carry on with the exercise sessions and attended two more sessions than planned. Three patients on the other hand had cystectomy in under four weeks and were hence unable to attend all 8 sessions as outlined in the protocol but attended for their repeat CPET assessment. A further eleven patients dropped out at various times over the course of the exercise programme (fig 11). These deviations from the protocol were noted.



**Figure 11: Number of exercise sessions attended by participants**

### 3.1.9 Intensity of exercise during sessions:

Participants' mean heart rate (HR) during cycling exercise periods was 94.84 % (range 92.69%- 96.1 %) of their peak heart rate as determined by CPET (table 5). The average percent heart rate across the weeks was calculated by the mean heart rate during exercise in that particular week divided by the peak heart rate achieved during CPET testing.

This was accompanied by a median rating of 14 for perception of effort on the Borg scale.

**Table 6: Distribution of peak heart rate during exercise**

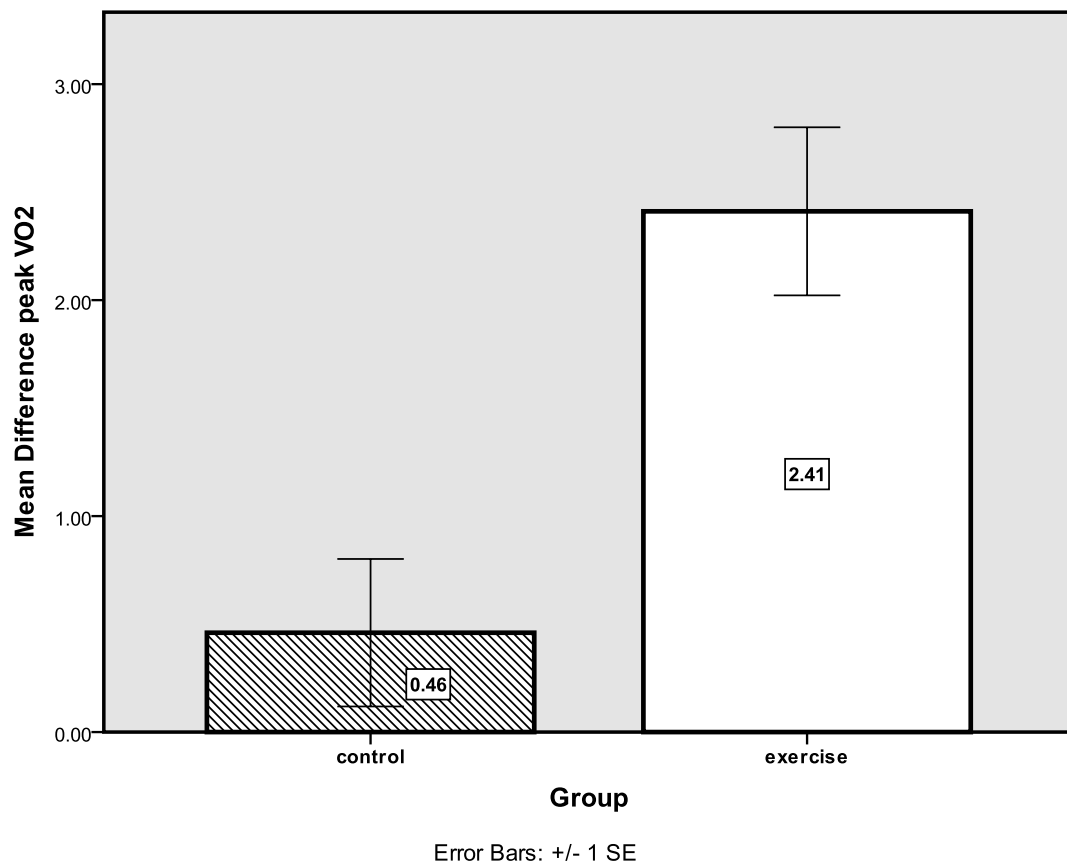
	Week 1	Week 2	Week 3	Week 4	Week 5
Number of patients	30	27	25	20	4
Mean percent HR (average HR in that week /peak HR at CPET )	95.12	96.5	96.1	92.69	93.80
Std Deviation	7.36	1.7	2.9	1.59	4.45

### 3.2 Changes in CPET variables:

#### 3.2.1 Changes in VO<sub>2</sub> max:

The mean initial VO<sub>2</sub> max (peak VO<sub>2</sub>) in the control group was 20.53 (±6.9) ml/kg/min and the mean initial VO<sub>2</sub> max in the exercise arm was 19.01(± 4.58) ml/kg/min. On repeat CPET analysis before RC the VO<sub>2</sub> max were 20.8 (± 5.4) ml/kg/min and 21.61 (±5.5) ml/kg/min respectively.

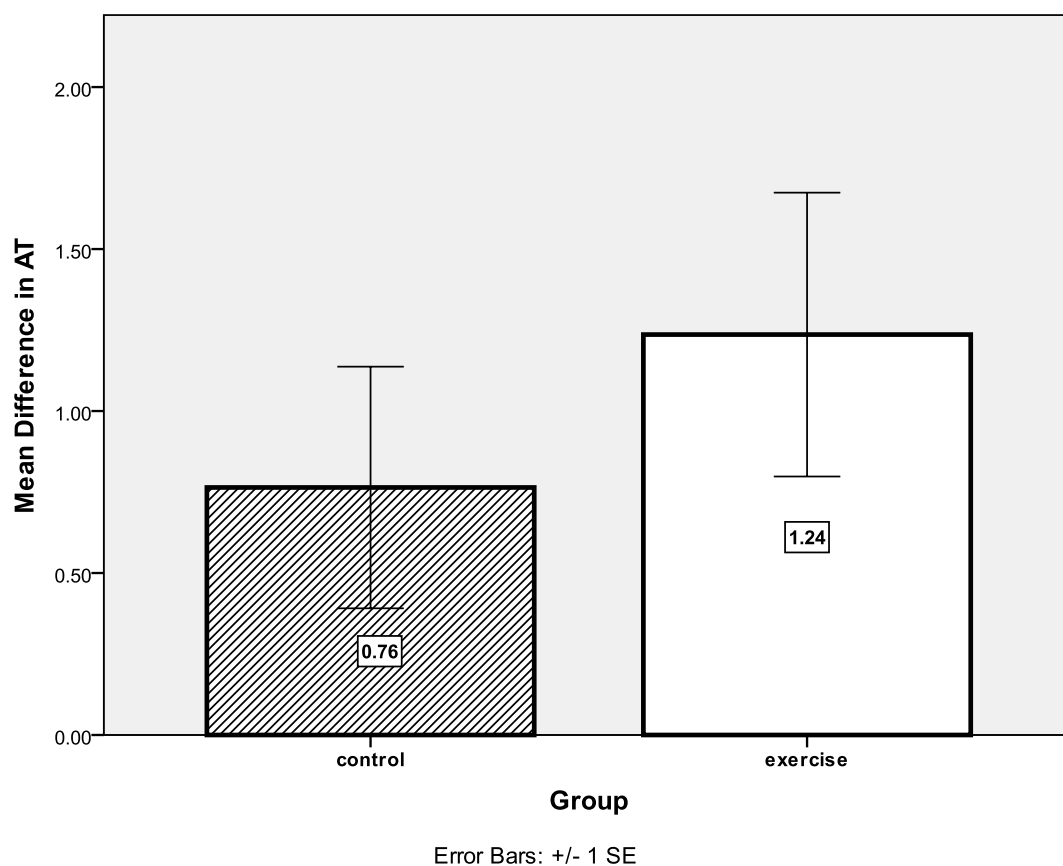
Using univariate analysis (ANCOVA) it was found that the mean difference in the VO<sub>2</sub> max between the exercise and control group was 1.9 (0.87 – 3.00, 95% CI) ml/kg/min. (p=0.001) (fig.12).



**Figure 12: Mean difference in VO<sub>2</sub> max between CPET testing sessions**

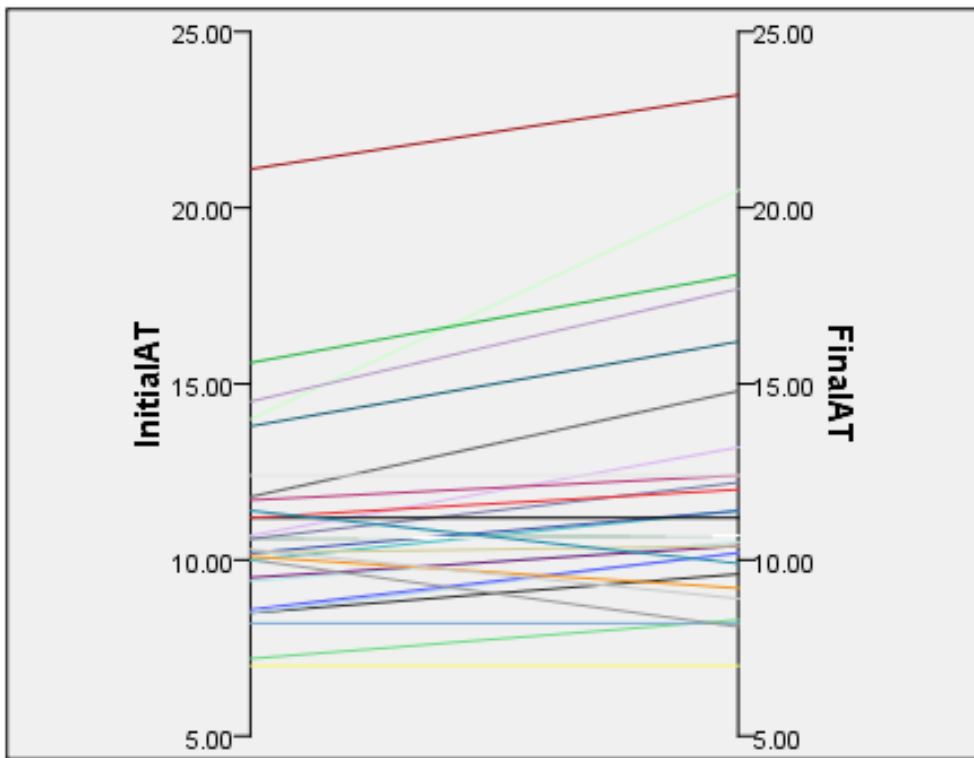
### 3.2.2 Changes in AT (Anaerobic Threshold):

The mean initial anaerobic threshold (AT) in the control group was 10.06 ( $\pm$  2.7) ml/kg/min and the same in the exercise group was 9.01 ( $\pm$  2.5) ml/kg/min. At repeat CPET assessment the mean anaerobic threshold in the control arm was 10.33 ( $\pm$  2.46 SD) ml/kg/min and in the exercise/exercise arm was 10.4 ( $\pm$  1.87) ml/kg/min. Using similar univariate analysis (ANCOVA) to test the difference between the change of anaerobic threshold, it was noted that there was a difference of 0.33 (- 0.68 to 1.3, 95%CI) ml/kg/min the (p= 0.5) between the exercise and the control group before RC. (fig 13)

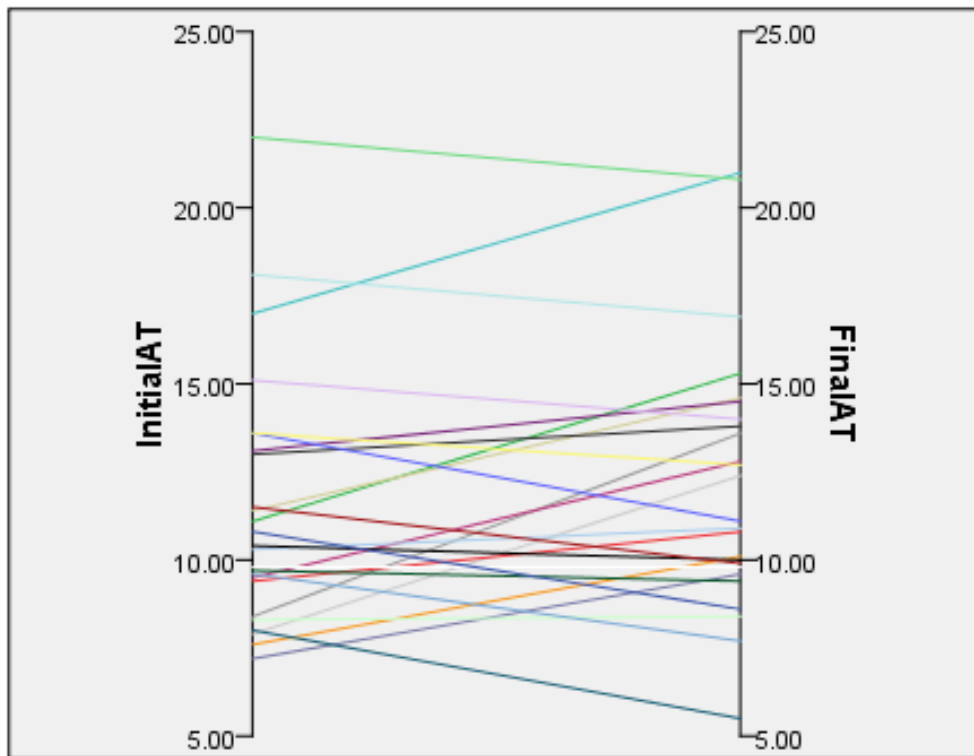


**Figure 13: Mean difference in AT between CPET testing sessions**

Looking at individual changes in AT in participants in exercise and control group respectively (figure 14 and figure 15) it appears that participants in exercise group had a steeper change in AT after 4 weeks. There were 2 participants in the control group who had participated in self-directed exercise and an improvement was noted in their AT as well.



**Figure 14: Change in AT in exercise group**

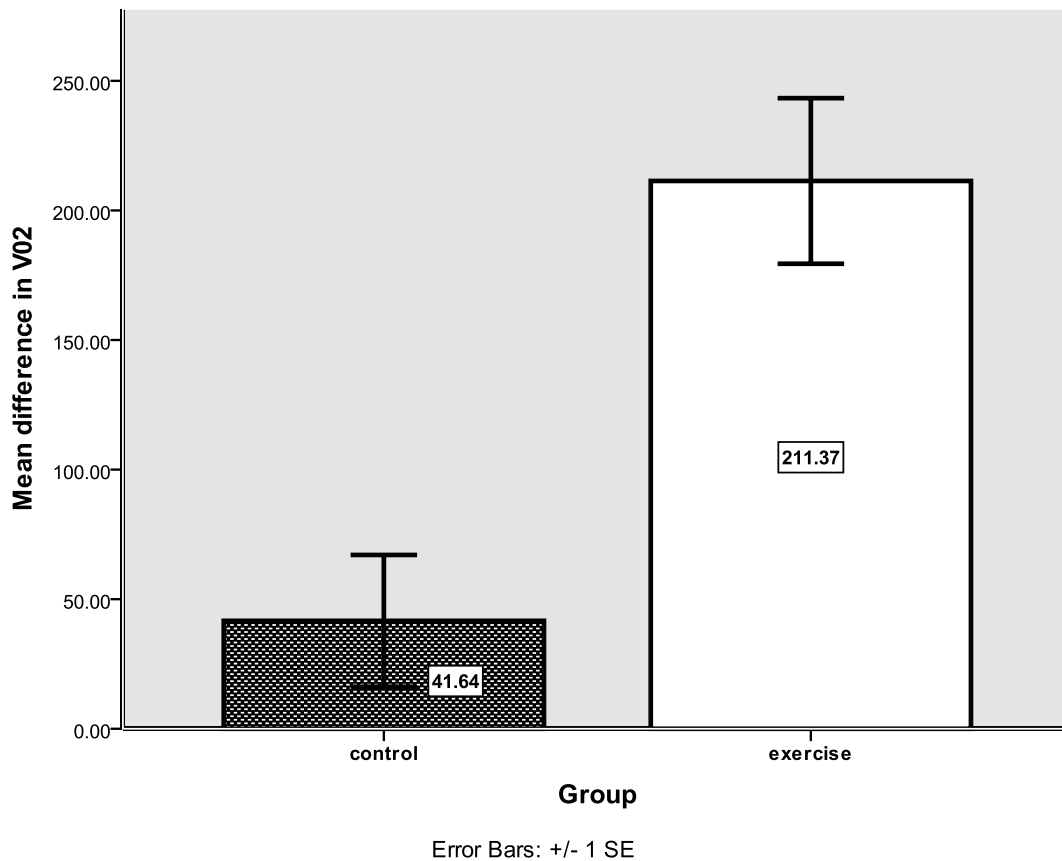


**Figure 15: Changes in AT in control group**

### 3.2.3 Changes in VO<sub>2</sub> (Oxygen consumption)

The control group had a mean VO<sub>2</sub> of 1538.07 ml ( $\pm 511.7$ ) initially and at the repeat CPET testing, at the end of the study period, the mean was 1594.4 ( $\pm 461.3$ ) ml. In the exercise arm the values were 1545.6 ml ( $\pm 438.3$ ) and 1779.0 ml ( $\pm 533.8$ ) respectively. The mean difference between the exercise and control group was found to be 168.9 ml (95% CI 86.2 - 251.7) ( $p < 0.001$ ) (fig 14).

