

**Improving the perioperative
management of resectable colorectal
liver metastases**

**Thesis submitted in accordance with the requirements of the
University of Liverpool for the degree of Doctor of Medicine**

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Dedication

To my wife and children. Without your love and support I would not be where
I am now.

To the NHS and all the health care staff who helped pick me up when I was
broken, I will be eternally grateful.

Declaration

The work presented in this thesis was carried out in the Institute of Translational Medicine, University of Liverpool and was undertaken while working as a research fellow at Liverpool Hepatobiliary Centre with funding from the Madel Research Fellowship.

The material contained within this thesis has not been, nor is currently being presented wholly, or in part, for any other degree or qualification. I declare that all the work presented in this thesis has been carried out by me except where indicated below:

- Some assistance in the running of laboratory experiments by Dr Philip Starkey.
- Histological preparation was carried out by the pathology Lab at the University of Liverpool School of Veterinary Science, (Leahurst).
- Histological analysis was undertaken by a NHS hepatobiliary pathologist Dr Katherine Brougham, Royal Liverpool Hospital.
- Blinded analysis of cardiopulmonary exercise tests was undertaken by Dr Sandy Jack (University of Southampton).
- The blinded statistical analysis of the prehabilitation trial data was undertaken by Dr Dan Lythgoe (trials statistician).

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Abstract

Background

Colorectal liver metastases (CRLM) are more prevalent with advancing age. Worldwide trends towards longer life expectancy result in a more prevalent disease in an increasingly aged co-morbid population. Utilising enhanced recovery after surgery (ERAS) and better preoperative assessment of patients using cardiopulmonary exercise testing (CPET) may in part mitigate the challenges of dealing with a more elderly co-morbid population. However significant challenges remain.

Prehabilitation seeks to prevent injury, or minimise its impact before it occurs. This thesis describes the development and validation of a prehabilitation program in patients prior to hepatectomy for colorectal liver metastases.

Methodology

An exercise program was developed within a laboratory and validated in 12 health volunteers. This program was then tested in a randomized clinical trial of patients prior to hepatectomy for colorectal liver metastases.

The measurement of liver function and prediction of post hepatectomy liver failure (PHLF) is a challenge. Further work measuring liver function is needed, and a component of this thesis demonstrated the application of liver slicing as a model of human hepatic functioning.

Results

The part of this thesis demonstrates that a 4 week exercise program can deliver meaningful ($1.5 \text{ ml.kg}^{-1}.\text{min}^{-1}$) improvements in the Oxygen uptake (Vo_2 uptake $\text{ml.kg}^{-1}.\text{min}^{-1}$) at the anaerobic threshold (AT).

Within the main component of this thesis (the randomized trial) 38 patients were randomized (20 prehabilitation, 18 standard care). 35 (25 male, 10 female) completed both preoperative assessments and were analysed. There were no differences in baseline characteristics. Prehabilitation led to improvements in the preoperative Vo_2 uptake (Oxygen uptake $\text{ml.kg}^{-1}.\text{min}^{-1}$) at both anaerobic threshold (AT) ($+1.5 \text{ ml.kg}^{-1}.\text{min}^{-1}$, 95% Confidence Interval (CI) $0.2 - 2.9 \text{ ml.kg}^{-1}.\text{min}^{-1}$) and peak exercise ($+2.0 \text{ ml.kg}^{-1}.\text{min}^{-1}$, 95% CI $0 - 4.0 \text{ ml.kg}^{-1}.\text{min}^{-1}$). The O_2 pulse (Oxygen uptake per heart beat) at the anaerobic threshold improved ($+0.8 \text{ ml.beat}^{-1}$, 95% CI $0 - 1.9 \text{ ml.beat}^{-1}$) and a higher peak work rate ($+13 \text{ watts}$, 95% CI $4 - 22 \text{ Watts}$) was achieved. This was associated with improved preoperative QoL, with overall SF-36 increasing by 11 (95% CI $1:21$) ($p < 0.05$) and overall SF-36 mental health by 11 (95% CI $1:21$) ($p < 0.05$).

Conclusions

Prehabilitation can deliver improvements in CPET scores, and QoL. This may impact on perioperative outcome.

Chapter 1: Introduction

An aging increasingly morbid population undergoing treatments of greater complexity means that even preserving current outcomes is challenging. However there is a desire for better results in all aspects of healthcare. This is at a time where there is worldwide pressure on healthcare budgets, leaving less funding to address these challenges.

Consequently innovative approaches to improving care and delivering cost effective treatment is urgently needed. This thesis seeks to explore the surgical management of patients with colorectal liver metastases and identify areas where care can be improved and develop strategies to address these areas.

1.1 Colorectal Cancer

1.1.1 Incidence and prevalence of Colorectal Cancer

Colorectal cancer is a common malignancy with 1.2 million new diagnoses annually worldwide and 42,000 in the United Kingdom¹. Worldwide colorectal cancer is estimated to cause 608,000 deaths annually, whilst in the United Kingdom it is the 3rd highest cause of cancer related death, accounting for 10% of all cancer deaths². The incidence of colorectal cancer in 2012 was 55.6 and 36.7 per 100,000 population in men and women respectively. Standardised mortality rates of 20.6 and 13.7 per 100,000 populations in men and women respectively equates to a cancer related mortality of 37% of all the patients diagnosed with bowel cancer³. This represents an increase in the incidence of colorectal cancer from 2008 figures, in tandem with a climb in the mortality rate from the 2008 estimate of 34%^{3,4}. Data from cancer research UK suggests that in 2014 there was a slight fall in new cases, however the survival to 10 years following a cancer diagnosis has continued to fall, and now stands at 57%¹. This probably reflects a changing demographic of the patient population, with an increasing burden of frailty⁵. The UK incidence and mortality have been highlighted as areas of concern, as survival here appears to be worse than comparable countries⁶.

1.2 Colorectal Liver metastasis

Blood borne spread via the portal system is common, and a compulsory first visceral step⁷. This is evident in the frequency of hepatic metastasis, where 20 - 25% of patients have liver metastasis evident at diagnosis and up to 40 - 50% of all patients develop hepatic metastases during the course of the disease⁸.

The liver is often the first site of metastasis, and in 30-40% the only site of metastatic spread⁸. One of the keys principals in hepatic resection is a belief that resection of liver metastases before further systemic spread can be curative⁷.

1.2.1 Incidence and prevalence of colorectal liver metastases

Whilst hepatic metastases are common, only 30–40% of patients will have disease confined to the liver⁹. In these patients only a minority are eligible for curative intent liver surgery, currently estimated at around 20-25%. This means only around 3-5% of all patients are considered for hepatectomy, and 6-10% with advanced colorectal cancer¹⁰.

1.2.2 Changing patterns of disease

To effectively develop strategies to improve outcomes for patients with colorectal liver metastases (CRLM) it is important to have an appreciation of the current demographic of the patient population presenting with the

disease, and how this is likely to change. Understanding the changing demographic of the patient population is challenging and is likely to be effected by global population changes, national health initiatives, and treatment strategies.

1.2.2.1 Aging populations

Whilst the prediction of the numbers of patients presenting with resectable CRLM is uncertain, there can be greater confidence in predicting the likely changes to the age demographic. The worldwide and UK populations are increasingly elderly, with the over 65 population expected to make up around 20% of the UK population by 2025, compared to just 17% currently^{5,11}. Cancer in general, and colorectal cancer in particular, are directly linked to age, with 70% of colorectal cancer diagnoses occurring after the age of 65, and 50% in patients over 70⁵. Thus, as populations continue to age, we can expect more cases to be diagnosed in an increasingly aged population⁵.

This has significant implications for practice where age has been shown to be associated with poorer short-term peri-therapeutic, and long-term oncologic outcomes¹²⁻¹⁵. The reasons underpinning this may relate to differences in tumour and patient biology, but inaccurate perceptions of poor outcomes in older patients by clinicians have been identified as significant contributors¹⁴⁻¹⁸. A UK Department of Health review, published in 2012, acknowledged that age may be a surrogate marker for other factors that may make less aggressive treatment justifiable¹⁹. However, even taking this into account it

was suggested that age discrimination in UK cancer care was leading to inappropriate under investigation and treatment. It was suggested this led to detrimental effects on cancer survival in older people. This highlighted the need to focus on improving outcomes in elderly patients¹⁹.

A key aim should be to devise pathways to select appropriate treatment for elderly patients, ensuring that those with significant co-morbidity are not inappropriately over treated, whilst still being able to select those in whom aggressive treatment can be tolerated.

1.2.3 Defining resectable CRLM

1.2.3.1 Criteria of resectability

When hepatectomy was first undertaken for CRLM, it was performed in highly selected physiologically fit patients believed to have the best prognostic features. Using these criteria around 10% of patients with liver only metastases were resectable²⁰.

Gradually these early resection criteria were challenged with evidence demonstrating that patients beyond these limited criteria could experience long-term survival following liver resection^{21,22}.

The latest UK national guidance written in 2011 recommended that resection of CRLM should be offered provided:

- The patient is assessed fit enough to undergo surgery
- Complete resection or ablation can be achieved leaving an adequate future liver remnant (FLR).

Extrahepatic disease was not considered a contra-indication to resection provided the disease is potentially resectable²³. There are no absolute contraindications to resection issued in this guidance, but the relative contraindications to liver resection or ablation in normal circumstances are summarised in Table 1-1²³.