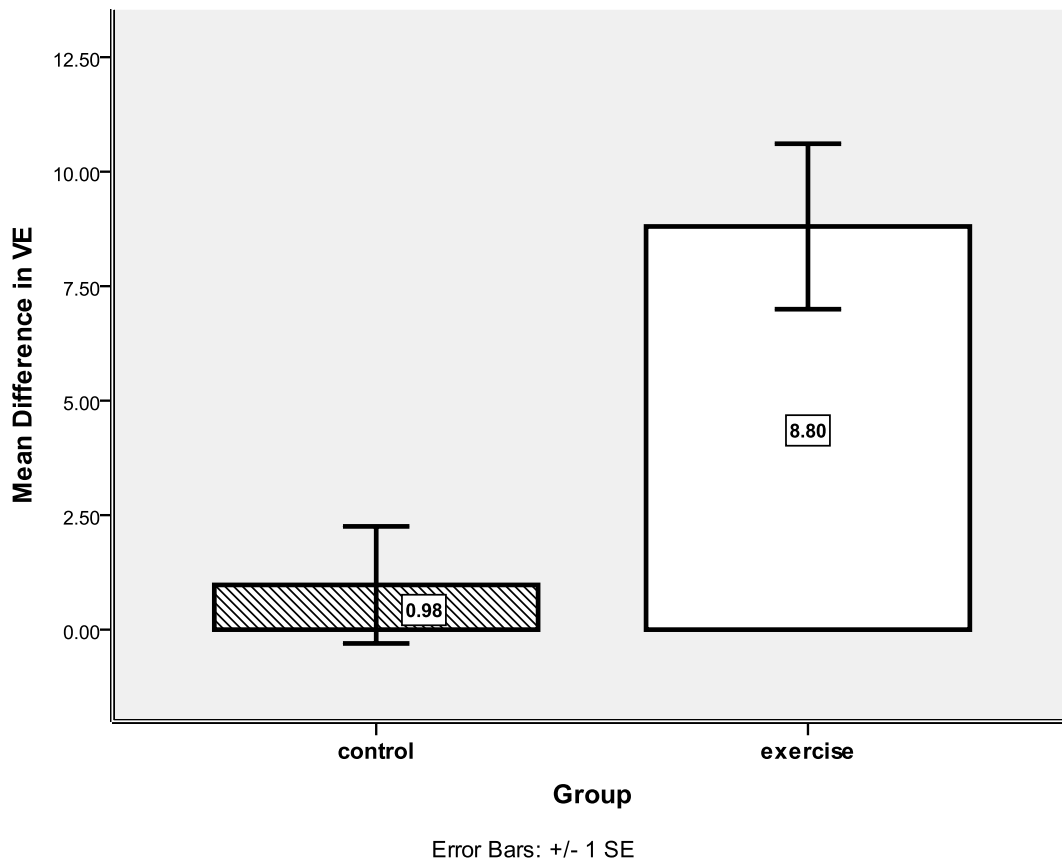




**Figure 16: Changes in VO<sub>2</sub>**

### 3.2.4 Changes in Minute Volume at VO<sub>2</sub> max

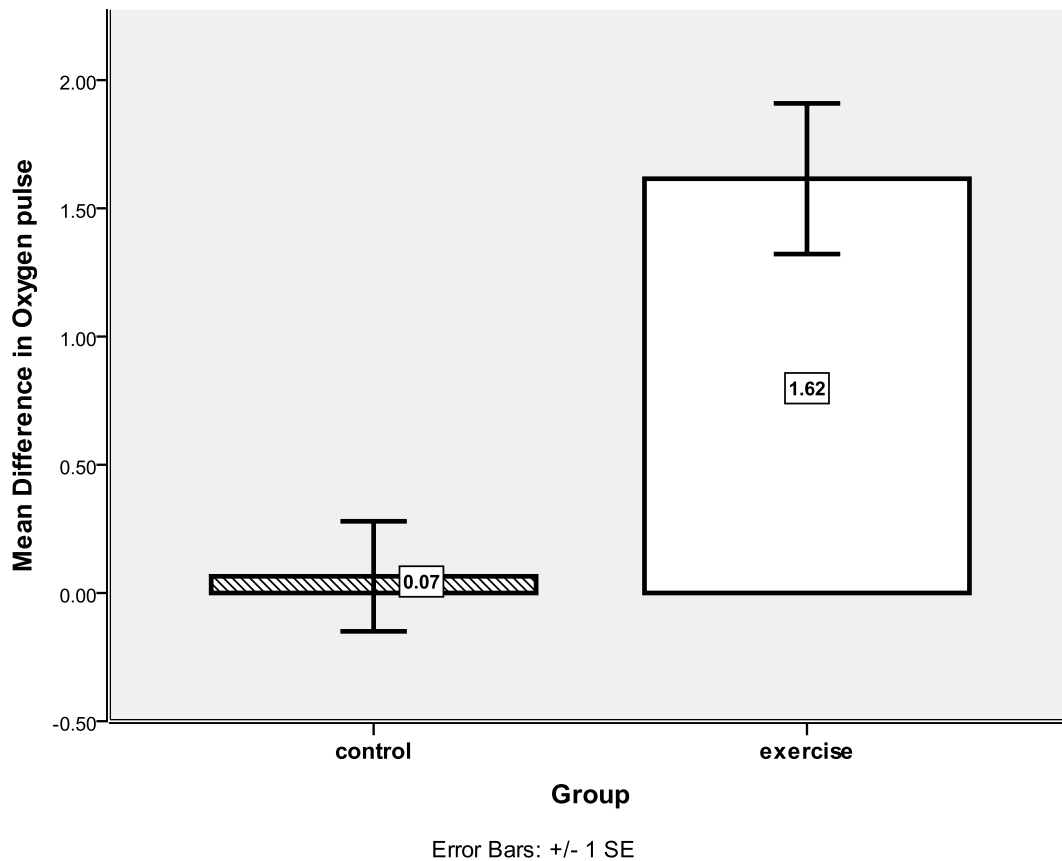
$V_E$  (minute volume) indicates the total amount of gas that is inhaled or exhaled per minute. Although in a normal adult it varies between 5 to 8 L/ min at rest the values are much higher when a person is exercising. In the current study the initial mean minute volume (at peak  $\dot{V}O_2$  and standardised BTPS) in the control group was 65.8 ( $\pm 20.82$ ) L/min and the final mean value and end of the study period was 67.81 ( $\pm 19.12$ ) L/min. The mean minute volume in the exercise group initially was 71.35 ( $\pm 22.64$ ) L/min and increased to 79.96 ( $\pm 24.19$ ) L/min at the end of the study period. The mean difference between the two groups was 8.10 (95% CI 3.5 –12.6 L/ min) L/min ( $p=0.001$ ) (fig 15).



**Figure 17: Mean difference in  $V_E$  at  $VO_2$  max between CPET testing sessions**

### 3.2.5 Changes in Oxygen pulse:

Oxygen pulse denotes the oxygen uptake per heartbeat. The initial oxygen pulse in the control group was 10.9 ml/beat ( $\pm 2.7$ ) and the final value at the end of the study was 11.03 ml/beat ( $\pm 2.19$ ). The values in the exercise arm were 11.1 ml/beat ( $\pm 2.6$ ) and 13.06 ml/beat ( $\pm 2.8$ ) respectively. The mean difference between the two groups was 1.60 ml/beat (95% CI 0.87- 2.3) ( $p < 0.001$ ) (fig16)



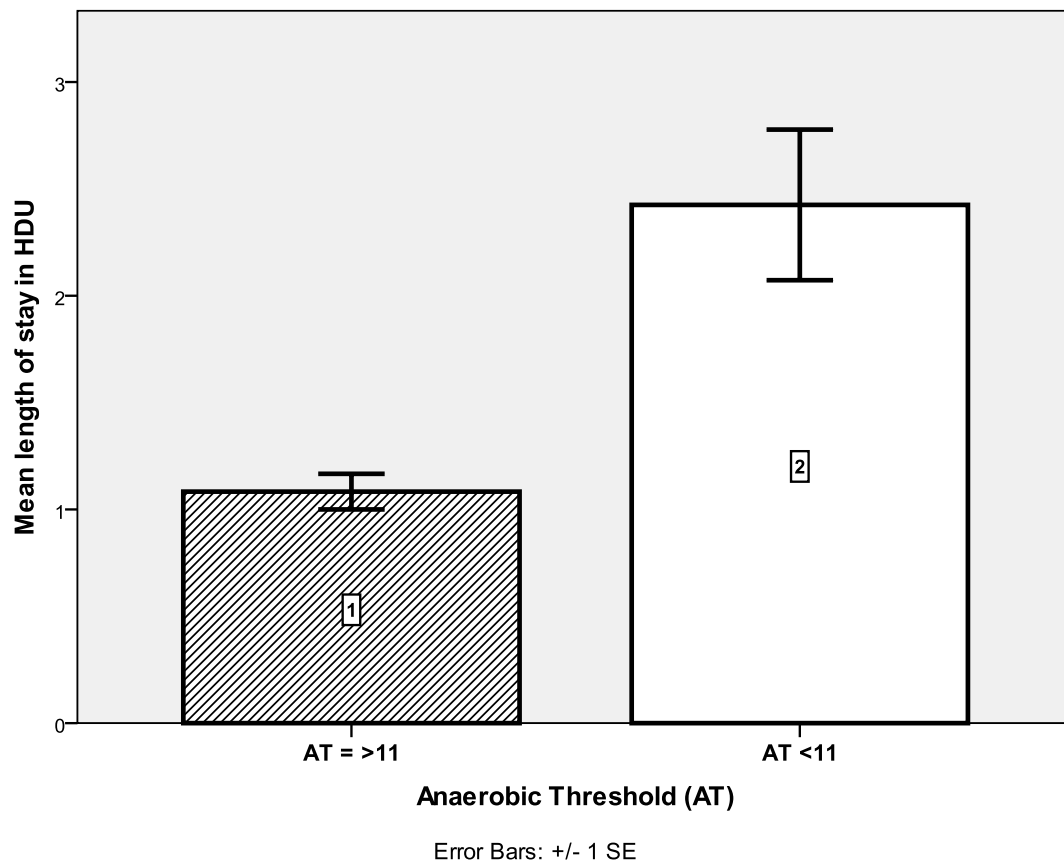
**Figure 18: Mean difference in Oxygen pulse between CPET sessions**

### 3.3 Relationship between preoperative fitness level and post-operative outcomes in the current study:

In line with the published literature we looked at post-operative outcomes and associations between anaerobic threshold (AT). As the number of patients in this study was small (n=60) we chose to utilise the cut-off value of anaerobic threshold at 11ml/kg/min as this has been proven in larger studies to predict favourable outcomes.

### 3.3.1 Length of stay in high dependency unit (HDU):

All patients who undergo RC are routinely booked into HDU post operatively, for closer monitoring, at our institution. The mean length of stay in the high dependency unit (HDU) of those patients who had anaerobic threshold of more than or equal to 11 ml/kg/min was 1.08 ( $\pm$  0.28) days, range (1–2 days). The mean length of stay for patients in HDU who had anaerobic threshold of less than 11 ml/kg/min was 2.4 ( $\pm$  2.2) days, (range 1-10 days) (fig 17). It was found that the length of stay in the high dependency unit was non-normally distributed and hence using Spearman's correlation analysis (non-parametric) there was found to be negative correlation of - 0.41 ( $p$  =0.002) between initial anaerobic threshold and length of stay in the high dependency unit indicating that patient with lower AT tend to stay longer in HDU.

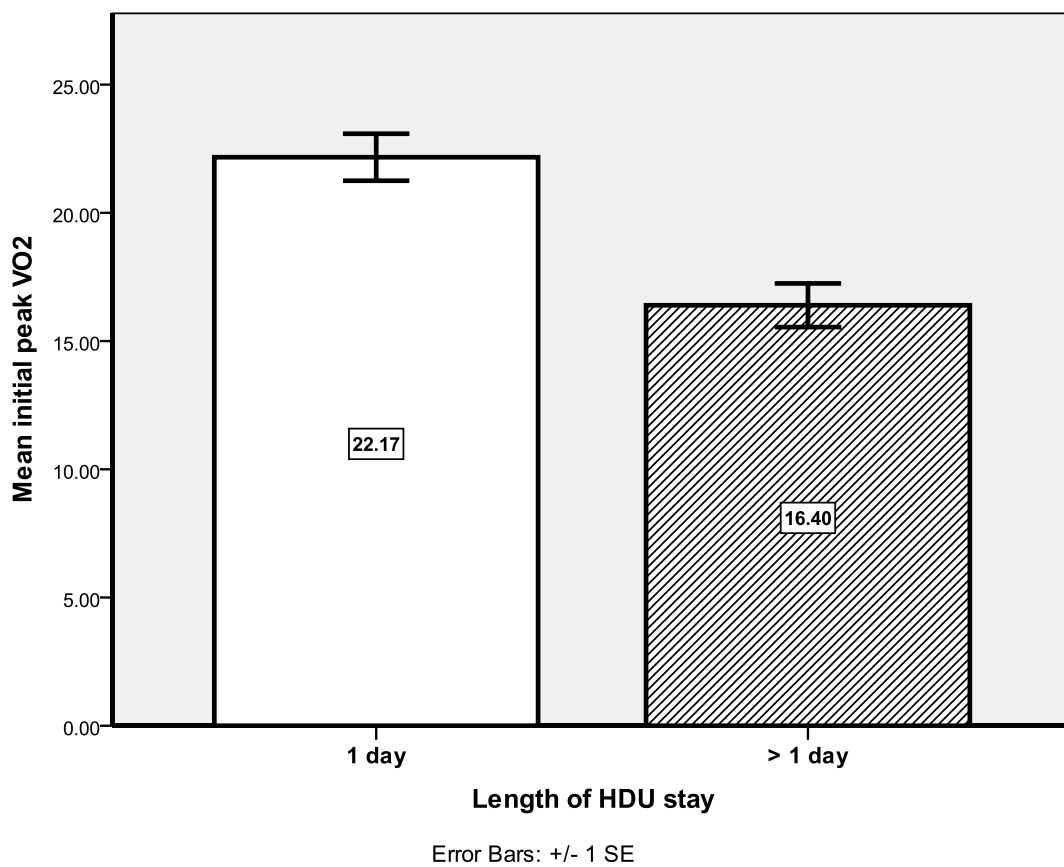


**Figure 19: Mean length of HDU stay based on a cut off AT of 11ml/kg/min**

The mean initial peak  $\dot{V}O_2$  of patients who stayed in the high dependency unit for one-day (the minimum stay in HDU in our institution) after operation was 22.17 ( $\pm 5.34$ ) ml/kg/min compared to the mean peak  $\dot{V}O_2$  of 16.39 ( $\pm 3.90$ ) ml/kg/min patients who stayed longer in the high dependency unit (fig 18) . Using the Independent t - test this difference appears to be significant ( $p < 0.001$ )

Using Spearman's correlation there is a negative correlation of -0.59 between the initial  $VO_2$  max and length of stay in the high dependency unit indicating similarly that patients with higher  $VO_2$  max stayed lesser number of days in HDU.

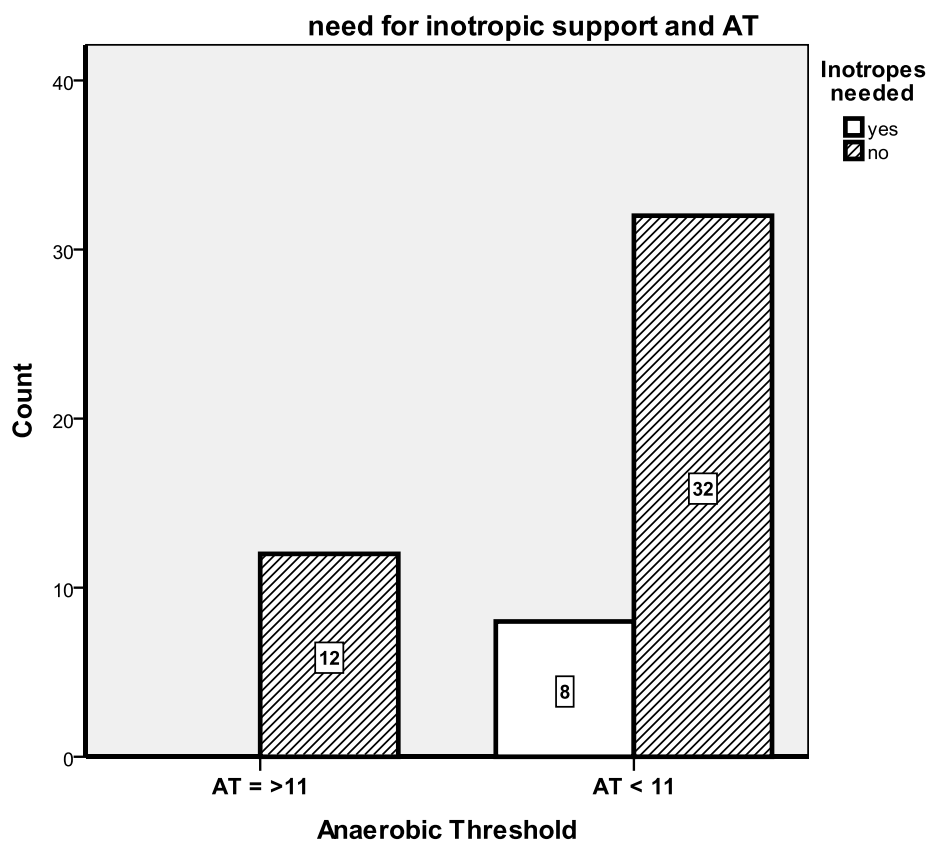
( $p < 0.001$ )



**Figure 20: Initial  $VO_2$  max and LOS in HDU**

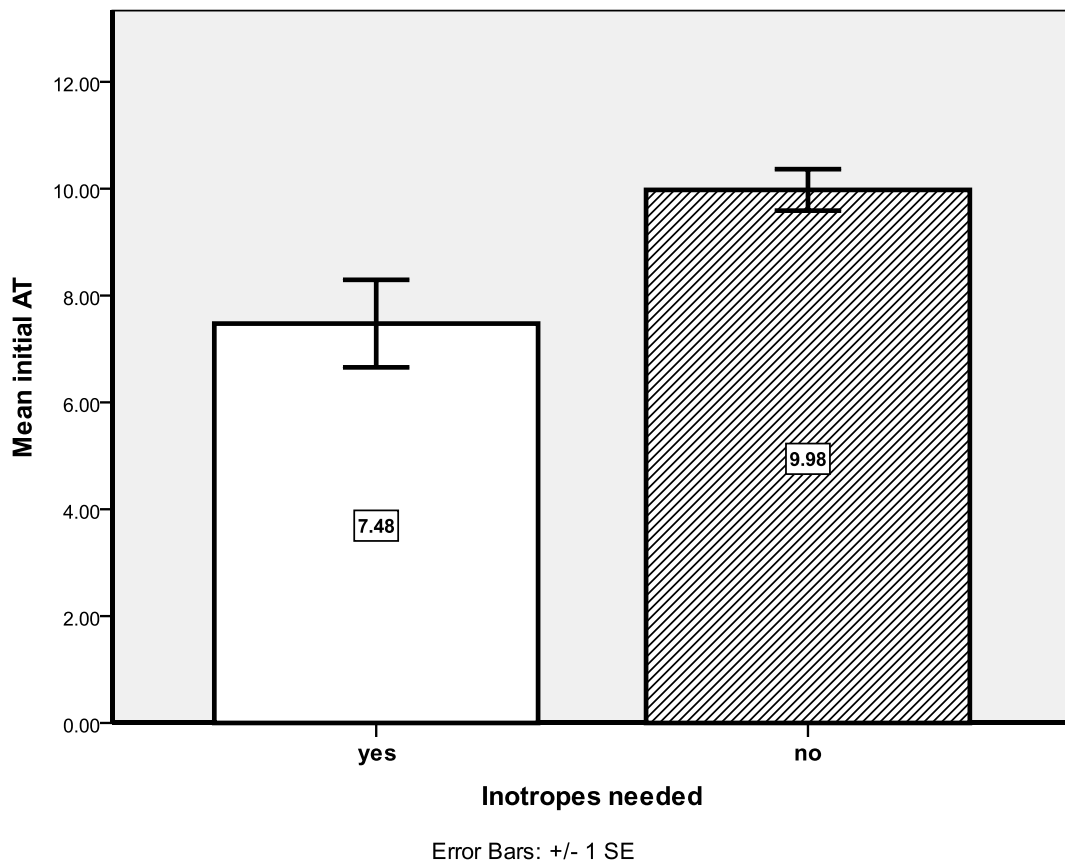
### 3.3.2 Need for inotropic support:

Inotropes are medications that are used often in the high dependency unit to maintain adequate blood pressure in patients after major surgery. They need careful monitoring and hence are not suitable to be administered in a general ward. In the current study none of the patients whose anaerobic threshold was more than or equal to 11 ml/kg/min needed inotropic support in the high dependency unit. On the other hand, 8 patients who required inotropic support, all had AT of less than 11 ml/kg/min (fig 19). Although not statistically significant ( $p=0.09$ ) using the chi square analysis, there appears to be a trend suggesting that need for post-operative inotropic support could possibly be related to the preoperative anaerobic threshold.



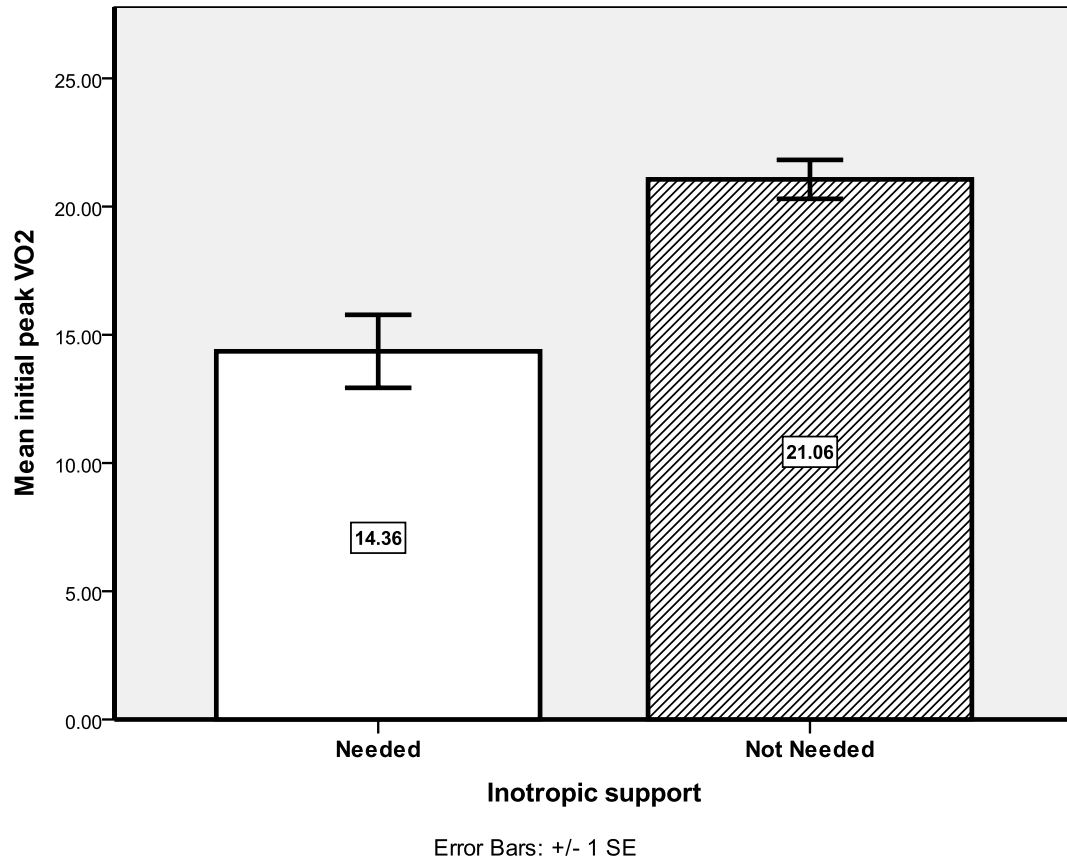
**Figure 21: Need for post-operative inotropic support and AT**

Comparing those patients who needed inotropic support with those that did not, we found that the mean anaerobic threshold was 7.48 ( $\pm 2.3$ ) ml/kg/min and 9.98 ( $\pm 2.5$ ) ml/kg/min respectively. Using one-way ANOVA, the mean difference was found to be significant ( $p= 0.01$ ) (fig 20).



**Figure 22: AT and use of inotropes**

The mean initial peak  $\dot{V}O_2$  of patients who needed inotropic support post operatively was found to be 14.36 ( $\pm 4.27$ ) ml/kg/min whereas in those patients who did not require inotropic support, the mean  $\dot{V}O_2$  max was 21.06 ( $\pm 5.1$ ) ml/kg/min ( $p=0.001$ ) (fig 21).



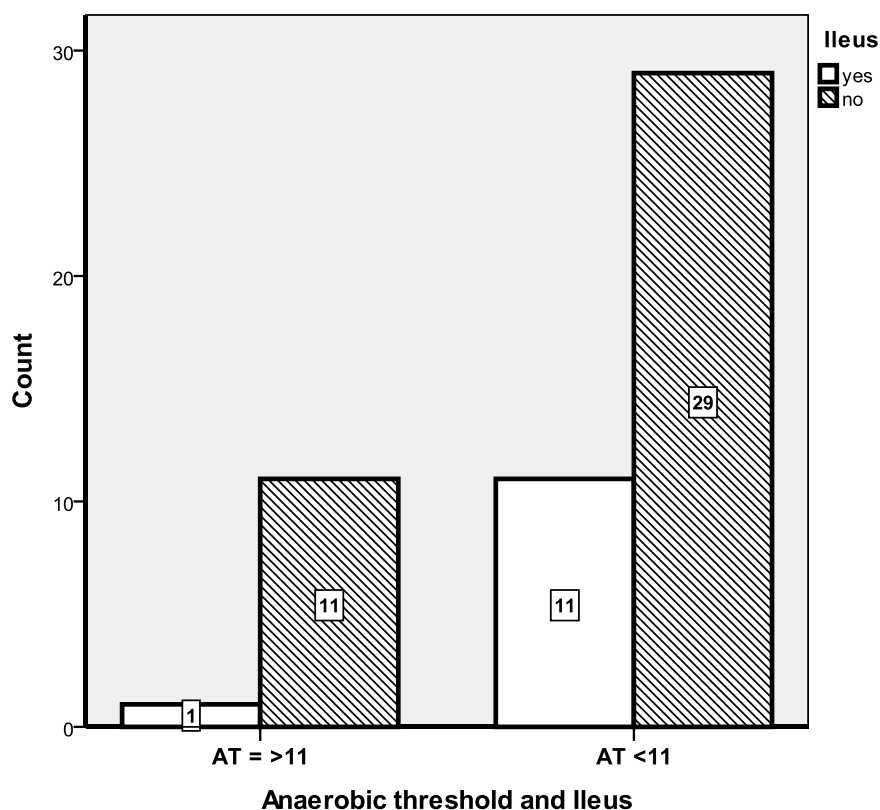
**Figure 23: Need for inotropes and initial  $\dot{V}O_2$  max**



### 3.3.3 Post-operative ileus:

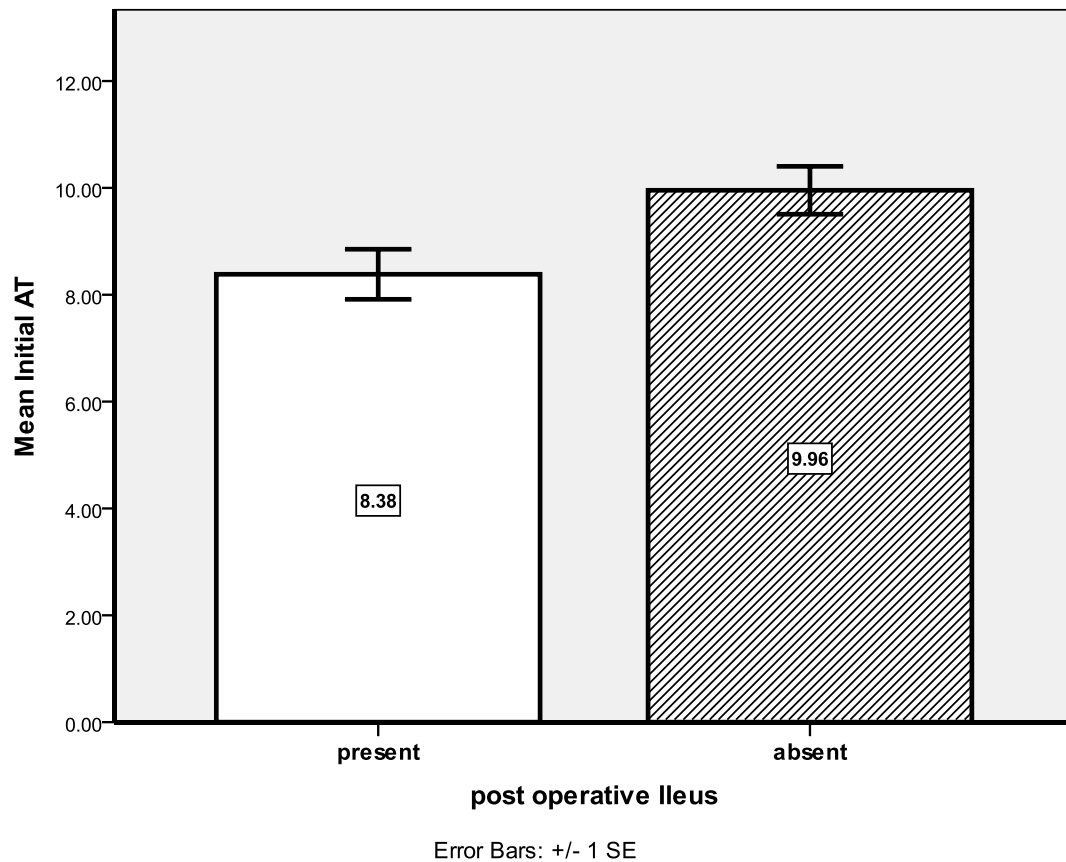
Post-operative ileus (non-motility of the bowel) is a recognised complication and an important cause of morbidity after cystectomy or any other major abdomino-pelvic surgery. In the current study ileus was noted to be present if there was a delay of longer than 3 days in establishing oral intake or if the patient needed a nasogastric tube.

Using the cut-off anaerobic threshold of 11 ml/kg/min, prevalence of ileus was found to be higher (n= 11) in those patients with a low anaerobic threshold compared to those (n=1) with a high anaerobic threshold, although this was not statistically significant (p= 0.1) (fig 22).



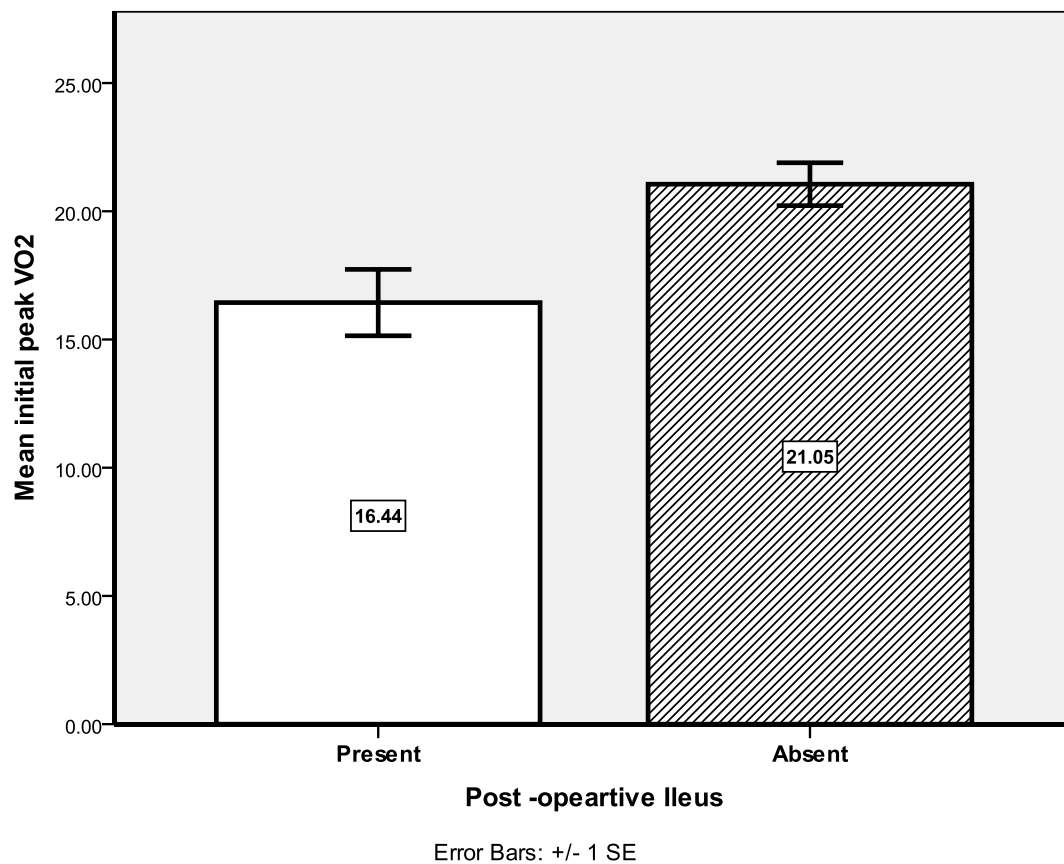
**Figure 24: Incidence of post-operative ileus based on a cut off AT of 11ml/kg/min**

In those patients that had post-operative ileus the mean anaerobic threshold was found to be lower ( $8.3 \pm 1.6$  ml /kg/min) compared to those patients that did not have post-operative ileus ( $9.9 \pm 2.8$  ml/kg/min). Although not statistically significant ( $p=0.07$ ) there appears to be a trend towards low anaerobic threshold and presence of post-operative ileus. (fig 23)



**Figure 25: Initial AT and ileus**

Comparing patients who developed post-operative Ileus versus those who did not it was found that the mean initial VO<sub>2</sub> max was 16.44 (± 4.66) ml/kg/min and 21.05(± 5.4) ml/kg/min (fig 24). Using the one-way ANOVA the mean difference between these 2 groups was found to be statistically significantly different (p=0.008)



**Figure 26: VO<sub>2</sub> max and ileus**

### 3.3.4 Chest infection:

Using the same cut-off anaerobic threshold of 11 ml/kg/min, it was noted that the prevalence of chest infection was higher (n=4) in those patients who had low anaerobic threshold compared to those (n=0) who had high anaerobic threshold (p=0.2) (fig 25).

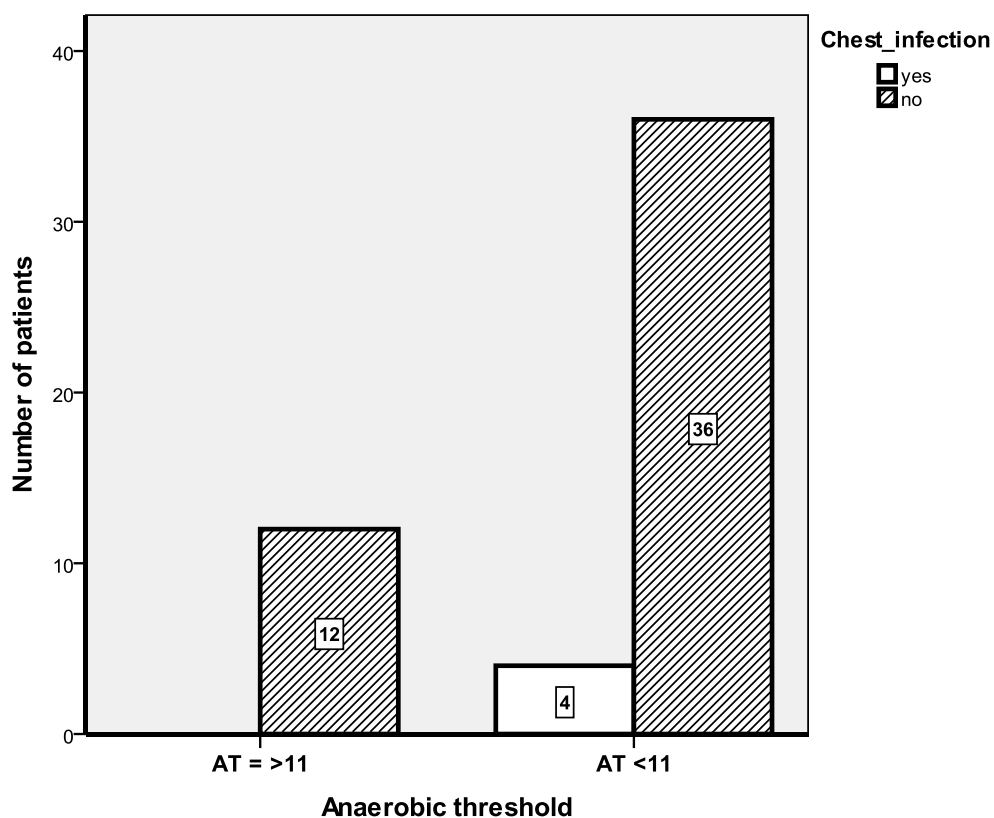
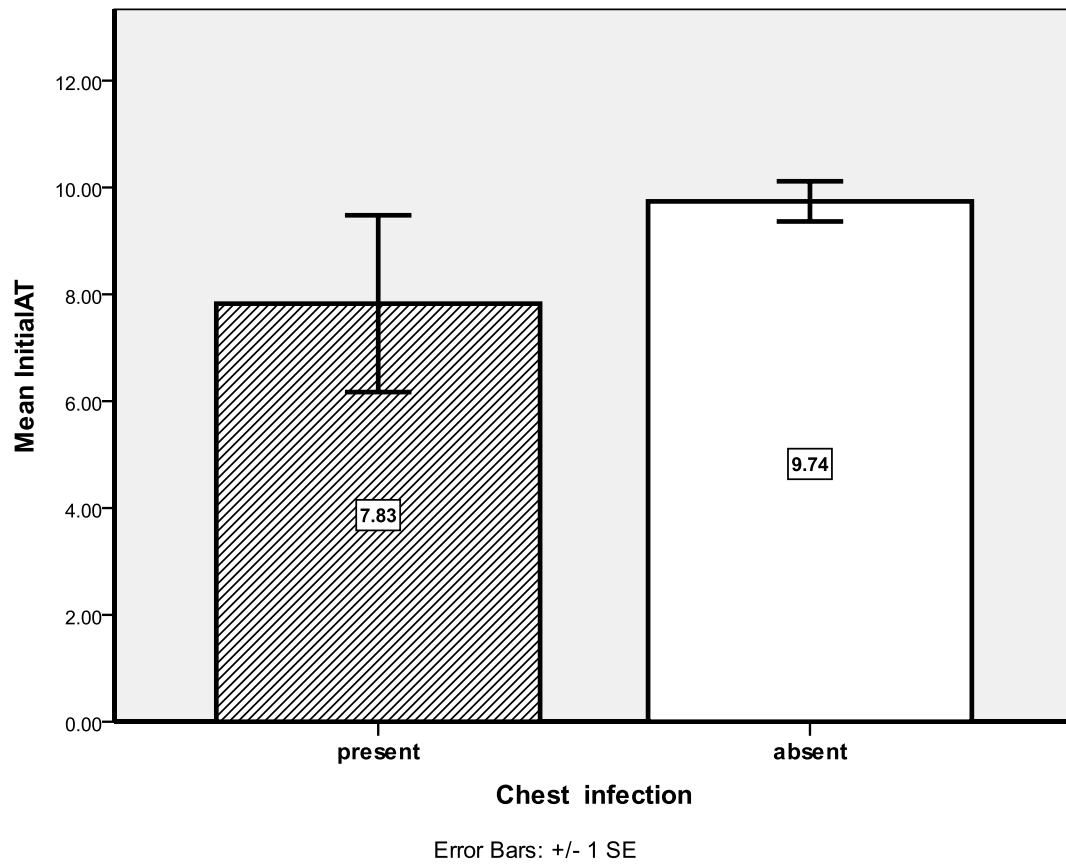


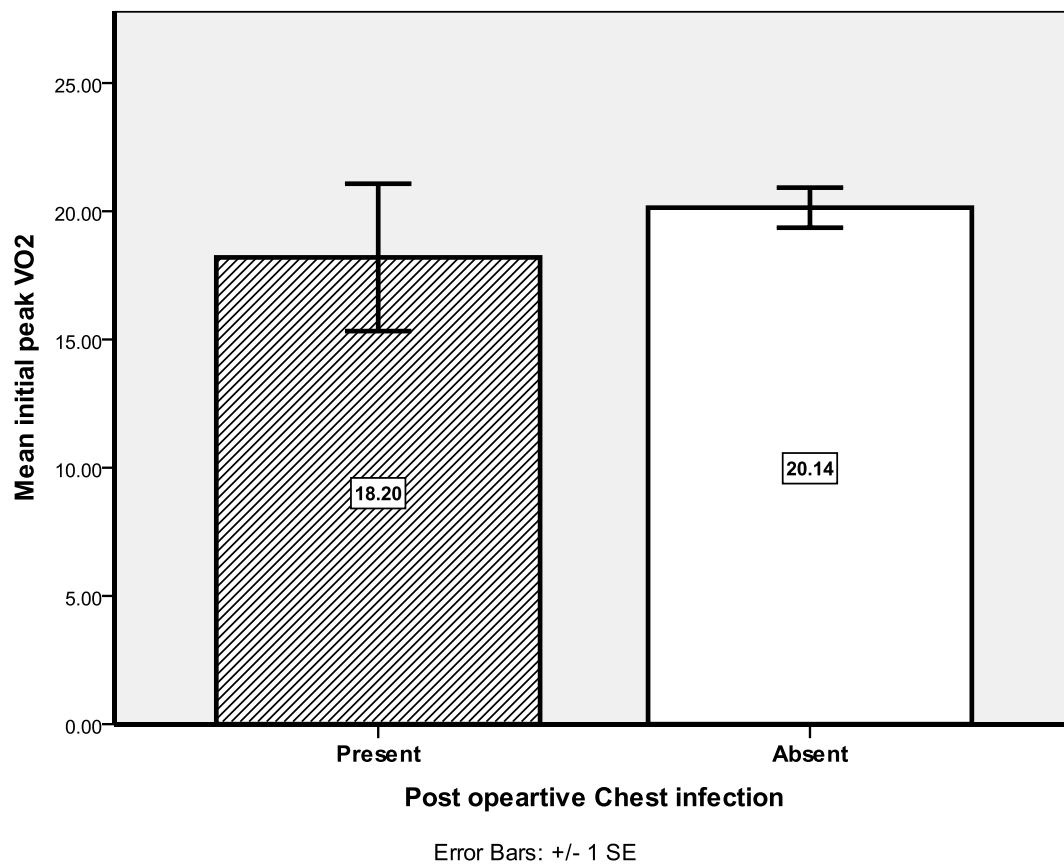
Figure 27: Chest infection and AT cut off of 11 ml/kg/min

Similarly, the mean initial AT in patients who had post-operative chest infection was 7.8 ( $\pm 3.3$ ) ml/kg/min compared to mean initial AT of 9.7 ( $\pm 2.6$ ) ml/kg/min in those patients who did not ( $p= 0.1$ ) (fig26).