Table 1-1 Relative contraindications to resection or ablation of CRLM

Non-treatable primary tumour
Widespread pulmonary disease
Loco-regional recurrence
Uncontrollable peritoneal disease
Extensive nodal disease, such as retroperitoneal or mediastinal lymph nodes
Bone or CNS metastases.

This shift to defining resectability based on what will remain, rather than by what is removed, has led to an increase in the number of patients eligible for resection at diagnosis from 10% in 1999 to around 25% currently¹⁰.

1.3 Assessment of fitness

The first criterion in assessing CRLM resectability is making an assessment of the fitness of a patient to undergo major cancer surgery. Establishing that it is technically feasible to resect disease, and preserving an adequate hepatic functional volume, is irrelevant without an appreciation of whether or not the patient has physiologically capable of surviving a proposed intervention. Consequently the assessment of fitness should be seen as an integral part of the preoperative assessment process.

Specifically targeted research defining fitness for hepatectomy is limited, but methods of defining preoperative fitness include scoring systems questionnaires and quantitative fitness measures (Table 1-2)²⁴.

Table 1-2 Methods of assessing patient fitness

Scoring Systems
American Society of anaesthetists scoring system
Revised cardiac risk index
Surgical probability model
Questionnaires
Dukes activity questionnaire
Quantitative fitness assessment
Cardiopulmonary exercise test (CPET)
6 minute walk test

The American Society of Anaesthetists (ASA) score is widely employed and has been shown to correlate with outcome²⁵, but ASA is deemed insufficient to adequately risk stratify patients¹⁹. Other scoring systems and questionnaires have yet to be validated in patients undergoing hepatectomy, and are often seen as open to bias and subjective interpretation²⁶.

Quantifying patient fitness in an objective fashion is an attractive concept, and two common methods that address this are the 6-minute walk test, and cardiopulmonary exercise testing (CPET)^{27,28}.

1.3.1 CPET

CPET is a non-invasive method for evaluating cardiopulmonary fitness, and can help to identify hidden cardiorespiratory limitations that could suggest significant underlying pathology^{27,29,30}. The test requires patients to exercise

using a fixed cycle, treadmill or arm based system. This allows tailoring of the exercise for different patient groups (lower limb joint surgery patients can be assessed using arm exercises, for example). Exercise bikes tend to be used, as they are safe, familiar, reduce artefact interference during continuous monitoring and allow a more accurate quantification of external work rate. Higher levels of exertion can be achieved on a treadmill³¹, but patients may require an extended period of familiarisation with the equipment³². The arm crank system as yet lacks evidence for use in the clinical setting, and the translation of values produced via the different modalities had not until recently been correlated³³. Recent work suggests a correlation between arm crank scores, and that generated by a cycle ergometer, however it was insufficient to adequately translate across modalities for comparative purposes³³.

CPET measures gas exchange, blood pressure, oxygen saturation, and electrocardiogram (ECG) in response to an increasing workload. Optimal exercise time is 8-12 minutes, as shorter exercise times may underestimate VO_2^{\max} (described in Table 1-3)²⁹⁻³¹. During the exercise protocol, numerous variables are monitored including blood pressure, pulse, breath-by-breath measurement of inspired oxygen and expired CO_2 , and peripheral oxygen saturation.^{7, 8} Using this information a number of physiological values are measured, or calculated. Definition of these parameters is summarised in

Table 1-3³⁴. Currently a variety of these variables have been suggested as predictive of outcome, in different surgical cohorts.

Table 1-3 CPET terminology

Term	Name	Explanation
AT	Anaerobic threshold	Point within an exercise test at which anaerobic energy production starts to supplement the aerobic energy production.
Vo ₂	Oxygen uptake	Volume of O ₂ extracted from the inspired gas
Peak	Peak exercise	Highest work rate achieved in a symptom limited cardiopulmonary exercise test (averaged over the last 30 seconds of exercise)
Vo ₂ (ml.kg ⁻¹ .min ⁻¹)	Relative oxygen uptake	Oxygen uptake relative to weight
Vo ₂ (l.min ⁻¹)	Absolute oxygen uptake	Oxygen uptake (not adjusted for weight)
V _E / Vo ₂	Ventilatory equivalent of oxygen	Measure of the efficiency of uptake of o ₂
V _E / Vco ₂	Ventilatory equivalent of carbon dioxide	Measure of the efficiency of ventilatory removal of Co ₂

1.3.2 CPET in surgery

CPET was first described in the context of abdominal cavity surgery by Older et al over two decades ago³⁵. He first demonstrated its use to predict risk in patients over the age of 70 undergoing major abdominal surgery³⁵. More recently he has demonstrated the use of CPET to successfully stratify these patients' postoperative care to ward, high dependency unit, or intensive

care³⁶. This work predominantly used ischaemic changes on ECG and the anaerobic threshold to predict outcome.