**Figure 28: Initial AT and chest infection**

The mean initial VO<sub>2</sub> max in patients who suffered from chest infection in the post-operative period was 18.2 (± 6.4) ml/kg/min compared to 20.14 (± 5.5) ml/kg/min for those patients who did not have chest infection (fig 27). Although there was a slight difference between the two groups it was not found to be statistically significant (p= 0.4)



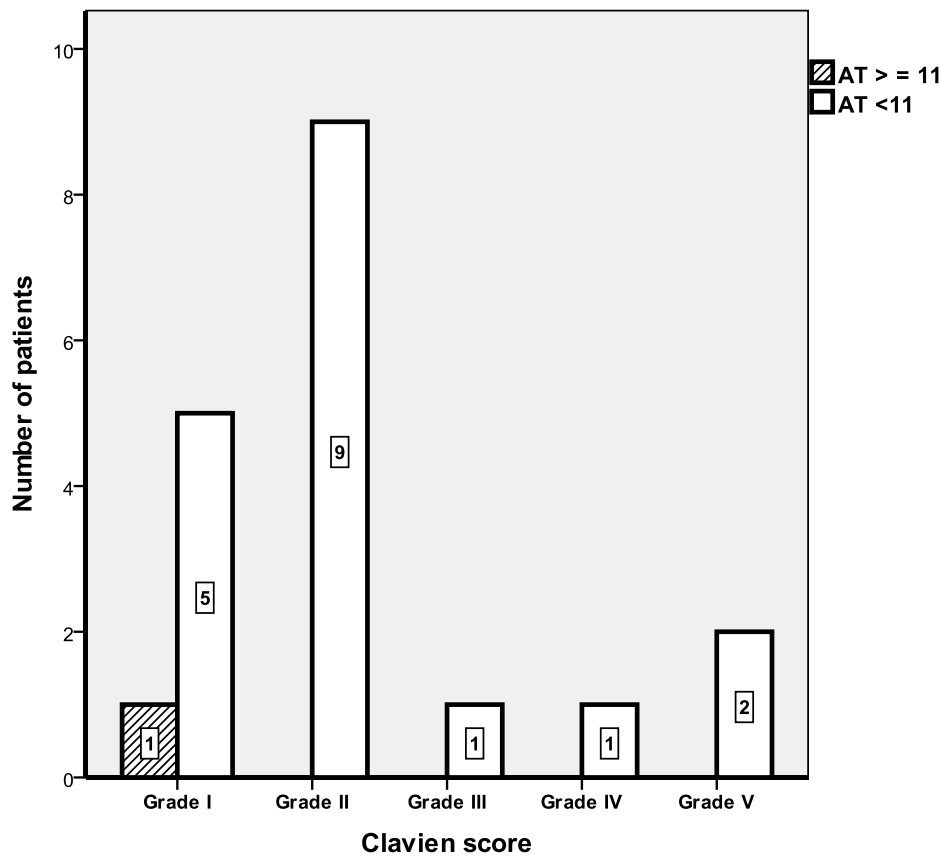
**Figure 29: Chest infection and initial VO<sub>2</sub> max**

### 3.3.5 Prevalence of complications according to Clavien classification:

The prevalence of postsurgical complications was more pronounced in those with a baseline anaerobic threshold (AT) of less than 11 ml/kg/min. In this cohort Grade I complications were seen in 5 (9.09%) patients, grade II in 9 (16.36%) patients, grade

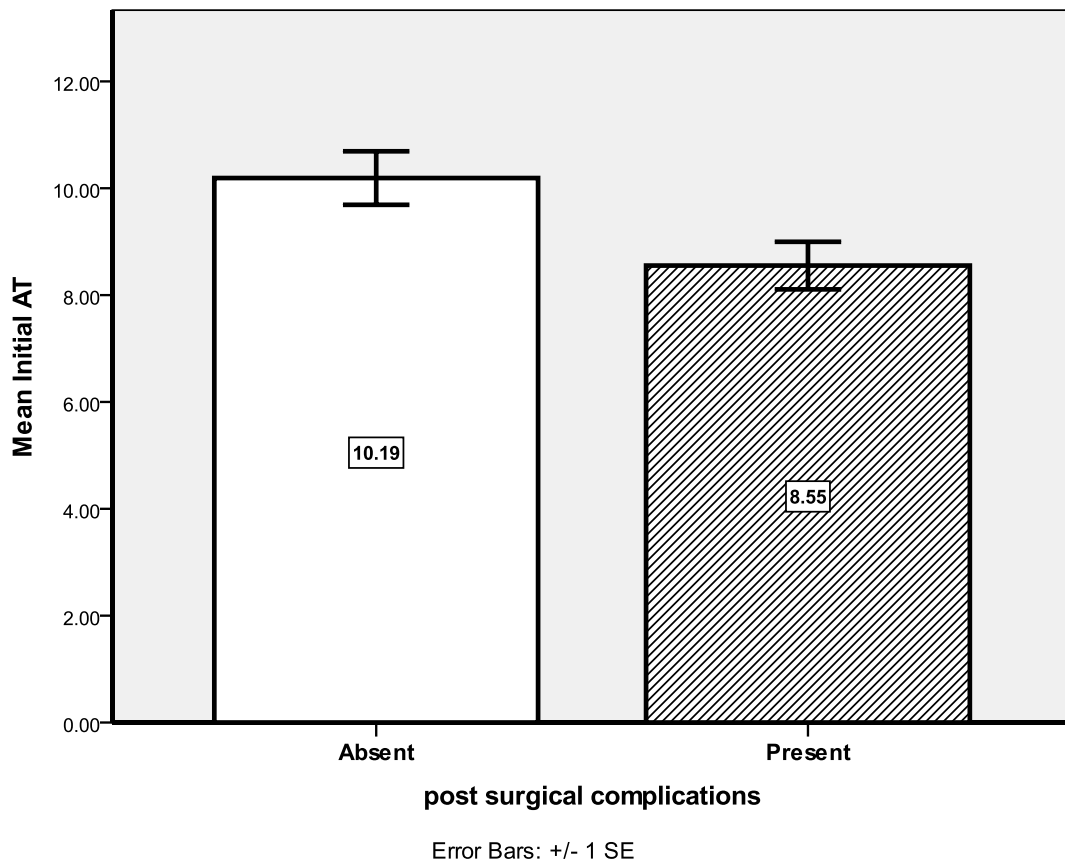
III and IV complications in 1(1.67%) patient each and 2 (3.64%) patients died after surgery (grade V complication) (fig 28).

In contrast in those patients who had anaerobic threshold of more than or equal to 11 ml/kg/min at baseline there was only one patient who had Grade I post-operative complication and none had any other grade of complications.



**Figure 30: Prevalence of complications using Clavien classification in patients with an AT above or below 11 ml/kg/min at baseline**

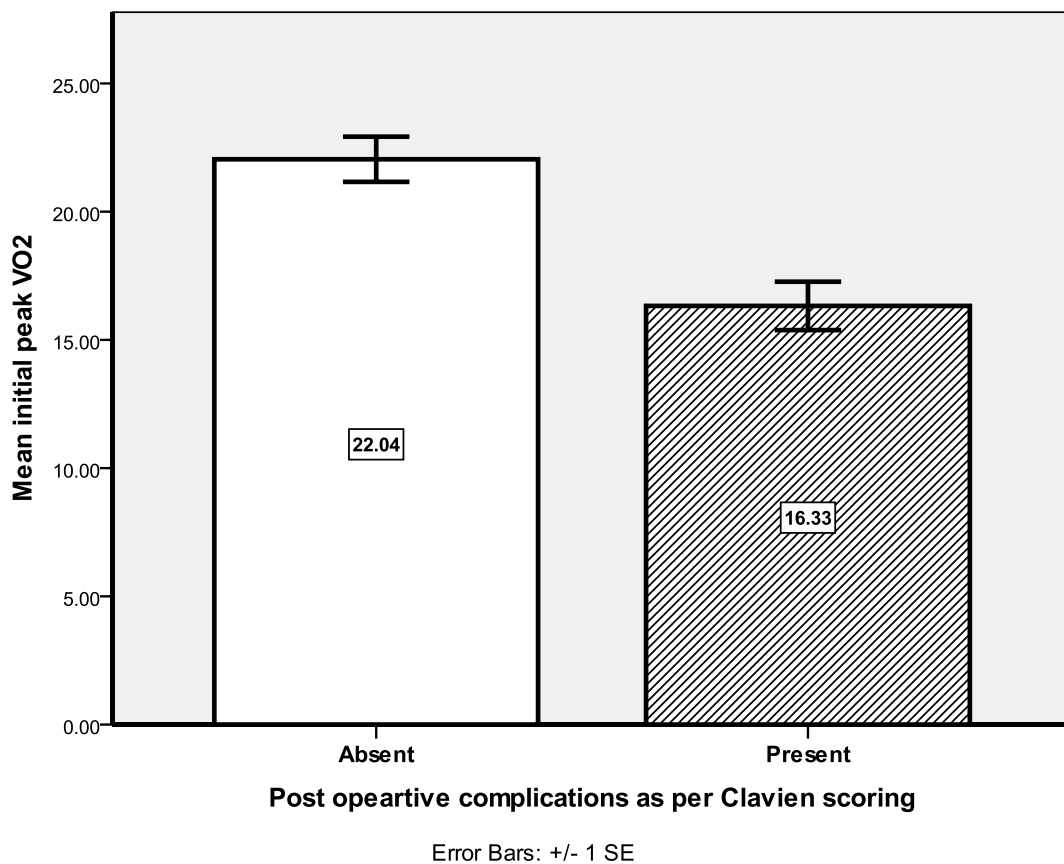
Similarly, the mean initial anaerobic threshold of patients who did not have any postsurgical complication was found to be higher ( $10.1(\pm 2.8)$  ml/kg/min) compared to those who had any postsurgical complications, where the mean initial anaerobic threshold was found to be  $8.5 (\pm 1.9)$  ml/kg/min ( $p= 0.03$ ) (fig29).



**Figure 31: Baseline AT and presence of post -surgical complication**



Those patients who had uncomplicated and straightforward recovery after surgery were found to have a higher mean initial VO<sub>2</sub> max of 22.04 (± 5.21) ml /kg/min compared to those who had some deviation from the normal (i.e. had Clavien score of one or more). The mean VO<sub>2</sub> max in the later group was 16.32 (± 4.21) (fig30). This difference was found to be statistically significant (p<0.001)



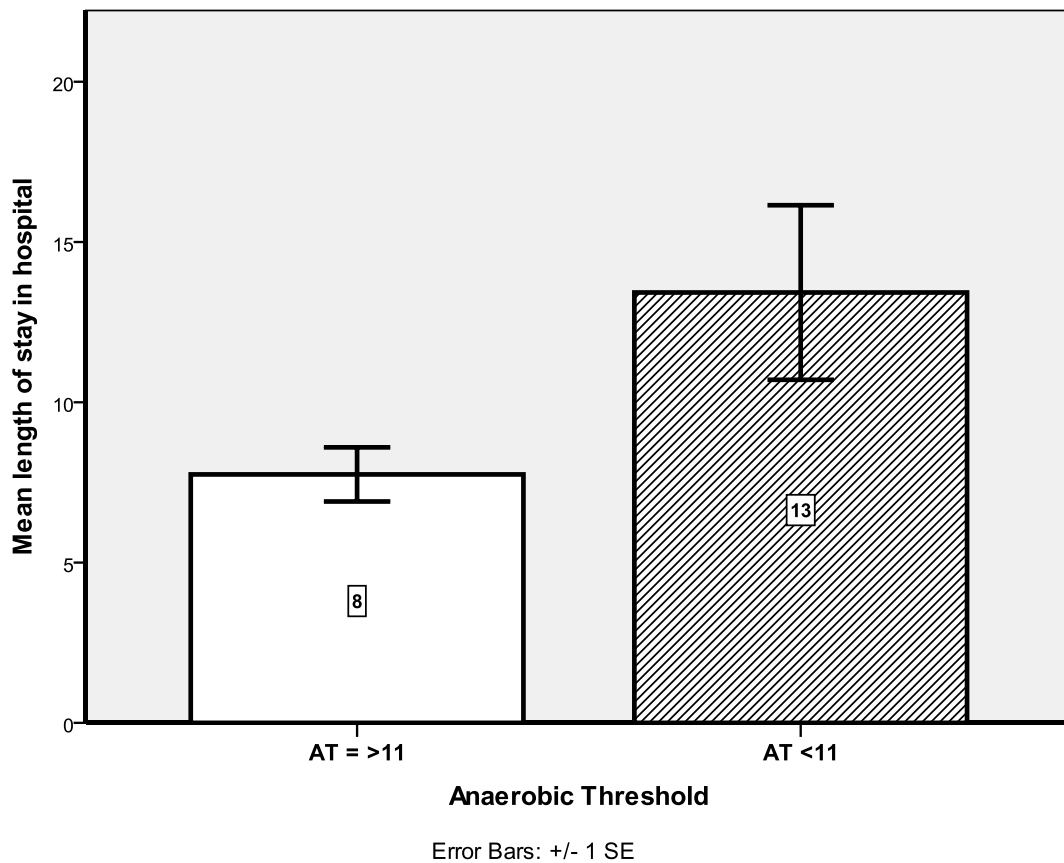
**Figure 32: Initial VO<sub>2</sub> max and post- operative complications**

### 3.3.6 Length of stay in hospital:

The median length of stay for the patients in the study population was 7 days. Median LOS in both the exercise and control groups were also 7 days.

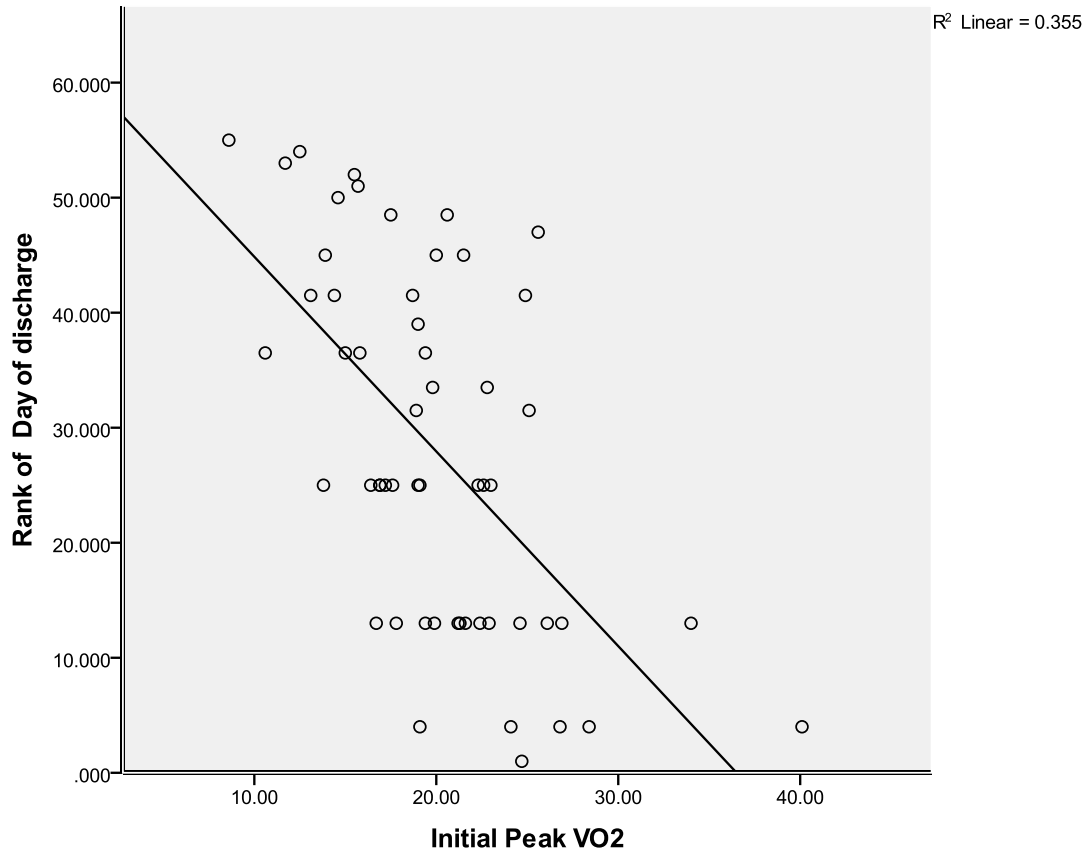
The mean length of stay in the hospital for patients with a baseline anaerobic threshold of more than or equal to 11 ml/kg/min was 8 days (range 5-14 days). Those patients with baseline AT of less than 11 ml/kg/min had a mean hospital length of stay of 13 days (range 4-90 days). (p=0.2) (fig 31)

Using Spearman's correlation analysis, it was seen that the initial anaerobic threshold had a negative correlation factor of -0.24 (p= 0.07) suggesting that there was a trend towards higher baseline AT and shorter LOS.



**Figure 33: LOS in relation to baseline AT of 11 ml/kg/min**

Similarly using Spearman's correlation there appears to be a strong negative link (the correlation coefficient being -0.59) between the day of discharge of the patient from the hospital and their initial VO<sub>2</sub> ma. (p<0.001) suggesting that patients with poor cardiorespiratory fitness tend to stay longer in the hospital (fig 32).



**Figure 34 Correlation between LOS and initial VO<sub>2</sub> max**

### **3.4 Effect of preoperative exercise on post-operative recovery:**

In this section it was analysed whether a short period (4 weeks) of preoperative exercise according to a protocol led to any changes in the post-operative outcomes and whether there was any appreciable difference in the post-operative outcomes between the “exercise” and “control” groups. Although it is recognised that the study was underpowered to look into these relationships and hence these outcomes were not primary outcomes for the study.

#### **3.4.1 Length of stay in HDU:**

There was no statistically significant difference between the length of stay in the high dependency unit between the control and exercise group patients. The mean length of stay in both groups was 2 days (range 1-7 days in control and 1-10 days in exercise group).

### 3.4.2 Need for inotropic support:

In the control group 25% (n= 7) patients needed inotropic support compared to 7.4 % (n=2) in exercise group (fig 33). Although not statistically significant (p=0.07), comparing these two groups using chi square method, there appears to be a trend that people in the exercise group required less of inotropic support compared to the control group.

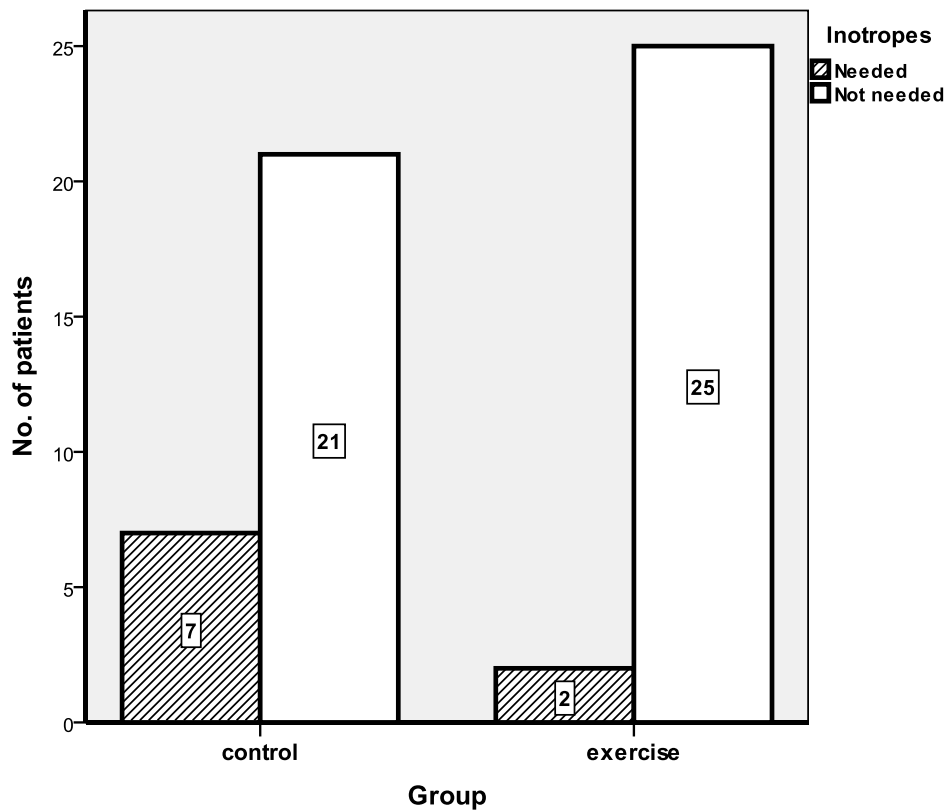
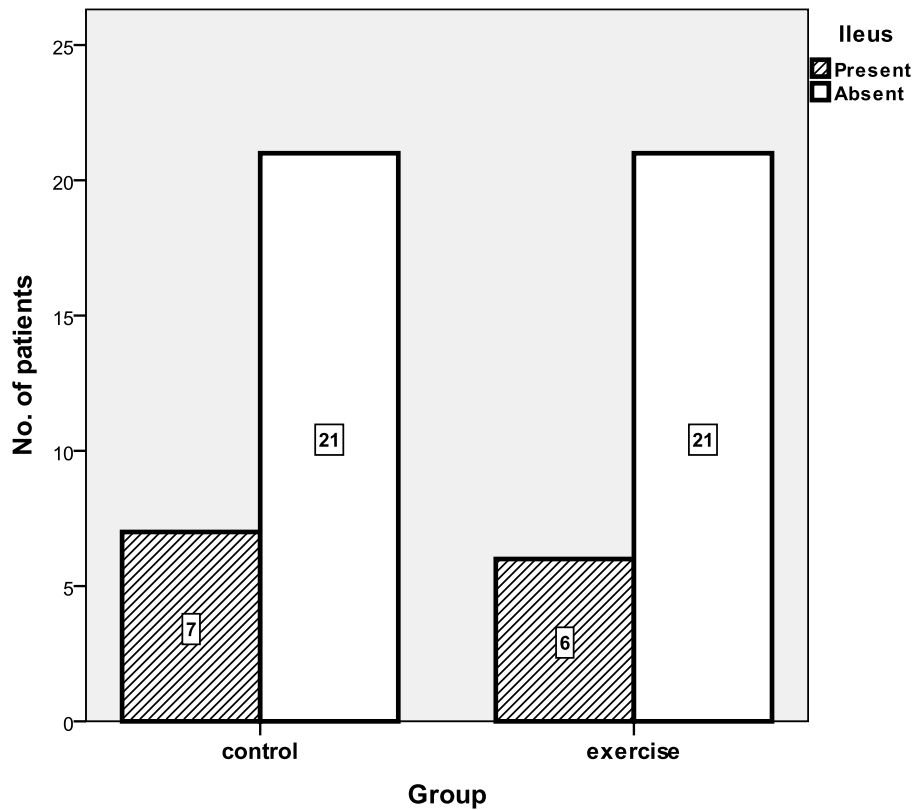


Figure 35: Effect of group allocation on the need for Inotropes

### 3.4.3 Prevalence of post -operative ileus:

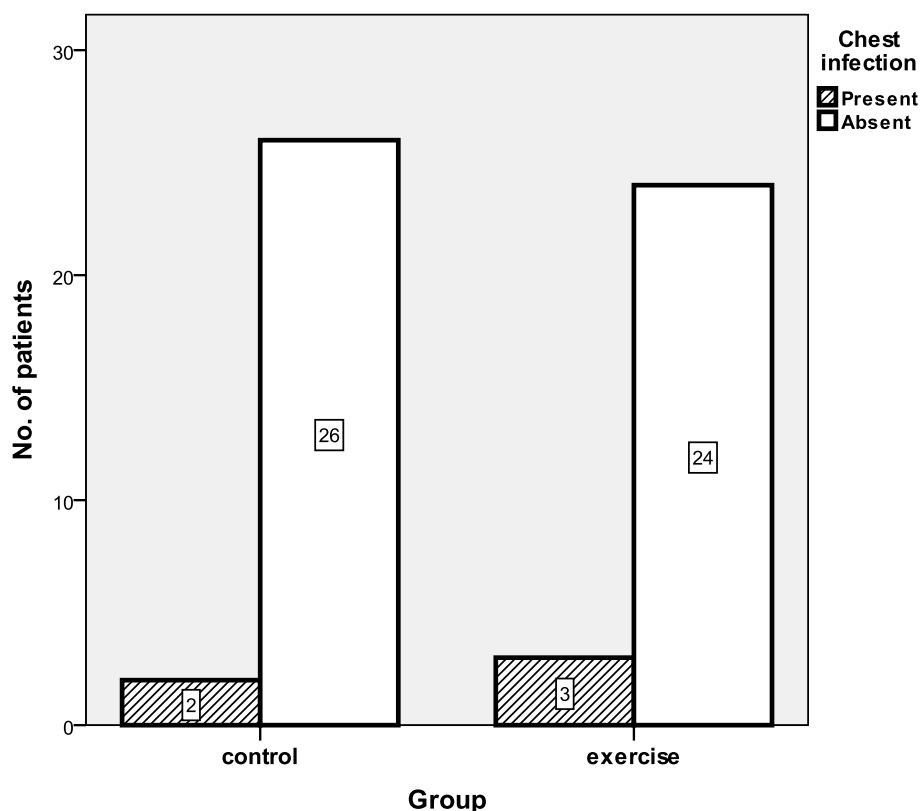
There was very little difference in the prevalence of post-operative ileus between the control and exercise groups. 25 % (n=7) of patients in the control group and 23.07 % (n=6) patients in the exercise group suffered from post-operative paralytic ileus. (p=0.8) (fig 34)



**Figure 36: Effect of group allocation on post-operative ileus**

### 3.4.4 Incidence of Chest infection:

Incidence of chest infection was also similarly distributed between the two groups. 7.14% (n=2) patients in the control group and 11.1% (n=3) patients in the exercise group were found to have post-operative chest infection. (fig 35)



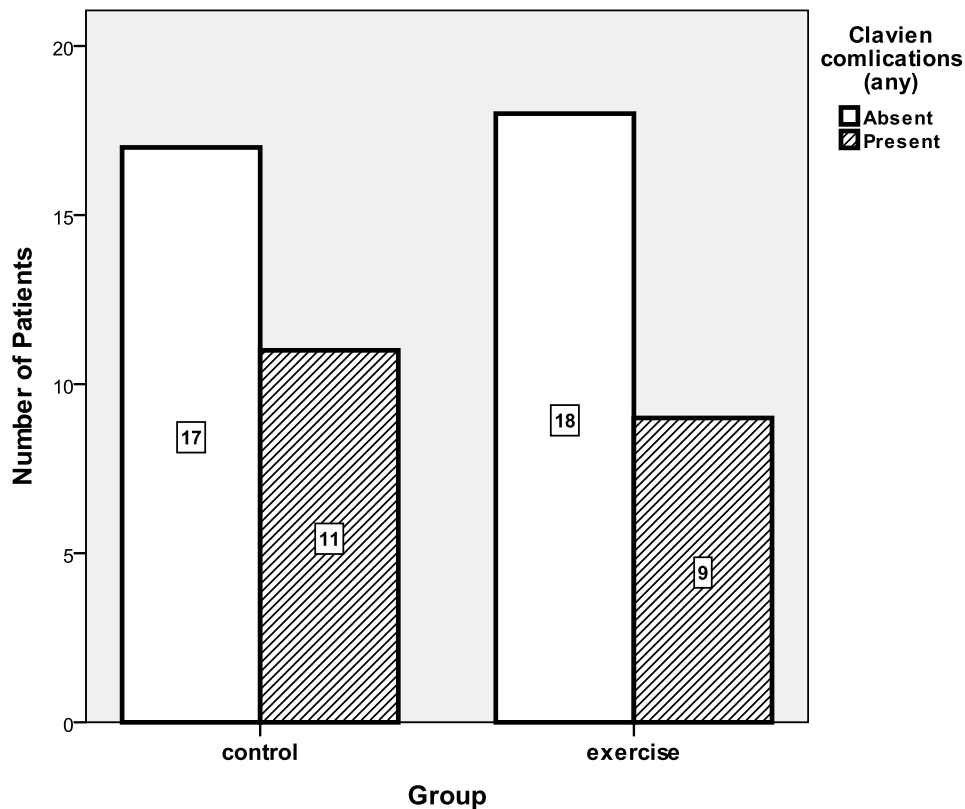
**Figure 37: Effect of group allocation on incidence of chest infection**

### 3.4.5 Incidence of complications:

39.28% (n=11) patients in the control group had some deviation from the normal post-operative course of recovery (i.e. had a Clavien score of Grade I or more) compared to 33.33 % (n=9) in the exercise group (fig 36). There was no statistically significant difference between these two groups (p=0.8). Considering the common factors known to influence post-operative recovery after RC, such as estimated blood loss (EBL) during surgery and operating time, the groups seemed to have been evenly matched

with no statistically significant difference (0.8 and 0.2) (142). The mean blood loss and operating time in the control group were 811( $\pm$ 717) ml and 310 ( $\pm$ 59) minutes respectively. In the exercise group the EBL and operating times were 603( $\pm$ 306) ml and 327 ( $\pm$ 61) minutes respectively.

Looking at the 30-day readmission rates it was noted that 12.7% (n=7) of patients having had RC were readmitted after discharge of which 4 (7.2%) were in the exercise group and 3 (5.5%) were in the control group.

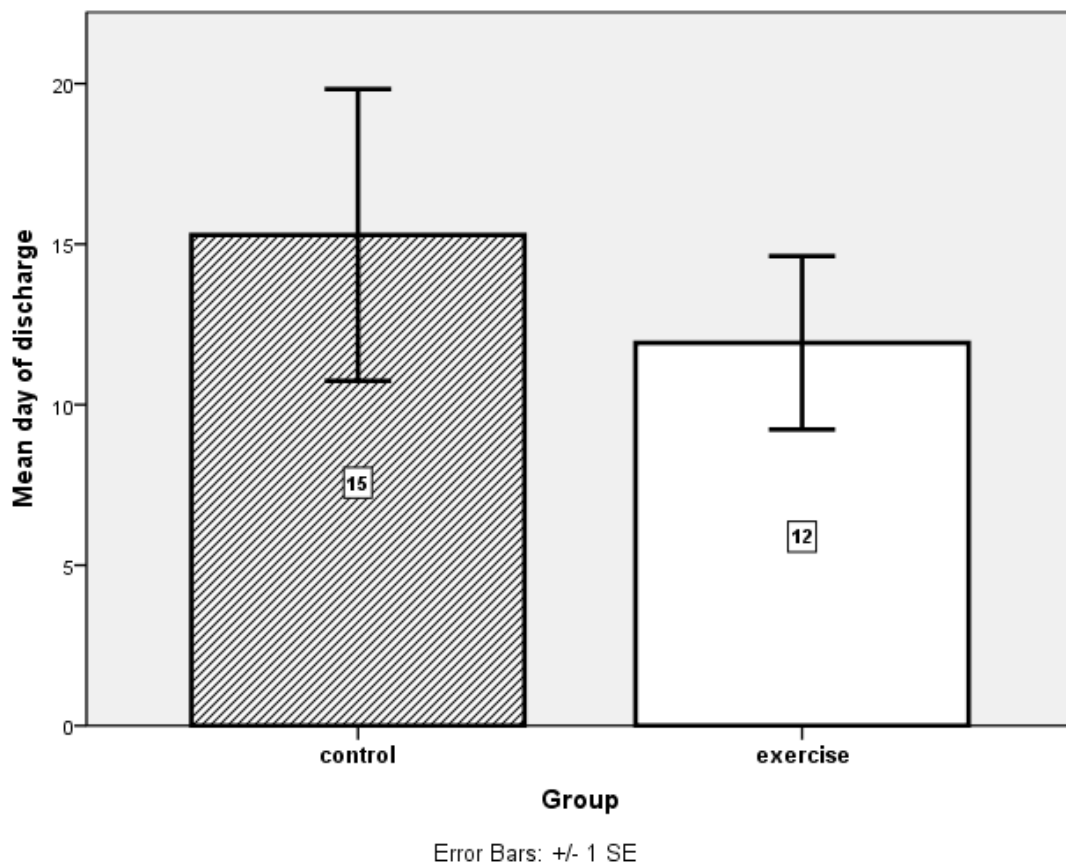


**Figure 38: Post op complications and group allocation**



### 3.4.6 Length of stay (LOS):

The mean day of discharge from the hospital was 12 ( $\pm 14$ ) days (range 4- 78 days) in the exercise group compared to 15 ( $\pm 24$ ) days (range 5-107) days in the control group (fig 37). The median length of stay in both groups were equal at 7 days. Using the Independent sample Mann Whitney U test there is no statistically significant difference ( $p= 0.8$ ) between the length of stay between these two groups.



**Figure 39: LOS and group allocation**

## **3.5 Qualitative analysis and focus group meeting outcomes**

### **3.5.1 Research Design & Participant Description:**

The patients who had participated in the exercise group (n=30) were approached at least six weeks after they have recovered from their surgery to see if they would be willing to attend a focus group meeting to share their thoughts about preoperative exercise. Based on their availability 15 participants were chosen to attend the focus group meetings. 13 participants eventually attended as 2 could not attend, due to last minute work commitments. Partners of the participants were also free to join these meetings as it was noted that during the exercise sessions some patients had attended with their partners to the exercise physiology laboratory at the UEA. Two of the participants who attended were female and the remainder male (n=11). Three partners (1 male and 2 females) of the participants also attended and shared their thoughts.

3 focus group meetings took place in total to keep the number of participants in each of the group around 4-5. As the study had staggered recruitment, spreading the focus group meetings also ensured that all meetings took place less than three months after the study finished in order to minimise recall bias.

### **3.5.2 Setting:**

The participants were invited to come to Norfolk and Norwich Hospital education department seminar rooms, where the interviews were conducted. The place of the interview was deliberately distinct from the exercise physiology laboratory where the patients had attended regular exercise sessions, avoiding either negative or positive associations with a particular site or building.

### **3.5.3 Data Collection Procedure:**

The interviews were conducted by Kelly Semper (qualitative research analyst who was not directly involved in the trial) and Prof John Saxton (supervisor to the PI). The principal investigator (SB) or any person involved directly with the participants in administering the exercise session or conducting the CPET were not present during the interview. All the three focus group meetings were recorded and later transcribed.

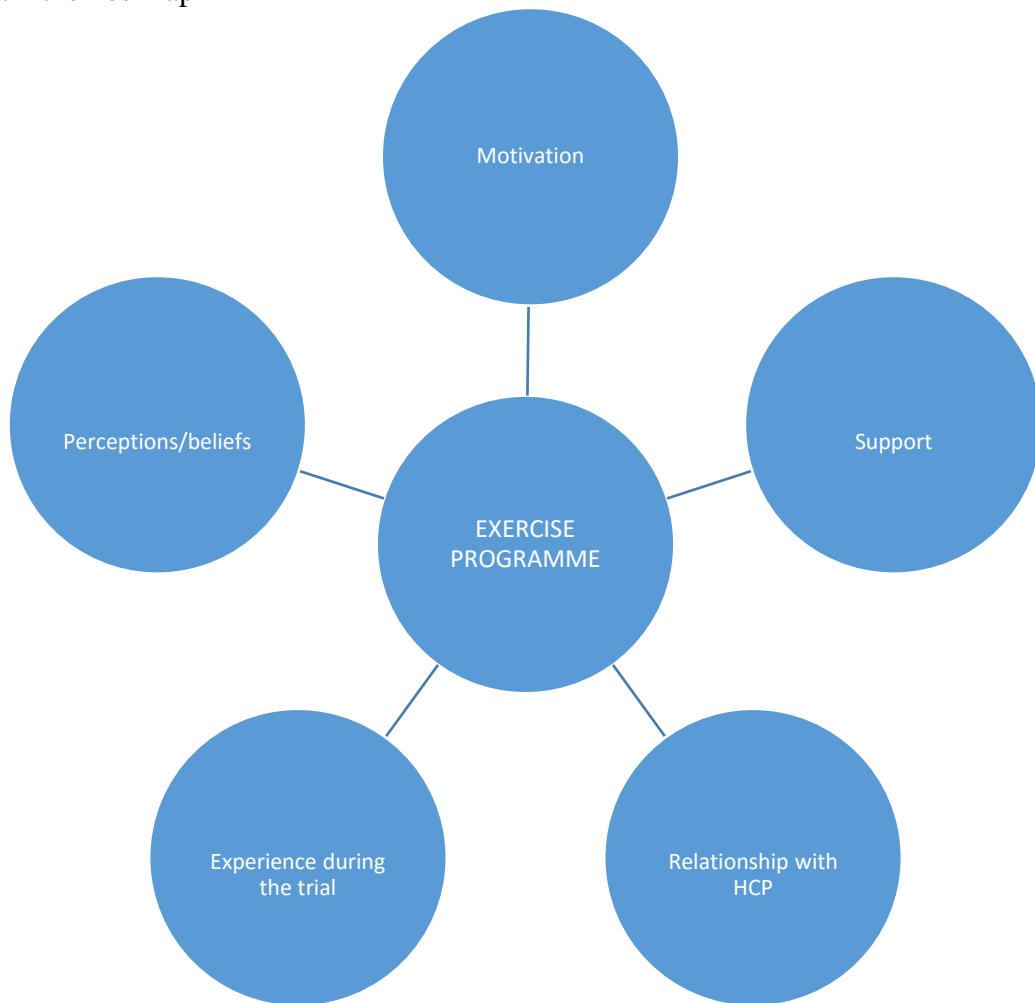
The focus group meeting was conducted using open ended questions to glean out maximum information possible regarding the experience the participants had during the exercise sessions. The participants were also encouraged to interact with one another and share their views. The conductor of the focus group meeting ensured that the discussion focused mainly on the preoperative phase and exercise sessions, although they were also free to express any thought they had about any perceived benefits or harm from the exercise sessions before the surgery.