Since this time CPET variables have been shown to correlate with outcome following colorectal surgery, major urological surgery, aortic aneurysm repair, oesophagectomy, and in elderly patients following major surgical intervention^{29,30,35,37-41}. Many of these studies were un-blinded retrospective analyses of practice where CPET was utilised in patient management. Utilising CPET in this manner is thought to serve to underestimate its predictive power as practice is alerted to mediate the effects of poor cardiopulmonary fitness⁴². Two large series where clinicians were blinded to the results of CPET have been published, including patients undergoing major pancreatic or sarcoma surgery, and including patients deemed of poor fitness by the Veterans Activity Questionnaire Index (VASI) undergoing a mix of major intra-abdominal surgery^{40,43}. The outcome measure for both studies was morbidity as assessed by the postoperative morbidity score (POMS). Both studies found that fitness as determined by CPET was strongly correlated with postoperative morbidity, with those having lower fitness having more postoperative complications. This finding of poorer fitness correlating with poorer outcome is as expected and demonstrates the effectiveness of CPET in quantifying patient fitness.

CPET produces a wealth of variables and two systematic reviews have concluded that different variables appear to be more valuable predictors in

different surgical contexts^{29,30}. The explanation for this is unclear, and this has been highlighted in the literature as an area for research focus⁴⁴. The most consistently identified variable is the relative oxygen uptake at the anaerobic threshold, often simply referred to as the anaerobic threshold (AT). This variable is attractive for preoperative prediction as it occurs at a low level of exercise achievable in most patients, and it is independent of volition. In marathon runners it has been shown to strongly correlate with performance⁴⁵. There is however significant debate about the physiological basis and reliability of detection of the anaerobic threshold, particularly in patients who acutely hyperventilate^{46,47}. Current literature suggests that whilst CPET can accurately assess fitness, decisions regarding surgery should be based on careful interpretation of the whole CPET data set in light of the proposed surgical intervention³⁴.

1.3.3 CPET in liver surgery

There are very few studies utilising CPET in hepatic surgery^{34,40,43,48-50}. In patients undergoing hepatic transplantation a small study suggested that a peak VO_2 of less than 60% of predicted (based on age, sex and weight), or a relative VO_2 at the AT of <50% predicted was associated with mortality at 100 days⁵¹. This study, however, had a number of limitations including its size, statistical approach, and differences between the management of the two cohorts (survivors vs. non survivors). They did not report any data on correlations between CPET values and the extent of the liver disease. More

recently further work has firmly established VO_2 at AT as a predictor of survival following hepatic transplantation⁵⁰. In other liver transplant studies CPET has been studied before and after transplantation, with significant improvements demonstrated 1 year post grafting⁵².

The largest reported series in hepatectomy (the author's), used CPET as an integral part of management, and also used an enhanced recovery after surgery programme³⁴. This study found where CPET is used in management few CPET variables correlate with complications or hospital stay³⁴. Specifically the anaerobic threshold does not correlate with outcome, though this study is limited by the lack of blinding of clinicians to the results of the CPET. Interestingly those with lower AT undergo less aggressive procedures with more critical case use, at greater cost⁵³. This may go some way to explain the absence of a relationship, and would be in agreement with previous suggestions that using CPET in management diminishes its predictive capacity⁴².

1.4 Defining an adequate FLR

The second criterion of resectability is establishing the capacity to leave an adequate FLR. Postoperative hepatectomy liver failure (PHLF), or hepatic insufficiency, where the remaining liver post resection is inadequate to meet the needs of an individual, is one of the leading causes of morbidity and the leading cause of mortality following liver surgery^{10,54,55}. It is defined as a

postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions⁵⁶. A series of over 2,600 consecutive resections has identified an overall incidence of hepatic insufficiency of 2.6%⁵⁴. This, however, underestimates the nature of the problem, as many of the patients within this series underwent resections of such a low volume hepatic insufficiency would not have been expected.

In patients undergoing major hepatic resection following chemotherapy, hepatic insufficiency has been reported to occur in up to 16%^{10,57}. The expanding armamentarium of chemotherapeutics, and adjuvant therapies means patients who have been treated with extended chemotherapy make up an increasing proportion of surgical candidates.

Currently defining the adequate functional reserve is challenging. Hepatic functional capacity is widely variable within humans. One measure of hepatic viability, Adenosine triphosphate (ATP), has been shown to vary between 2-14 nmol mg⁻¹, in comparison to rats where it is typically around 10-12 nmol mg⁻¹⁵⁸. This is likely a result of interplay between underlying genetic predisposition, patient factors and the effects of other treatments.

Surrogate markers of poor hepatic reserve, and consequently a higher risk of postoperative hepatic insufficiency and death, include diabetes, advancing age, obesity, pre-existing liver disease, portal hypertension, and preoperative sepsis⁵⁹. In addition to these preoperative risk factors, a number of

perioperative factors can also affect the risk of postoperative hepatic insufficiency. These include smaller liver remnant, prolonged operative time, blood loss in excess of 1000ml, and postoperative biliary leaks¹⁰. There remains considerable debate about the safe limits for liver resection and decisions must be based on an assessment of preoperative and likely intraoperative factors, in conjunction with an appreciation of an individual's liver function.⁵⁹

Unfortunately, no single test or biological marker has been able to adequately identify hepatic function and predict postoperative outcome⁵⁹. The most commonly used methods include scoring systems, and dynamic liver function assays. This is often done in conjunction with volumetric analysis of preoperative and predicted postoperative hepatic volume.

Scoring systems are typically applied in patients with pre-existing liver dysfunction and include the Child–Turcotte–Pugh score and the Model for End-Stage Liver Disease (MELD) score⁶⁰. These have been shown to be reliable predictors of risk in patients with known pre-existing liver disease, but are of little value in patients undergoing resection for CRLM, where the majority have no known underlying liver disease⁶¹.

Indocyanine green (ICG) test is available to aid in the assessment of hepatic functional capacity, but is infrequently used⁵⁹. It is a water-soluble agent, taken up by hepatocytes and transported into the biliary system. It is not

metabolised by the liver or reabsorbed via the entero-hepatic circulation⁶². It can be used to estimate functioning hepatic mass, liver blood flow and the energy status of the liver^{63,64}. Retention of ICG of 10-14% at 15 minutes has been used in patients with underlying liver disease to help determine a safe limit for hepatic resection, with poorer scores precluding major hepatectomy. Concerns exist that this may result in patients who could safely undergo hepatectomy being denied surgery based on a low ICG clearance⁶².

Other tests of preoperative hepatic function include hepatobiliary scintigraphy and the MEGX test (metabolism of lidocaine to mono-ethylglycinexylidide)⁶⁵. Hepatobiliary scintigraphy has been shown to correlate with outcomes determined by volumetric assay but is affected by tumour burden, and has not gained widespread use⁶⁶. The MEGX test in conjunction with volumetric analysis has helped predict patients at risk of PHLF⁶⁷. The requirement to administer lidocaine intravenously, and the concern over individual variability due to medication interaction with the Cytochrome P450 pathway have led to limited uptake of this test.

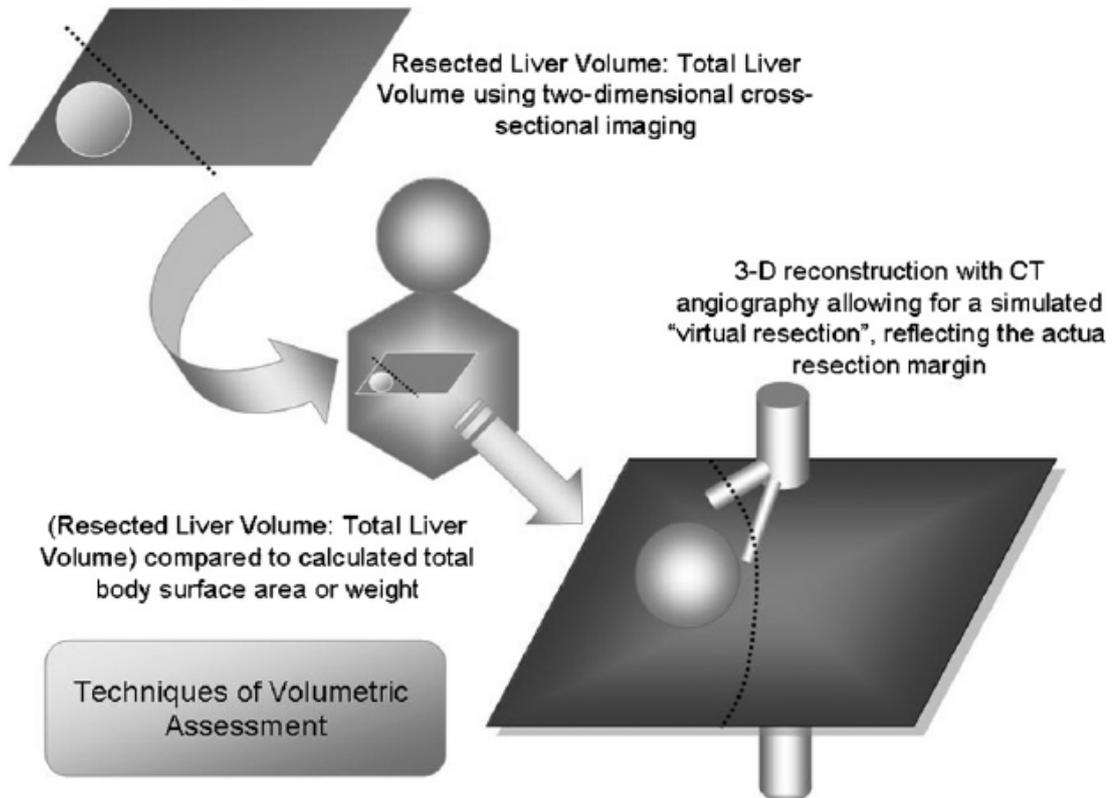
The absence of reliable definitions of hepatic functional reserve has led to hepatic volume, and predicted post resection hepatic volume in conjunction with patient factors being used to define resectability.