### **3.5.4 Thematic analysis of focus group data:**

Detailed analysis of the data revealed the overwhelming message that the exercise programme was seen as a positive experience by the participants. They not only perceived a physical benefit with the exercise but also a significant psychological benefit; they were doing something to help themselves get better, influencing some control over the outcome of their operation when at the time of a cancer diagnosis the feeling of having any control is often lost.

Five main themes were identified which emerged during data collection and further analysis; “Motivation”, “Perceptions” “Relationship with the Health Care Professional(HCP)” “support” and “the experience of the exercise sessions”. Within these 4 main themes we found sub themes which we coded as such (see maps). We will now report each theme individually, supported by the words of our participants.

## Main themes map



### 3.5.4.1 Theme 1: Motivation (influencing/controlling own destiny):

The participants in this study were clearly self-motivated. They were keen to participate and to do anything which would help improve their recovery. They tended to have a positive approach to the forthcoming surgery, and were motivated to get better. The following quotes from the participants in the focus groups (fg) demonstrates this finding.

“....it’s a fairly major serious operation and anything that would help to recover...”  
(Ron focus group 2 (fg2))

“....I pushed myself harder to get better, I was fairly fit anyhow, but I pushed myself harder to get there” (Rodney fg2)

“.....and I was already trying to get myself fairly fit before you know walking and doing a bit of exercise because I thought that it would all help afterwards and when I was approached and asked to do this trial I thought it was brilliant absolutely brilliant, so I was really pleased that I got the exercise” ( Pat fg3)

“....they'd say well lets have another weight on and see what you can do, cos I was determined when they did that to still keep up to say 50-60 revs per minute you know”  
(Raymond fg3)

“it's definitely a big help because you know yourself that when your heart's pumping and you feel better don't you and when you finish you just think that's brilliant you know I really enjoyed that.....when you've got a really good reason to do it that makes you more positive and you know that hopefully it's going to help you it's a really good reason to do it isn't it you've got a definite goal” (Pat fg3)

Others also helped to motivate the participant. Encouragement from supervisors leading the exercise sessions had a positive influence and motivated some participants to keep going.

“I had chemotherapy and that really made me feel ill and so I was even worse I didn't want to do much at all then, but going up there every week and meeting two people who I got on well with who are very friendly and that was motivation I think as much as anything”( Brian fg1)

“they worked with you” (Brian fg1)

“...if you get on well with the instructors you're 99% of the way there, there's no doubt about that” (Roger fg2)

“It's good to have somebody measure your progress” (Trevor fg2)

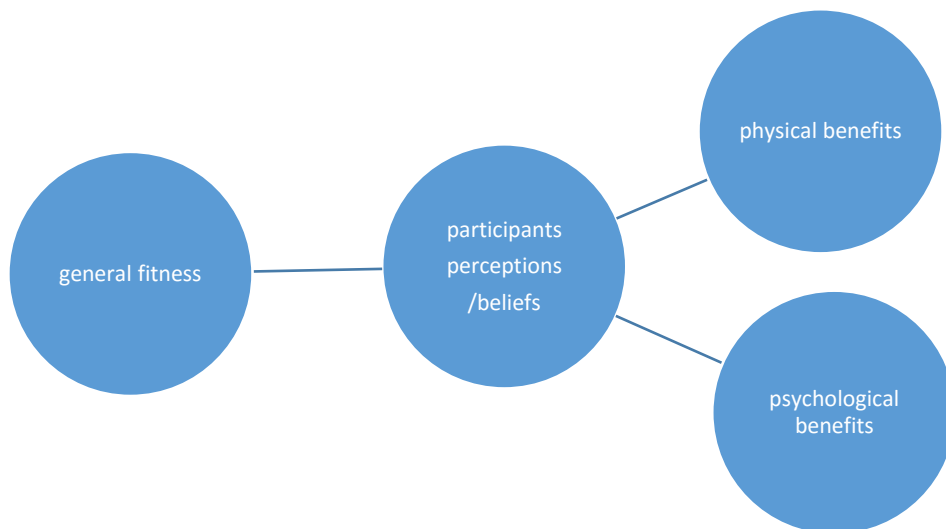
“The good part was the instructors spent all the time we were there all their time with us and that was very encouraging” (Trevor fg2)

“...the encouragement of the people making you, go on a bit more a bit more that was a big help cos I was ready to say I can't do anymore, but they just gee'd you on” (Clifford fg3)

“yeah they were very good with you know go on just a bit more” (Sheila fg3)



#### 3.5.4.2 Theme 2: Participants perceptions/beliefs:



#### **Participants' belief about their baseline physical fitness:**

The general theme in the focus group meeting was that the participants perceived themselves to be fairly fit pre operatively. Many already did regular exercise for

example walking dogs (Roger fg2) playing golf (Robert fg1) playing bowls (Ken) regular walking (Pat), cycling (Raymond fg3) or had an active job –(Brian fg 1 and Colin fg1).

“.....i thought I was fairly fit until I got on that bike.” (Colin fg1)

“But I've always been fit all my life..” (Robert fg1)

“I was quite fit cos I used to jog and I think I went up about 12% or something like that” (Trevor fg2)

“I work all day long normally” (Raymond fg3)

“Brian had a very physical job which had kept him fit all his life but he had given up work and the chemotherapy had made him feel quite ill, he describes getting out of breath even going to the shops but he could feel his fitness improving during the study” ( Brian’s wife fg1 )

“.....I knew I was very unfit, so it was going to be hard to start with especially during the chemo, but after the chemo I could feel myself getting better on the bike you know we were doing what was it a minute or 2 minutes each session and I knew from the start when I started to when I was like on the last one how much better that was for me.....” (Brian fg1)

### **Belief about the Physical benefits of exercise programme:**

Physically many participants felt themselves improving their fitness with the exercise sessions.

“....the first time I couldn't do it, I did one 5 minute interval, but by the end of the process after about 3 sessions I was doing more and with weights on” (Rodney fg2)

“I thought it was very beneficial..... I couldn't have done it, had the op without”

“....because the test of my heart rate and everything was better after the exercises” (Clifford fg3)

“....you could see yourself getting better each week” (Pat fg3)



“you could yeah” (Clifford fg3)

“going a bit further, a bit faster” (Sheila fg3)

“...you didn't puff you weren't puffing so much” (Clifford fg3)

“..yeah that's right” (Sheila fg3)

“...felt better near the end” (Robert fg1)

Although not everyone saw physical improvement which they found disappointing

“I was a bit disappointed actually because having done the initial test and then gone through all the exercises the results were almost exactly the same..... He said the problem is you were already fairly fit before you started and so he said that sometimes happens” (Ron fg2)

### **Belief about the Psychological benefits:**

The benefits of taking part and improving physically also had an effect on the participants' psychological well being

“Oh yes it gives you a lift doesn't it, it obviously helps you if they tell you that you've improved that you know your health has improved to that extent you feel satisfied” (Ken fg1)

“Well I think it actually gave me a bit more confidence for the operation because of course you are going to be worried if you have been diagnosed and I thought well if they have put me on the exercise programme perhaps it's not as bad as they thought, so it actually gave me confidence to be on the exercise group .....” (Roger fg2)

It helped the participants feel good doing something to help themselves.

“you feel better” (Pat fg3),

“mentally encouraging” (Trevor fg2)

“You’re thinking you’re doing something good you’re helping yourself for the operation” (Ron fg2)

“I think it's something that you can do to help yourself when there's not much else you can do, but you did feel you were trying to do something to make it more successful” (Pat fg3)

Some described it as the logical thing to do to try to improve their fitness before major surgery.

“....logical that if you make yourself fit you’re going to have a better time getting through the operation” (roger fg2)

“it’s a known fact people always say.....they say the fitter you are the more you recover” ( Brian’s wife fg2)

For others it acted as a diversion, filling in the time whilst awaiting their surgery.

“It filled in the time you are waiting to go in for a large operation. It fills the time in that's one small part, but for me that was a big part it filled the time in, I had 2 or 3 weeks going to the gym, quite enjoying it because prior to that I used to go to the gym anyway, so I didn't really find it that difficult, but it filled the time in nicely until the day came when you had to come in to hospital to have the operation.” (Colin fg1)

Ken agreed with this “...it took your mind of it, yeah” (ken fg1)

“you feel as if you’re doing something to prepare yourself for the big day rather than sitting and waiting for it” (Trevor fg2)

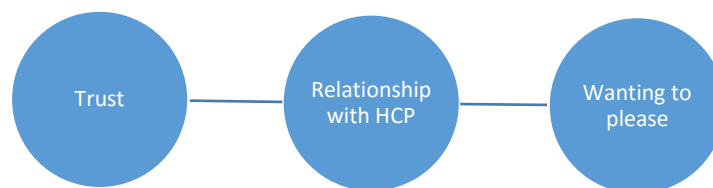
“..yeah, but I think that helped because it's something else to take your mind off of it a bit isn't it” (Raymond fg3)

Others didn't worry so much and were able to keep themselves occupied.

“.....I kept myself occupied cos there's no use keep thinking about it cos you've got to have it done” (Robert fg1)

“I've never been a worrier, I'm not an emotional person and my glass is always half full always, so I actually didn't even think about my operation until the morning I went in. It just didn't cross my mind as to what was going to happen. As far as I was concerned I was just going in to hospital and that was it. People kept saying to me aren't you worried about going in and I said no.....” (Brian fg1)

### 3.4.5.3 Theme 3: Relationship with the HCP/recruitment:



We observed that the relationship with the healthcare practitioner (HCP) played a part in the participants' decision to take part. Trust in the HCP was demonstrated by the following statements

“...so if a medical person says get fit and you’ll possibly have a better outcome after operation then I think I’ll do it” (Colin fg1)

“...when it was explained to me what it would do that it would probably help recovery, although I felt able to recover anyway anything that could help does encourage you. If somebody says something is going to help you then you know you take that advice” (Brian fg1)

“.... well I mean the Doctor tells you well I'd like you to do these things and you just would normally believe in what he says is good for you...you don't go against them otherwise that would be silly” (Raymond fg3)

“I think we've become attuned to well medical people say things and you take it as read” (Ken fg1)

“.....my own doctor was keen on it for starters” (Roger fg2)

“..my own GP has always backed me 100% right the way through whatever I wanted to do he said yeah you do it” (Roger fg2)

“...and seeing the doctors “as gods” (colinfg1), “respecting their knowledge” (Brian fg1) as “they’ve had years of training” (Colin fg1)

Wanting to please the HCP was also demonstrated in the focus group meetings repeatedly.

“....when Mr Rochester first saw me and told me I was going to need this operation he sold this thing to me then and you're not going to say “no” are you?.....you're not going to say no to a bloke that in a few weeks is going to open you up and take your bladder out are you?” (Colin fg1)

“Mr Banerjee came to see me and asked me if I would participate in this exercise or in exercise to improve my health before the operation and to see what the recovery time was afterwards, so I said yes well I'll do anything like that to help obviously” (Ken fg1)

Focus group 3 were asked directly if it helped that a HCP was asking them to take part in the study, all agreed that it was influential in their decision to take part.

“Mr Banerjee was very cordial and told me all the benefits it was very good, yeah I think that was a big help” (Clifford fg3)

“I think it was good it was Doctor Banerjee and also we learnt a lot of information from him about the operation because he is a Urologist isn't he so he can answer a lot of questions and talk to us and it was really useful having the conversations with him, we learnt a lot” (Pat fg3)

#### **3.5.4.4 Theme 4: Support from family members:**

Results showed that many of the participants were well supported by their spouse or family member in both taking part in the trial as well as recovery from the surgery.

“I think if it wasn't for my wife I think I would be struggling still” (Robin fg2)

“.....my wife is extremely supportive, so it helps....”(Ron fg2)

“Whenever I complained about anything .....my wife would say look you're alive” (Ron fg2)

“.....you know when he doesn't feel like doing something you must, you must you know and it's really hard work” (Sheila fg3)

“I was finding it hard to get out of my chair one Sunday and if she hadn't kicked my butt I wouldn't do things” (Clifford fg3)

Some wives or a family member accompanied their husbands to the lab and even took part, (Robin's wife) others encouraged their husbands to continue the exercise at home

"I just sat and watched, but I was there" (Clifford's wife Sheila fg3)

"...my daughter came with me to most of them... she was there and very supportive,"  
(Pat fg3)

### 3.5.4.5 Theme 5: the overall experience of participation in the exercise programme

All the participants when asked about their experience of the study had only positive comments to make. “Good” (Colin 1, Robert 1, Robin 2, Barry 3), “enjoyable” (Barry 3, Ron 2, Roger 2, Trevor 2,) “good fun” (Ray 3) “interesting” (Brian 1) “helpful” (Colin fg1 ,Vincent fg3 ,Pat fg 3).

Vincent (fg3) commented that “starting is the problem.....doing it in the first place that’s the difficult bit”.

Mostly the participants would recommend it to others.

“I would recommend it to anyone that needs it” (Clifford fg3)

Some participants even commented that they had continued to carry out self-directed exercise following recovery from the surgery.

“ I have started doing brisk walking as soon as I recovered ” (Brian fg1). Colin (fg1) agreed “ I am totally sold to this idea...I am definitely going to continue”

Some felt that 2 sessions a week were about right (Trevor, Ron, Vincent) but others felt they could do more (Roger, Rodney, Trevor ,Clifford)

## Chapter 4: Discussion

### 4.1 The study population; representative of the target population being studied

In the study population the mean age was 72 years (range 52 -85 years). This was in line with the age distribution of patients who undergo radical cystectomy for bladder cancer (143). The study population also had an expected prevalence of co-morbidities and smoking habits. Hypertension (56.6%), Ischemic heart disease (IHD) (18.3%) and Diabetes (11.6%) were the most common disease observed in the participants. This matches closely the prevalence of these common diseases in the general population between 60-80 years.

68.3 % of the participants were either ex-smokers or were currently smoking. Smoking is a well-recognised risk factor for bladder cancer and not surprisingly a sizeable proportion of the study population had this habit at some point in their life. As expected there was a preponderance of male patients. There were a total of 7 female participants to 53 males.

60% (n=15) of eligible patients i.e. those patients who had muscle invasive disease at presentation, had neoadjuvant chemotherapy. Published literature have shown that historically 1-17% of patients undergoing cystectomy were offered neoadjuvant chemotherapy. Recent trends however have shown an increase in utilisation of neoadjuvant chemotherapy to about 30- 57%. ((144)

It was noted that the patients were similarly matched in terms of demographics such as age, BMI, smoking habits and prevalence of comorbidities. The distribution of fitness parameters at the start as determined by initial CPET analysis (i.e before randomisation) such as VO<sub>2</sub> max, AT, V<sub>E</sub> and oxygen pulse were also similarly distributed in the control and exercise groups. This indicates that there is a possible causal relationship between the intervention (i.e preoperative exercise) and change in CPET parameters at the end of the study.



## 4.2 Feasibility outcomes recorded show that a randomised control trial is feasible

The primary outcome measure for this study was to confirm whether a randomised controlled trial, looking at benefits of pre-cystectomy exercise or prehabilitation, is feasible or not. Patients undergoing cystectomy are often elderly, smokers with significant comorbidity. It was not yet clear whether such a group of patients would be willing or able to undertake preoperative physical exercise.

Recruitment to the trial was satisfactory. Of the 112 eligible patients that were approached, 60 agreed to take part in the trial over a 2-year recruitment period. We postulate that the main reasons that the recruitment rate was so good at 53.3% was that it was a short intervention (4 weeks) and that eligible participants were first approached about the trial by their treating physician before being approached by the principal investigator. Thematic analysis of the focus group meetings confirmed that the patients felt motivated to do something in the preoperative time they had to influence the outcome of their surgery. They felt well supported by their family members and partners. Surprisingly many participants in the exercise group thought they were fit because of their active lifestyle (i.e. walking regularly or having a manual job etc.). After the CPET they were able to compare their fitness in relation to their predicted cardiorespiratory fitness levels which possibly acted as a motivational tool to get even fitter. Another recurrent theme during the focus group meeting was that participants perceived and believed that they had both a physical and psychological improvement following the exercise sessions which made them better prepared to undertake the stress of major surgery.

When participants of the focus group meeting were asked to summarize their overall experience of the exercise programme, adjectives such as “enjoyable” “interesting” “good fun” and “helpful” were used. A number of the participants confided that they had started performing self-directed exercise following their recovery from radical cystectomy. Quite a few people in the exercise group felt that they would recommend preoperative exercise to friends and family if they were in the similar circumstances.

The main reason for nonparticipation as given by eligible patients was distance from the exercise physiology lab located at the University of East Anglia from their home. As highlighted previously, the Norfolk and Norwich Hospital covers a wide geographical area as it is one of the tertiary referral centres for bladder cancer in the East of England. For future larger multicentre study, the recruitment rate is likely to be higher if the exercise labs are located in different areas allowing easy access to the participants. Only a small minority of patients (5.7%) felt that they were not ready to undertake physical exercise on a regular basis as they had led a sedentary life. The other common reason for nonparticipation (in 7.6% of non-participants) was the presence of either catheters or nephrostomy tubes which patients thought might prevent them from either undertaking CPET analysis or regular physical exercise. Interestingly however two of the participants who had taken part in the trial had nephrostomy tubes and catheters.

Although the trial participants were from an ageing population with a number of comorbidities no problem was encountered during the CPET analysis either at the baseline or after the four-week period. The participants understood the instructions with regards to achieving the maximum output while undertaking the incremental exercise on the cycle ergometer whilst undergoing CPET. Compliance with randomisation was very good. All participants were happy to be randomised into either of the two groups (exercise or control) and no one withdrew consent following randomisation due to unsatisfactory group allocation. 2 participants however in the control arm participated in self-directed exercise after being randomised.

Retention into the trial was very good with low dropout rates. In the control arm 83.3 % (n=25) patients attended both the initial and final CPET assessment where as in the exercise group 86.7 % (n=26) attended both. 2 patients in the control group and 3 in the exercise group did not have surgery at the end of the trial period and opted for radiotherapy instead, either as a personal choice or after being deemed unfit by the anaesthetists to undergo surgery.

Adherence to the exercise sessions as per the protocol was also very good, 66.7 % (n=20) participants attending at least four weeks of exercise sessions. 10% (n=3) participants had dates for cystectomy before four weeks and hence had their repeat CPET assessment before the planned 8 exercise sessions. A further 10% (n=3) dropped out during the trial from the exercise group after deciding to opt for radiotherapy. The rest of the patients (n=2) who did not complete four weeks of exercise did so because of lack of time in their day as they were both self-employed. Interestingly 4 patients requested permission to continue exercise sessions as their date for surgery was more than four weeks away. These patients had their repeat CPET assessment after the scheduled four weeks and had another CPET assessment just before surgery. During analysis only the first and the second CPET assessment values (i.e. four weeks apart) were used.

Level of exhaustion as perceived by the participants during exercise sessions was recorded using the Borg RPE scale and all the participants were achieving scale of 13-15 during the exercise sessions (suggesting that the participants found the exercise effort between “somewhat hard” and “hard”). In spite of exercising at quite close to their peak heart rate and moderate- high level of physical exhaustion there was no evidence of any adverse events in the participants during the trial.

Different authors have utilised various cut-off levels to prescribe exercise for elderly cancer survivors (such as heart rate at AT, 60 to 80% of VO<sub>2</sub> max etc.) The American College of Sports Medicine (ACSM) convened a panel of experts to review the available evidence supporting exercise prescription guidelines for cancer survivors (145). The panel concluded that cancer survivors follow the 2008 Physical Activity Guidelines for Americans ( $\geq 150$  mins/week of moderate-intensity, or  $\geq 75$  mins/week vigorous-intensity aerobic exercise or an equivalent combination of moderate- and vigorous intensity aerobic exercise) for cancer survivors, yet few studies have tested this empiric prescription in a formal randomized controlled trial. There are no published guidelines as to safe and desirable level and intensity of exercise in cancer patients before major uro-oncological surgery. The current data shows that it is safe to exercise patients at close to 90% of their peak heart rate even in an elderly cohort of patients but further evidence would need to be collected to prove that this is the case.