1.4.1 Defining the minimum future liver remnant volume

The volume of hepatic resection is inextricably linked to the risk of PHLF and mortality. The larger the resection the higher the risk of PHLF⁵⁹. Given this established fact, and the difficulties to quantifying the hepatic function, much work has been done to establish safe volumes of resection.

A variety of techniques have been employed to measure liver volume. The simplest form (Figure 1-1) utilises CT reconstruction to estimate the ratio of likely resected volume as a proportion of total liver volume⁶². Resection of more than 75% of total liver volume is associated with a 90% incidence of post resection hepatic failure, increased complications and a longer length of stay⁶⁸.

Figure 1-1 Overview of volumetric analysis of liver volume ⁶²



Techniques have been developed to take into account non-functioning liver that has either been replaced or obstructed by tumour, and incorporate the patients size into the calculation^{69,70,59,71}.

Current standards suggest that in a patient with normal hepatic function, a minimum volume of FLR can be considered as 20%⁷². This, however, needs to be considered in conjunction with other intraoperative factors including the expected extent of hepatic ischemia, and the intraoperative blood loss.

Unfortunately, this safe limit is increasingly difficult to utilise in clinical practice as patients undergo more complex treatment pathways, with multi agent chemotherapy and intrahepatic therapies. These treatments, in particular chemotherapy, can have negative effects on hepatic function. The effect is however idiosyncratic⁷³. As a result defining hepatic function is becoming increasingly important in clinical practice.

1.4.2 Perioperative chemotherapy for CRLM

In the last 10 years survival (OS) in patients with metastatic colorectal cancer has improved significantly⁷⁴. Given that only a minority of patients with liver limited metastases are potentially treatable with curative intent surgery, much of this can be attributed to advances in systemic therapies. It is outside the scope of thesis to explore the detailed chemotherapeutic options for patients with colorectal liver metastasis, however they can be broadly considered in 4 main categories.

1.4.2.1 Conversion Chemotherapy

Conversion chemotherapy aims to bring patients with initially irresectable hepatic metastases, to curative intent surgery. These patients, brought to secondary resection by systemic therapy, enjoy comparable long-term survival to patients with upfront resectable disease at the time of presentation

(10 year survival 23%vs 30%⁷⁵), and far superior to those receiving palliative systemic chemotherapy⁷⁶.

1.4.2.2 Neo-adjuvant and adjuvant chemotherapy

Whilst chemotherapy is considered standard of care in patients with high-risk stage II and all stage III cancers,²³ in patients with established liver limited stage IV disease the role is less clear⁷⁷.

Recurrence is common following hepatic resection of CRLM, occurring in over two thirds of patients within 2 years of surgery⁷⁸. Chemotherapy in either neoadjuvant or an adjuvant setting aims to treat occult metastases, thereby reducing early recurrence^{79,80}. Currently UK comprehensive cancer network guidelines recommend considering 6 months perioperative chemotherapy for all patients with resectable metastatic liver lesions, but the paucity of evidence is acknowledged⁷⁷.

1.4.2.3 Loco-regional chemotherapeutic therapies

In addition to systemic chemotherapeutic options for CRLM, there have been advances in a variety of other therapies. It is beyond the scope of this thesis to detail these therapies, however they include:

1. Hepatic arterial infusion (HAI) chemotherapy^{81,82}.

2. Drug eluting beads for trans arterial chemo-embolisation (DEB-TACE)^{83,84}.
3. Selective internal radiation therapy (SIRT)⁸⁵⁻⁸⁸.

1.4.2.4 Chemotherapy induced liver injury

Whilst chemotherapy and liver targeted therapies have a number of potential benefits, the consequences of hepatic toxicity must be considered. The three agents most commonly used in the management of CRLM are 5-Fluorouracil (5-FU), Irinotecan, and oxaliplatin⁷³. All can cause hepatic injury⁷⁷.

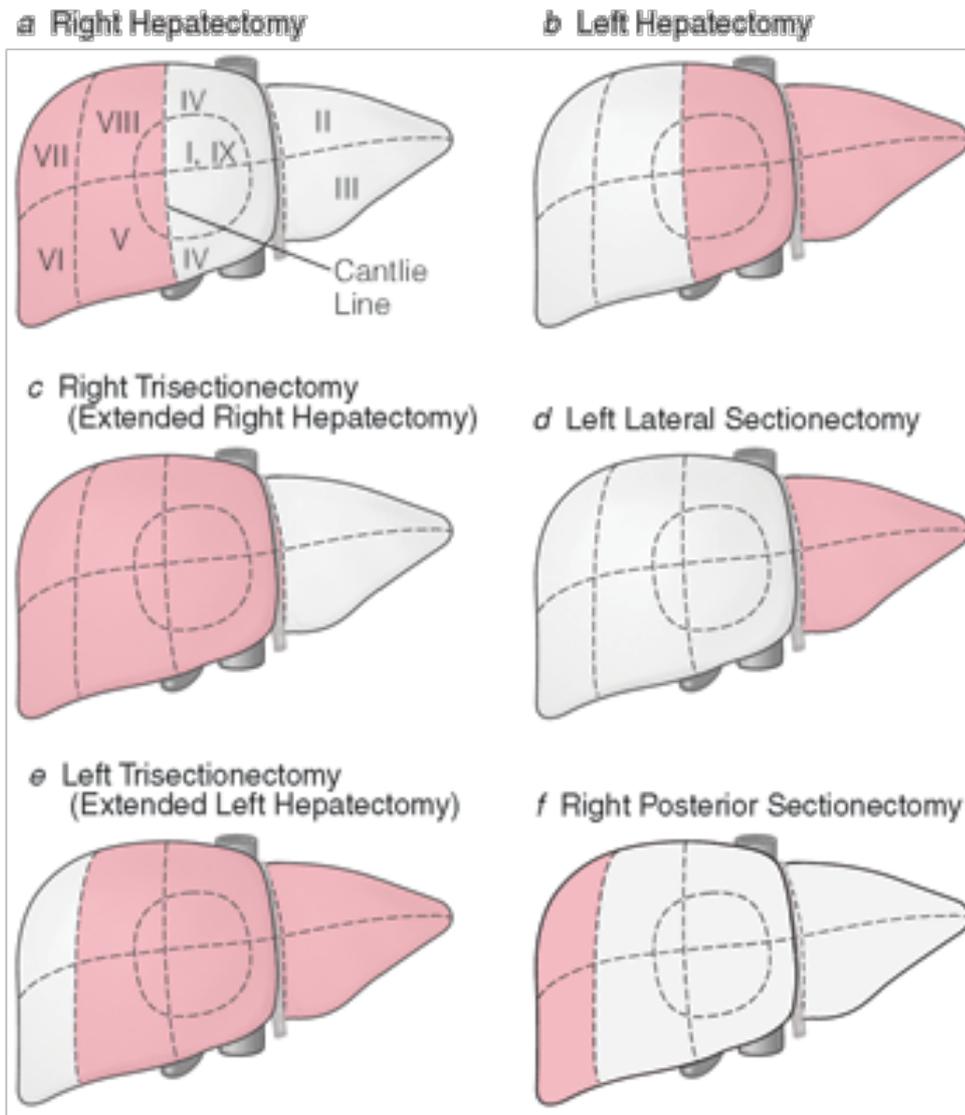
Unfortunately, despite understanding that chemotherapy can have significant effects on hepatic function, identifying those individuals where significant chemo-toxicity has or will occur remains a challenge⁷³. Developing a model of hepatic function and biomarkers of chemo-toxicity to allow this is a research priority.

1.5 Surgery for CRLM

Early hepatectomy relied on utilising the internal hepatic anatomy to resect entire lobes, sections or segments (Figure 1-2)⁸⁹. This had the advantage of allowing control of haemorrhage intra-operatively, making resection feasible before the onset of improved anaesthetic techniques. The disadvantage of this original approach meant that in many cases extensive normal hepatic

tissue was resected increasing the volume of resection and consequently the risk of PHLF ⁹⁰. The descriptions were standardised in 2000 using the Brisbane criteria and then revised by the International Society of Hepato-Pancreato-Biliary Surgery (IHPBA)⁹¹.

Figure 1-2 Common anatomical hepatectomies



Non-anatomical hepatectomy has evolved as surgical and anaesthetic techniques evolved. It aims to remove all metastatic deposits, preserving as much liver tissue as possible. This is determined by the proximity and involvement of the hepatic blood flow, and biliary drainage. This surgery has contributed to a progressive reduction in the incidence of major anatomical resection, but has led to increasing difficulties in assessing the extent and risk of surgery⁵⁴. Particularly when parenchymal preserving surgery is used in conjunction with other liver directed therapies and advanced surgical techniques⁵⁴.

1.5.1 Anaesthesia for liver surgery

Anaesthetic advances have had a significant impact on both the extent of feasible surgery, and the outcomes following surgery. Whilst this thesis does not seek to examine the changes in anaesthetic technique one of the greatest contributions has been the widespread adoption of low CVP anaesthesia. The CVP is kept between 2mmHg and 5mmHg which limits the distension of hepatic veins and sinusoids, and consequently the massive blood loss previously associated with hepatectomy⁹². This anaesthetic approach has an accepted consequence of a risk of inadequate organ perfusion and potential organ injury⁹². The complexities of intraoperative management in these patients continue to increase as the bounds of surgery are extended, particularly with the use of advanced hepatic reconstruction.