### 4.3 Changes in CPET outcomes in the exercise group

The CPET parameters (such as the  $\text{VO}_2$  max, AT, oxygen consumption, minute oxygen consumption at  $\text{VO}_2$  max and oxygen pulse) were found to be normally distributed in the study population and hence univariate analysis (ANCOVA) (with their baseline/initial CPET variable at the start of the trial as the covariate) was utilised to look for the difference in variance in these parameters between the control and exercise groups.

It was found that after the four weeks of exercise some of the CPET outcomes had improved in the exercise group in comparison to the control group. The mean  $\text{VO}_2$  max had increased by 1.9 (95% CI 0.87 – 3.00) ml/kg/min. ( $p=0.001$ ) and the mean oxygen consumption ( $\text{VO}_2$ ) had increased by 168.9 ml (95% CI 86.2 - 251.7) ( $p < 0.001$ ). Similarly, the minute Oxygen consumption at  $\text{VO}_2$  max had increased by an average of 8.10 (95% CI 3.5 –12.6) L/min ( $p=0.001$ ) in the exercise group in comparison to the control group.

Oxygen pulse which denotes uptake of oxygen per heartbeat was found to have increased by an average of 1.60 ml/beat (95% CI 0.87- 2.3) ( $p < 0.001$ ) in the exercise group.

Anaerobic threshold (AT) had also increased by 0.33 (95% CI - 0.68 to 1.3) ml/kg/min (although this was not found to be statistically significant,  $p=0.5$ ).

These findings illustrate that despite the period of “prehabilitation” being short, the patients generally improved their cardiorespiratory fitness levels as assessed by CPET. There is very limited evidence investigating the role of short preoperative aerobic exercise with the view to improve post-operative recovery. A recent systematic review by Valkenet et al looking at 12 studies of patients undergoing joint replacement, cardiac or abdominal surgery showed that inspiratory muscle training in the immediate preoperative period reduces risk of postoperative pulmonary complications. The intervention (exercise) period in most of these studies also appear to vary between 2-6 weeks, as preliminary results suggest that the maximal benefit is appreciated in the first few weeks after which the effect plateaus (146) . The intensity and modality (either inspiratory or aerobic exercise) of training are important aspect to consider to achieve

optimal outcomes (147). However, there does not appear to be a consensus amongst the authors about the type of exercise, frequency, duration and intensity that needs to be prescribed in the preoperative period. Of the various studies looked at in the systematic review there was a variety of interventions including inspiratory muscle training, strength training and or cardiovascular fitness training. While some interventions were unsupervised (home based) some partly and some fully supervised by physical therapists (148–151). We were not aware of any other study looking at the role of preoperative exercise in patients undergoing radical cystectomy.

#### **4.4 CPET assessment outcomes as a predictor for post-operative recovery**

Complications after major surgery has significant impact on short and long-term mortality and morbidity. (152) A recent study of 6577 patients undergoing RC, showed that even one postoperative complication may double the odds of postoperative death, with postoperative respiratory tract infections and systemic infection having the most significant influence.(153). The use of cardiopulmonary exercise testing (CPET) as a preoperative risk stratification tool for a range of non-cardiopulmonary surgery is increasing. The utility of CPET in this role is dependent on the technology being able to identify accurately and reliably those patients at increased risk of perioperative events when compared with existing risk stratification tools such as ASA grading.(80)

##### Rationale behind using a cut off AT of 11ml/kg/min

Older et al demonstrated an increased post-operative mortality and morbidity in elderly patients undergoing major abdominal and cardiothoracic surgery if they had a low preoperative anaerobic threshold. They also suggested that an anaerobic threshold of 11 ml/kg/min seems to be the cut-off point beyond which there is a higher rate of cardiovascular morbidity and mortality (0.8% vs 18%).(82) Wilson et al in 2010 after analysing a large number of patients from a different series undergoing major abdominal and cardiothoracic surgery (n=847) came to similar conclusions. They showed that a cut of AT of 11ml/kg/min was able to predict hospital mortality (AUC 0.68, 95% CI 0.59 to 0.76) with a sensitivity of 88% and a specificity of 47%.(84)

Snowdon et al found that both AT and VO<sub>2</sub> max predicted complications in 116 patients following major abdominal surgery. The optimal AT to distinguish those at increased risk of postoperative complications was found to be 10.1 ml/kg/min in their study.(154) In a recent study of 69 patients undergoing cystectomy Snowden et al demonstrated the optimal threshold value for the prediction of complications by AT to be 12 ml/min/kg.(93) These studies show that, for intra-abdominal surgery, the AT is associated with postoperative outcome and has the capacity to predict morbidity and mortality with a reasonable degree of accuracy. Although there is no consensus amongst authors as to the absolute cut off of AT, it appears to be between 10-12 ml/kg/min. In fact in a recent systematic review Grocott et al recommended that an AT of 11 ml/kg/min appears an acceptable threshold to use in a clinical setting to indicate increased perioperative risk following major intra-abdominal surgery.(80)

Although the sample size is small in our study we looked at the relationship between preoperative CPET parameters and post-operative outcomes. As our study population had similar characteristics to the studies above (i.e. elderly and undergoing major intra-abdominal surgery) rather than having to redefine a cut off AT we decided to use an AT of 11ml/kg/min as our cut off. These measures were recorded as secondary outcomes from the feasibility trial.

In our institution there is usually a gap of 6 weeks between patients having neoadjuvant chemotherapy and RC, this is to allow for optimisation of physiological function before the further stress of surgery. Studies have shown an increase in complications when RC was performed too soon after neoadjuvant chemotherapy (155)(156). Only a small study till date has shown a poorer oncological outcome when cystectomy was delayed beyond 3 months (156). Hence at our trial we recruited patients after 2 weeks of finishing chemotherapy and once they were in the trial for 4 weeks ,their surgery was not delayed due to participation in the trial thereby minimising chances of cancer progression.

We appreciate that several confounding factors such as the type of surgery, duration of surgery, blood loss and the expertise of the surgeon could all have a bearing on post-operative recovery rather than just fitness itself. Two of the patients (3.6%) out of 55

who went for radical cystectomy eventually had open cystectomy whereas the rest had laparoscopic surgery. Three of the patients (5.4 %) had a neo bladder reconstruction and the rest had standard ileal conduit. It is well recognised that the type of surgery (whether minimally invasive or open) and reconstruction (whether standard ileal conduit or reconstructed neobladder) does have a bearing on post-operative recovery (157,158) . In the present study as the numbers were quite small it was difficult to statistically analyse these patients separately and come to any logical conclusion and hence were analysed together (n=55). The mean blood loss and operating time in the control group were 811( $\pm$ 717) ml and 310 ( $\pm$ 59) minutes respectively. In the exercise group the EBL and operating times were 603( $\pm$ 306) ml and 327 ( $\pm$ 61) minutes respectively and the groups were found to be evenly matched to avoid confounding. The CPET parameters used in this instance were the baseline (i.e. *before* the participants were randomised into any group) variables so as to avoid any role of preoperative exercise acting as a confounding factor in the analysis.

#### Length of stay in HDU and need for post-operative inotropic support

All the patients after cystectomy at our institution are normally transferred to the high dependency unit. The possible need for inotropic support is one of the main reasons why patients after major surgery such as radical cystectomy are transferred to the high dependency unit.

There was found to be negative correlation of - 0.41 ( $p = 0.002$ ) between initial anaerobic threshold and length of stay in the high dependency unit indicating that patients with lower anaerobic threshold ended up staying longer in the high dependency unit. Similarly, there is a strong negative correlation between the length of stay in the high dependency unit and initial VO<sub>2</sub> max of -0.59 ( $p < 0.001$ ). The mean initial VO<sub>2</sub> max of patients stayed in the high dependency unit for one-day (the minimum stay in HDU) after operation was 22.17 ( $\pm$  5.34 ) ml/kg/min compared to the mean VO<sub>2</sub> max of 16.39 ( $\pm$  3.90) ml/kg/min patients who stayed longer in the high dependency unit( $p < 0.001$ ).

Comparing those patients in the current series of patients who needed inotropic support versus those that did not we found that the mean anaerobic threshold was 7.48 ( $\pm$  2.3) ml/kg/min and 9.98 ( $\pm$  2.5) ml/kg/min respectively (p=0.01). None of the patients with the anaerobic threshold of more than 11 ml/kg/min needed inotropic support (p=0.09).

Similarly, the mean initial VO<sub>2</sub> max of patients who needed inotropic support post operatively was found to be significantly lower at 14.36 ( $\pm$  4.27) ml/kg/min compared to that of patients who did not need inotropic support where the mean was 21.06 ( $\pm$  5.1) ml/kg/min (p=0.001).

These findings taken together support the notion that CPET parameters such as anaerobic threshold and VO<sub>2</sub> max could help to risk stratify those patients were more likely to need more intensive high dependency unit support (i.e. longer length of stay in HDU) and inotropic support. With an ever-increasing burden on the resources such as high dependency unit beds this may help in planning and optimising utilisation.

#### Post-operative ileus and chest infection

After major abdominopelvic surgery such as radical cystectomy post-operative ileus and chest infection are common complications leading to increased length of stay.(159)(160) . In the current series of patients who developed post-operative ileus versus those who did not it was found that the mean initial VO<sub>2</sub> max was significantly different at 16.44 ( $\pm$  4.66) ml/kg/min and 21.05( $\pm$  5.4)ml/kg/min respectively (p<0.01).

Apart from high VO<sub>2</sub> max and post-operative ileus there does not appear to be any statistically significant link between CPET parameters and post-operative outcomes. This could be partially because of the fact that we are primarily dealing with small number of patients (n=55) and although not statistically significant there appears to be a trend which needs to be studied by a larger randomised controlled trial

#### Deviation from standard post-operative recovery as per the Clavien Dindo classification



The Clavien classification of post-operative course of events is a well-recognised and accepted method of classification. We looked at the link between higher level of preoperative fitness as predicted by the CPET parameters and their post-operative outcomes.

It was noted that in the current group of patients that prevalence of postsurgical complications was more pronounced in those patients who had an anaerobic threshold of less than 11 ml/kg/min. Grade I complications were seen in 5 patients, grade II in 9 patients and grade III and IV complications in 1 patient each. 2 patients in this group died after surgery (grade V complication). In contrast amongst those patients who had anaerobic threshold of more than or equal to 11 ml/kg/min there was only 1 patient who had Grade I post-operative complication and none had any other grade of complications.

Those patients who had uncomplicated and straightforward recovery after surgery were found to have a higher mean initial VO<sub>2</sub> max of 22.04 (± 5.21) ml /kg/min compared to those who had some deviation from the normal (i.e. had Clavien score of one or more) who had a mean VO<sub>2</sub> max of 16.32 (± 4.21) (p <0.01). Similarly, the mean initial anaerobic threshold of patients who did not have any postsurgical complication was found to be higher (10.1(± 2.8) ml/kg/min) compared to those who had any postsurgical complications (8.5 (± 1.9) ml/kg/min) (p=0.03). The differences were more stark when a Clavien score 3 or more (which are often considered to be clinically more significant after RC) were considered. The VO<sub>2</sub> max was 14.6 (±6.3) ml/kg/min (p<0.001) and AT 7.9 (±1.9) ml/kg/min (p<0.001). These results indicate that clinically significant complications were more common in patients with worse cardiorespiratory reserve.

These results indicate that a higher level of preoperative fitness may offer some degree of post-operative resilience with a greater physiological reserve to withstand post-operative complications. Given the small number of patients that trend highlighted in the study needs to be further explored with a larger study.

## Length of stay

Length of stay in the hospital after surgery is an easy to measure post-operative outcome measure to look at the efficiency of an intervention. Although various other factors such as the type of surgery (open or laparoscopic), type of reconstruction (ileal conduit or neo bladder reconstruction), social circumstances like care available at home after discharge often play a role to determine when the patient is finally discharged home after radical cystectomy. On average in the UK patients stay in roughly 14 -17 days after cystectomy(93,161). .

In the current study the length of stay of the patient post -surgery was non-normally distributed and hence nonparametric tests were used to look at the correlation between length of stay and CPET para meters.

Using Spearman's correlation there appears to be a negative link between the day of discharge of the patient from the hospital and their initial  $VO_2$  max. ((the correlation coefficient being -0.59) ( $p < 0.001$ ) and initial anaerobic threshold (correlation factor of -0.24 (  $p = 0.07$  ) ) suggesting that patients with poor cardiorespiratory fitness tend to stay longer in the hospital. The mean length of stay for patients with anaerobic threshold was lower than 11 ml/kg/min was 13 days compared to 8 days in those with higher anaerobic threshold ( $p = 0.2$ ).

These results suggest that in spite of other confounding factors dictating the length of stay after surgery for patients, cardiorespiratory fitness could potentially act as an important predictor. The relationship between CPET para meters and length of stay need to be further explored.

## 4.5 Does preoperative exercise change post-operative outcomes

Given the small sample size of exercise and control groups (n=30, in each arm) post-operative outcomes in relation to the intervention of preoperative exercise should be interpreted with caution. In fact, this was not one of the primary outcome of the feasibility study.

There was no statistically significant difference between the exercise and the control group in relation to length of HDU stay (mean stay 2 days in both groups), post-operative ileus (23.07% in exercise group vs 25% in the control group), incidence of chest infection (7.14% in control vs 11.1% in exercise group) or prevalence of Clavien complications (33.3 % in exercise group vs 39.2 % in the control group).

The mean length of stay (LOS) in the hospital was 12 ( $\pm$ 14) days (range 4- 78 days) in the exercise group compared to 15 ( $\pm$  24) days (range 5-107) days in the control group (p=0.8). There was no difference in the median length of stay in either groups with both being 7 days.

In the control group 25% (n= 7) patients needed inotropic support compared to 7.4 % (n=2) in exercise group during their stay in high dependency unit. This indicative evidence of a trend for a difference between the groups in inotropic support (p=0.07) warrants further investigation in a properly powered randomised control trial

## 4.6 Current results and similar studies: what does the current study add

This current study adds to the ever-increasing evidence suggesting that CPET testing is safe, reproducible and an effective method of assessing cardiorespiratory fitness. In spite of the test initially being developed for healthy athletes, Bisschop et al in their systematic review of 1158 preoperative cancer patients, demonstrated that the probability of adverse events from CPET testing was quite low. (1 %) (162). Lund et al in their systematic review of a large cohort of elderly (average age  $70\pm 5$  years) patients suffering from heart failure found CPET to be quite safe (163). Similarly, in our study there were no adverse events noted during CPET.

An increasing number of surgeons and anaesthetists are recognising the potential of using CPET as a risk stratification tool. The majority of the available literature indicates that CPET markers are associated with surgical outcome following non-cardiopulmonary surgery, and that for many types of surgery CPET has the capacity to identify high risk patients. However, the optimal predictor of high risk appears to differ between surgery types, with AT shown to be the common indicator utilised to identify higher risk patients for major intra-abdominal surgery (80). In our current cohort of patients both AT and  $VO_2$  max correlate well with length of stay in HDU and need for inotropic support. In line with published literature our study also found that a cut off AT of 11ml/kg/min correlates well with presence or absence of complications. On the other hand,  $VO_2$  max correlated well with length of stay (LOS) and presence or absence of paralytic ileus.

Although the number of patients was quite small there is encouraging evidence from this study to suggest that a short period of exercise prehabilitation is well tolerated and is *possibly* able to change certain CPET parameters effectively. We were not aware of any similar studies looking at the role of preoperative exercise in patients undergoing radical cystectomy. A larger randomised controlled trial is needed to investigate whether this improvement in CPET parameters can translate into better post-operative recovery as well as reduce the length of stay for patients.

## 4.7 Strength and Weaknesses of the study

This study was a well-executed randomised control feasibility study. The aims and outcome measures were clearly defined (i.e. the primary outcomes being feasibility outcomes and secondary outcomes being preliminary investigations of fitness and recovery parameters following RC and whether preoperative exercise can lead to an improvement in fitness). The participants were randomised according to a pregenerated randomisation sequence, with the exercise physiologists (BS and JS) running the CPET assessment as well as those interpreting the results of CPET analysis (JS and GC) blinded to group allocation. To avoid bias in qualitative analysis (i.e. focus group meetings) the interviews were conducted by a qualitative analyst (KS and JS) who were not directly known to the participants. The focus group meetings were held soon after the intervention (between 6 weeks and 3 months following surgery) to avoid recall bias. The place of the interview was deliberately kept away from the exercise physiology laboratory where the patients had attended regular exercise sessions, avoiding either negative or positive associations with a particular site or building.

It is appreciated that the current study was a single centre randomised controlled feasibility trial and as such the results of the study have to be interpreted with caution. Some of the patients had surgery before their four weeks of exercise was completed and hence may not have achieved the full benefit of “prehabilitation”, similarly certain patients had delayed cystectomy and hence carried on with their exercise sessions till their surgery and stayed on the trial longer than anticipated. There were 2 patients in the control arm who participated in self-directed exercise during the trial demonstrating the potential for intervention contamination in single centre studies. Although small in numbers some patients had open cystectomy (n=2) as well as neo bladder (n=3) reconstruction both of which can independently influence post-operative recovery. Similarly other confounding factors such as preoperative smoking status, chemotherapy, different surgeons, level of IHD in participants which were not matched in exercise and control groups could all have a bearing on recovery.

## 4.8 Future research

The results of this randomised controlled feasibility study are encouraging and suggest that a larger multicentre randomised controlled trial to investigate the role of preoperative exercise in patients undergoing radical cystectomy or any other major abdominopelvic oncologic surgery is warranted.

It is plausible that a short course of preoperative exercise session for a few weeks could act as an adjunct in the enhanced recovery pathway for such patients. The mean length of stay (and SD) in days in the exercise and control groups were 12 ( $\pm 14$ ) and 15 ( $\pm 24$ ), respectively. This three-day difference did not reach statistical significance according to Mann-Whitney U test. This was not unexpected given that the present work was a feasibility study. The relatively small sample size, combined with considerable heterogeneity in health status amongst the patients recruited, introduced the strong possibility that the study was underpowered. To inform future investigations, we calculated the number of patients required to be able to detect differences based on the magnitude of the effect size and power of this work. This was performed with the G\*Power 3.1 power analysis suite (Faul et al., 2007)(164). Briefly, post-hoc analysis was conducted by Wilcoxon signed rank test and the effect size (dz) calculated, using the mean (SD) length of stay described previously, assuming an  $\alpha$  error probability of 0.05. This was then used to determine the achieved power ( $1 - \beta$  error probability) of the present study, which was  $\sim 0.19$ . The achieved power was then adjusted to 0.8 (80%) in an *a priori* analysis using a Wilcoxon signed ranks approach, assuming the same effect size (dz) and  $\alpha$  error probability of the present study. According to this, the number of patients needed for a future investigation is 400, i.e. 200 per group. The calculations are provided as supplementary material in Appendix 1.

The potential of enhanced recovery in cystectomy is huge. On an average an acute surgical bed day costs around £225 and with a potential reduction of 3 days this could amount to £675 per patient (165). The average HDU bed day cost is £1152 and better risk stratification of patients (i.e. identifying those patients less likely to need inotropic

support or level 2 care) could potentially help better distribution of limited resources (166,167).

However, it should be noted that power calculations using this and other types of software assume a normal distribution of the parent data, which was not the case in our study. Also, based on the similarity of baseline characteristics of our patients between exercise and control groups (such as age, BMI, comorbidities, fitness levels, operating time and EBL) we assumed a ‘matched pairs’ design in the present work and future investigations. Taken together, it might be that our required sample size estimation is conservative.

#### **4.9 Conclusion :**

There is encouraging evidence from this study to suggest that a short period of prehabilitation before RC is well tolerated and is able to change certain CPET parameters effectively. It is plausible that a short course of preoperative exercise session for a few weeks could act as an adjunct in the enhanced recovery pathway for such patients.

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## Appendix :1 Power calculation to determine sample size

1) **t tests** – Means: Wilcoxon signed–rank test (matched pairs)

**Options:** A.R.E. method

**Analysis:** Post hoc: Compute achieved power

**Input:** Tail(s) =Two

**Parent distribution**=Normal Effect size  $d_z=0.1436739$   $\alpha$  err probability =0.05

**Total sample size**=60

**Output:** Noncentrality parameter  $\delta=1.0875249$  Critical  $t=2.0030085$   
Df=56.2957795 Power  $(1-\beta$  err prob) $=0.1877111$

2) **t tests** – Means: Wilcoxon signed–rank test (matched pairs)

**Options:** A.R.E. method

**Analysis:** A priori: Compute required sample size

**Input:** Tail(s)=Two

**Parent distribution**=Normal Effect size  $d_z=0.1436739$   $\alpha$  err prob=0.05  
Power  $(1-\beta$  err prob) $=0.8$

**Output:** Noncentrality parameter  $\delta=2.8114849$  Critical  $t=1.9661947$   
Df=381.9268 Total sample size=401 Actual power=0.8007905

## Appendix 2 : Study protocol

**Preoperative Exercise Protocol to Aid Recovery (PREPARE) for Radical Cystectomy**

**STUDY PROTOCOL VERSION 4 16.04.12**

Srijit Banerjee MB BS MRCS, Clinical Fellow in Urology, NNUH

John Saxton, PhD, Professor of Clinical Exercise Physiology, UEA

Robert Mills FRCS(Urol), Consultant Urological Surgeon, NNUH

Mark Rochester MA MD FRCS(Urol), Consultant Urological Surgeon, NNUH

### **Background**

Enhanced recovery protocols (ERPs), are a team approach to perioperative care for participants undergoing surgery. They minimize physiological stress caused by surgery and promote recovery. Significant reductions in hospital stay have been shown without increased complications or readmissions. ERPs decrease ileus, prevent loss of lean body mass, reduce atelectasis, promote oxygenation and preserve cardiovascular response to exercise after surgery. ERPs have spread from colorectal surgery to other surgical specialities. Components of an ERP are as follows: Preassessment is used to inform participants, to highlight and overcome psychosocial barriers to early recovery or discharge, and to trigger medical optimization if required. Participants receiving preoperative carbohydrate loading have an accelerated recovery and shorter hospital stay. Prevention of intraoperative hypothermia reduces sympathetic responses, cardiac arrhythmias and wound morbidity. High inspired oxygen level during the perioperative period increases intestinal oxygenation, reduces wound infection, and decreases postoperative nausea and vomiting. Goal-directed fluid therapy with oesophageal Doppler allows precise fluid balance, and this reduces surgical complications and

shortens length of hospital stay. Optimized pain relief allows early mobilization and opiate-sparing analgesia reduces nausea, vomiting and sedation. Epidural anaesthesia, is an important component of ERPs. Participants undergoing radical cystectomy are a particularly applicable group for ERPs, as the procedure is still associated with significant morbidity and a prolonged inpatient stay by comparison with other operations. Implementation of an ERP for radical cystectomy in one UK centre reduced postoperative stay by 3 days, with no effect on morbidity or mortality.

The major focus of the ERP literature to date has been on peri and post-operative care. Improving the outcome for these participants, however, could begin long before the participant arrives at the preoperative assessment visit. A surgical procedure such as radical cystectomy is associated with a catabolic state, similar to prolonged endurance exercise. An athlete would not attempt an endurance event without training, and it is our hypothesis that a period of preconditioning prior to major surgery in addition to enhanced recovery would be beneficial in a similar way for these participants. It is well known that physical functioning is a predictor of morbidity and mortality in various participant groups and among elderly people. The same trend appears to be present in the surgical population. Surgery is a stressful event, and the recovery period after invasive surgery often involves bed rest, which in turn may induce loss of muscle mass, deconditioning, and pulmonary complications which can lead to decreased quality of life, increased morbidity, longer hospitalization and even death. It follows that optimal physical functioning of participants before stressful surgery might result in better postoperative outcome. Several studies have shown that the preoperative aerobic capacity of lung participants correlates with the rate of postoperative pulmonary complications after lung resection. Similarly, a significantly shorter length of hospital

stay after total hip replacement was reported in participants who were more physically active before the surgery. Optimal preoperative physical functioning of participants can therefore be an important determinant of postoperative functioning, complication rate, and length of hospital stay. A recent systematic review has shown that preoperative exercise therapy consisting of inspiratory muscle training or exercise training prior to cardiac or abdominal surgery leads to a shorter hospital stay and reduced postoperative complication rates.

The Enhanced Recovery Partnership Programme has been recognised in the Quality, Innovation, Productivity and Prevention (QIPP) Challenge as a high impact example for change for the NHS. To date, work has focussed on optimising the post-operative course, and little work has focussed on pre-operative optimisation.

Through PREPARE participants will become partners in their own care. It combines the existing ERP framework with rehabilitation plans and cutting-edge preconditioning. PREPARE will reduce demand on HDU / ITU bed days, and shorten length of stay which in turn will reduce exposure to hospital acquired infections, and because participants are fitter sooner they can return to normal activities earlier. If it can be demonstrated that this approach is effective for cystectomy participants we will work towards spreading this innovation to other high risk complex surgical groups, such as vascular participants, those undergoing oesophagectomy, or major bowel resections.

## **Methods And Design**



After ethical approval 30 participants will be recruited to each arm of this study. These will be the participants who have been listed for radical cystectomy for bladder cancer from the Urology Specialist Multidisciplinary Team meeting at the Norfolk and Norwich University Hospital. They will then be randomised to receive either a four week intensive exercise training according to a preset protocol, or the standard enhanced recovery pathway. Post operatively these participants would be monitored and their post-operative course charted, including time to passing flatus, tolerating diet, mobilising and discharge time. The frequency of complications in the post-operative period will be recorded according to the Clavien classification.

## **Assessment of cardiopulmonary fitness before and after the 4 week period of exercise training**

### Incremental cycle ergometry test ( CPET assessment )

Participants will undertake a continuous, incremental cycling test to volitional exhaustion on an electronically-braked cycle ergometer (Excalibur Sport, Lode, the Netherlands). Pedalling frequency will be set at 50 revs·min<sup>-1</sup>. After a 5-min warm-up against minimal resistance (0 W), the intensity of exercise will be ramped up by 20 to 30 W·min<sup>-1</sup>. Participants will be encouraged to continue cycling to volitional exhaustion or until a plateau in oxygen consumption is observed. Heart rate and 12 lead ECG will be recorded continuously by electrocardiogram (Cardioperfect, Welch Allyn, USA) and perceived exertion (Borg RPE Scale) will be assessed at 2 min intervals.

The following parameters will be recorded;

#### **1. Maximal oxygen consumption (Peak VO<sub>2</sub>)**

This will be calculated as the highest consecutive 20-second period of gas exchange data in the last minute before volitional exhaustion, which we expect to occur due to leg fatigue and/or breathlessness.

#### **2. Minute ventilation :**

The volume of oxygen consumed during exercise will be calculated from minute ventilation, measured using a pneumotach, and simultaneous breath-by-breath analysis of expired gas fractions (Ultima CardO<sub>2</sub>, MedGraphics, USA). Gas analysers and flow probes will be calibrated before each test. Oxygen consumption will be expressed relative to body mass (mL·kg<sup>-1</sup>·min<sup>-1</sup>)

#### **3. Anaerobic threshold :**

This will be derived using the ventilatory slope method.

#### **4. O<sub>2</sub> pulse :**

This parameter approximately equates to stroke volume and may reflect cardiovascular disease or ventilator constraint. It is measured as VO<sub>2</sub> /Heart Rate.

**5. VO<sub>2</sub> / power slope :** The relationship between oxygen uptake and work rate (in watts). It is reduced in any condition that reduces blood flow to the periphery and is not affected by obesity.

Criteria for termination of CPET assessment :

1. **Contraindications where CPET would not be initiated:**

- Acute endocarditis, myocarditis, pericarditis
- Severe, symptomatic Aortic Stenosis
- Acute MI in the last 6 months
- Unstable Angina
- Undiagnosed arrhythmias

2. **Reason for termination during CPET :**

- Patient's request: fatigue, dyspnea, pain
- 2nd or 3rd degree heart block or any new arrhythmia
- BP sys>240-250, BP dias >110-120

**Exercise protocol:**

Participants will attend an exercise physiology laboratory at the University of East Anglia for supervised exercise sessions comprising 45-60 min of aerobic exercise (intensity of 60-80% of peak power output achieved in the incremental cycle ergometry test. Participants will perform 6x5 min bouts of exercise at this intensity, with interpolated rest intervals of 2.5 min. Each exercise session will include a 5 min warm-up and 5 min cool-down.

This will consist of the following :

- 1) **Warm Up** : 5-10 min
- 2) **Cycle ergometry exercise** : 6 x 5 min intervals at 60-80% of peak power output achieved in the incremental cycle ergometry test. Each interval will be followed by a 2.5 min rest period. Heart rate and ratings of perceived exertion will be recorded in the final minute of each interval. Exercise intensity will be progressed at an appropriate rate for each individual.
- 3) **Cool Down** : 5-10 min

In addition they will be instructed to undertake self-directed aerobic exercise (e.g. brisk walking, cycling, gym exercise) for at least one 30 min session per week during this time period. All exercise sessions will be recorded in an exercise log. The participants will also be supplied with portable pedometers which they will use as a motivational tool during these self-directed exercise sessions and the distances travelled will be logged electronically.

The participants will also be asked to fill up a quality of life questionnaire using the pre-validated and standard FACT-BL questionnaire. This is a disease specific questionnaire that looks at various aspects of the participant's quality of life including physical well-being, social or family well-being, emotional well-being and functional well-being. The participants will be filling up the questionnaires at the start (weeks 0) , at week four ( that is at the end of intervention) and at 6 weeks post operative ( at the time of their follow-up).

### **Qualitative analysis :**

Approximately 8-10 people from both the intervention and control group will be purposefully sampled to participate in 2 focus group meetings (at the end of the intervention and 6-8 weeks following surgery) based on their specific consent. All focus groups will be conducted by Miss Kelly Semper ( qualitative research analyst, University of East Anglia) and will take place in private seminar rooms located at either the University of East Anglia or the Norwich and Norfolk University Hospital. For analysis purposes both focus groups will have to be audio recorded and this will also be made clear on all information sheets prior to consenting.

These focus groups will aim to gage feedback on the intervention such as feasibility and enjoyment from the view point of both exercise and control group participants. These focus groups will also aim to:

- Consider which elements of the protocol were perceived as being most and least helpful.
- Explore the participants' perception of the effect that they think the exercise has had on their well being and quality of life after surgery
- Uncover any potential barriers or problems associated with the exercise protocol
- Explore how this protocol could be refined and enhanced for use in larger scale interventions.

Broad thematic analysis will be used to elucidate experiences and views. Initial analysis will sort the data thematically and chart key themes and experiences. Final analysis will compare key themes across the two groups of participants, exercise and control.

### **Recruitment of participants for the study**

All participants who would be offered radical cystectomy as part of treatment for bladder cancer would be deemed suitable to be recruited for the study. Currently the participants are seen in the clinic following the urology SMDT by a consultant urologist to discuss the option of surgery. We aim to recruit the participants at this point and utilise the interval prior to surgery which is currently 4 weeks for the intervention. The majority of participants under 80 years of age have been through a period of neoadjuvant chemotherapy and have a window of opportunity of 4 weeks after their third cycle of treatment before they are ready for surgery to allow them to participate in the exercise programme. Those that are not suitable for chemotherapy will still have a 31 day window in which the preconditioning can take place.

Suitable participants will be offered the opportunity to join the study, and given a participant information sheet. They will then be contacted within 24 hours by the principal researcher for this project, Mr S Banerjee who will be able to answer any queries which are raised prior to obtaining informed consent and enrolment into the

study. Participants are free to withdraw from the study at any point without subsequent delay to their surgery or alteration of their management plan.

The participants would not have any financial incentive as part of being recruited for the study, although subject to fund availability we would try to reimburse the travel expenses that are incurred.

**Consent :**

The participants who would be recruited for the study will have to sign an informed consent. They will be supplied with an information leaflet about the study and would include the contact details of the principal researcher whom they can contact at any time before or after they enrol for the study to answer any queries. Participants would be given at least 24 hours to read the documentation before being asked whether or not they wish to take part.

**Place and details of the study**

The participants will undergo a supervised 4 week cycle of supervised cardio respiratory exercise at the physiology laboratory at the University of East Anglia (UEA). They will be asked to come to the laboratory twice per week for 4 weeks and would undergo a protocol based set of exercises . The exercises would last a total of 1 hour and would be tailored to the individual participant's background exercise tolerance: a participant with a higher baseline cardiorespiratory reserve would therefore be prescribed a more intensive cardio respiratory exercise than a peer with lower baseline fitness. At all times the intervention would be supervised by a qualified medical practitioner. In addition they will be instructed to undertake self-directed

aerobic exercise (e.g. brisk walking, cycling etc.) for at least one 30 min session per week during this time period. All exercise sessions will be recorded in an exercise log.

At the beginning and end of the study the participants would undergo cardio respiratory fitness assessment to assess any improvement in the exercise tolerance.

**Risks :**

Exercise sessions at the UEA will be supervised by a medical practitioner. The exercise protocol will be also tailored to the individual participant taking into account their background medical conditions and would only take them upto 85% of perceived exhaustion as predicted on the Borg RPE scale. The protocol of exercise will be designed by Prof John Saxton (Professor of Exercise Physiology at the UEA).

**Conflict of interest**

None

## Appendix 3 : Patient information leaflet about the study



### **PREPARE for Radical Cystectomy study Participant Information Sheet Version 5 09/05/2012**

We invite you to take part in a study we are running for patients who are due to have surgery for bladder cancer. Before you decide whether to enrol for the study we would like you to understand why the research is being done and what it would involve for you. One of our team members will go through the information sheet with you and answer any questions you have. We would suggest that you should take at least 15 minutes to read the information leaflet, and talk to others about the study if you wish.

#### **What is the purpose of the study?**

PREPARE is a study that is being run jointly by the urology team at Norfolk and Norwich University Hospital and the University of East Anglia to look at the role of exercise before surgery in improving recovery after your operation. It is known that the human body will deal with physical stress better if it is "preconditioned" or trained. Athletes will train before major events. Surgery, such as that for bladder cancer is a stress on the body and we believe that your body may recover better if it is trained beforehand using regular simple exercises.

#### **Why have I been invited?**

You will shortly be having major surgery for bladder cancer and as such can take part in our study.

#### **Do I have to take part?**

It is up to you whether to take part. We will describe the study and go through this information sheet with you. If you wish to take part, we will then ask you to sign a form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

#### **What will happen to me if I take part?**

If you decide to enrol, one of our study doctors will take you through the consent form and ask you to sign. There is a planned gap of about four weeks between the decision to offer you surgery and the date of your operation. This time window allows you take part in the study with no added delay to your treatment. You may be having chemotherapy for a few months before surgery, and it is usual to wait 6 weeks after this before your surgery. If this is the case for you, we will use that time to allow you to take part in the study.

The study involves regular sessions of supervised simple exercises that you will do at the lab at the University of East Anglia. You would be asked to attend twice a week, at convenient times for you, for four weeks, during working hours.



Each session would last about an hour. We will also give you some simple exercises to do at home (such as brisk walking or cycling) for about half an hour at least once a week.

The exercise plan will be tailored to your own ability, so if you are more fit you would do more heavy exercise than those who are less fit.

We will take some measurements before and after the four weeks of the study to see if your fitness is better. We will also see if your recovery is quicker or less complicated than for others who have not done any exercise before their surgery.

We would also need you to fill up certain questionnaires regarding your general wellbeing at different points during the study. This questionnaire called the FACT-BI questionnaire has been used in previous studies (prevalidated) in patients with bladder cancer. This should not take more than 5 minutes to fill up and one of our team members would be happy to go through this with you.

We are evaluating our treatment in a trial comparing this to standard care. Sometimes because we do not know which way of treating patients is best, we need to make comparisons. People will be put into groups and then compared. The groups are selected by a computer which has no information about you – i.e. by chance. Patients in each group then have a different treatment and these are compared.

If you are interested in taking part you will receive either the new treatment (i.e. exercise before surgery) or standard current treatment (which does not involve any exercise) to see which is best.

You *may* also be invited to participate in group discussion sessions with other participants. These meetings called “focus group meetings” are there for us to gauge the feedback and experience of participants during the study. Each focus group session lasts between 30 to 45 minutes.

### **Will I be paid any expenses ?**

The study is voluntary and as such you will not be for taking part, but we will reimburse you for travel costs due to your visits.

### **What will I have to do?**

You will be asked to attend the lab at the University of East Anglia in Norwich twice a week to do the exercises and have measurements. These sessions will last about an hour. You will also be given an exercise plan to follow three times a week at home. We will supply you with a pedometer, a small instrument that will measure amount of exercise you have undertaken at home.

However if you are in the group that receives standard care you will not need to attend these exercise sessions.

### **What are the possible disadvantages and risks of taking part?**

The exercise plan that you would do would only be based on your own fitness, and as such health risks such as heart problems or breathing difficulty are low (less than 1 in 10,000 episodes). All your exercise sessions in the lab will be supervised by a doctor. If you have any problems during these exercises we would advise you to stop and take necessary steps. During your participation in the study you would be covered by NHS and university of East Anglia (UEA) indemnity and insurance. The details of the cover is available on request.

### **What are the possible benefits of taking part?**

We hope that this short period of exercise *may* make you more fit and cope better with the stress of surgery. Your recovery after surgery *may* be more smooth. If the results of the study show that that is indeed the case then it is expected that *all* patients who would be undergoing major surgery would be asked to go through a period of preoperative exercise training to enhance their recovery after surgery.

### **What happens when the research study stops ?**

At the end of the study we will tell you how much improvement there has been in your physical fitness. If you wish after your surgery you may decide to continue on these simple exercise protocols to stay active and fit.

### **What if there is a problem?**

If you're unhappy about any part of the study you should discuss it at the first instance with the principal investigator Mr S Banerjee. Should this fail to resolve the issues you can speak to the supervising consultants Mr M Rochester , Mr R Mills or Prof John Saxton.

You can also take up the issues with the Patient Assistance and Liaison Services (PALS) in the Norfolk and Norwich University Hospital.

### **Will my taking part in the study be kept confidential ?**

All the details about you will be kept confidential and will only be accessible by the research team. Your GP and your consultant would be kept updated of the fact that you are taking part in our study. It is very likely that the results of the study will be published or presented in the future however the data will be anonymised so that your confidentiality is not breached.

### **What will happen if I don't want to carry on with the study?**

Participation for the study is completely voluntary and as such you may withdraw from the study at any point without the need to give a reason. This will not affect your routine care or any care that you would receive before, during or after your hospital stay. The data that we may have collected till that point may however still be used with .If you lose the ability to consent after you have been recruited into the study, you would be removed from the study but any data collected upto that point may still be used.

Participation for the focus group meetings are also voluntary. You may decide to participate in the trial but not for the focus group meeting.

**Who is organising and funding the research?**

The research is being jointly carried out by the urology department and the University of East Anglia..

**Who has reviewed the study?**

The study protocol is being reviewed by the research and development department at the Norfolk and Norwich University Hospital and ethics approval has been sought from the Norfolk Regional Ethics Committee.

**Further information and contact details**

Mr S Banerjee

Urology Department

Norfolk and Norwich University Hospital

Norwich

NR4 7UY

01603 286286, pager 1079