1.5.2 Laparoscopic liver surgery

Laparoscopic surgery for CRLM aims to provide curative resection whilst reducing the trauma associated with open surgery. There are no randomised controlled trials assessing the use of laparoscopic hepatectomy currently published. The largest randomised trial in laparoscopic liver surgery, ORANGE II, failed to recruit patients. The ORANGE II plus trial is on-going and is examining the role of laparoscopic hemi-hepatectomy⁹³.

Currently evidence is based on retrospective series. A meta-analysis of series published between 1998 and 2005 concluded that laparoscopic liver resection has the potential to reduce operative blood loss and allow earlier recovery with oncological clearance comparable with open surgery⁹⁴. It cautioned that because of the potential of significant bias arising from case series, randomised controlled trials were recommended, to eliminate bias and to compare long-term survival rates.

One of the largest early single-centre experiences of laparoscopic colorectal liver metastasis resection included 83 resections within a series of 133 liver resections⁹⁵. The median operating time for laparoscopic resections was 210 minutes (30-480 minutes), median blood loss 300ml (10-3000ml) and the median postoperative stay 4 days (1-15 days). Severe postoperative bleeding occurred in 5 patients (3.7%) requiring intensive care management or reoperation, overall serious complications occurred in 16 patients (13%). More recent studies including 100 patients undergoing consecutive

laparoscopic hepatectomies, within a series of 168 consecutive resections for CRLM, suggested that laparoscopic surgery is associated with shorter operative time, lower blood loss, lower major morbidity, and comparable long-term outcomes⁹⁶. However this study had significant selection bias, and was not a true comparative study.

1.5.3 Strategies to increase resectability

Given the main limitation to the technical aspects of surgical resection is the preservation of an adequate future remnant liver a number of strategies have been developed to help address this issue.

1.5.3.1 Ablation

Ablation has become a widely used method of treating colorectal liver metastasis, with an estimated 2000 patients treated annually in the UK. This treatment aims to destroy metastases gaining local control in patients deemed surgically irresectable either due to insufficient FLR, or poor patient fitness⁹⁷. It facilitates the combined resection and ablation approach to CRLM surgery^{98,99}. Ablative therapies commonly employed include radiofrequency ablation (RFA)⁹⁷, microwave ablation⁹⁹ and irreversible electroporation (IRE)¹⁰⁰. These modalities all have specific uses and may be the method of choice in specific circumstances; IRE in particular is an attractive option for metastases in close proximity to major vascular or biliary structures¹⁰⁰.

1.5.3.2 Portal vein embolization

Portal vein embolization (PVE) induces atrophy of the liver to be resected and hypertrophy of the liver that will remain (i.e. increases the FLR) with the aim of avoiding PHLF. A meta-analysis has confirmed that this technique increases significantly the volume of the FLR¹⁰¹. PVE appears to be safe, even when combined with conversion chemotherapy¹⁰².

1.5.3.3 Two stage hepatectomy

Two-stage hepatectomy is employed in patients where resection of all the metastases would leave insufficient functional liver, and where the metastases are distributed across both liver lobes. Two-stage hepatectomy involves a first stage of non-anatomical resection of metastases from the future remnant with PVE (or PV ligation during surgery) of the future liver to be resected. This is followed by a period of liver regeneration and a second stage resection.

A systematic review included 459 patients in whom a two-stage resection was planned¹⁰³. Two-stage resection was completed in 76.6% (range 69-92%) of patients who underwent first stage. Overall survival at 3 and 5 years was 59%, and 42% respectively. The success of this technique relies on patients undergoing hepatic regeneration sufficient to allow a second stage, whilst maintaining their fitness, and not developing progressive disease.

1.5.3.4 ALPPS (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy)

A purported alternative to the two stage liver resection is the ALPPS procedure, which involves an in situ splitting of the liver with portal vein ligation followed by a formal hepatectomy at a median of 9 days¹⁰⁴. This has been reported to demonstrate a median increase in the future remnant liver of 71%. This represents an exciting development in the field of liver surgery that may help to bring more patients to resection. The long-term results of this technique have yet to be validated and the technique remains controversial and a subject of debate.

1.5.3.5 Advanced hepatic reconstruction techniques

Despite evolving definitions of resectability, there remain a group of patients in whom technical resectability is only possible with the use of advanced surgical techniques. Typical cases might have metastases involving the hepatic inflow, the hepatic outflow, the inferior vena cava, or all three of these structures. Techniques employed to achieve macroscopic resection in these cases have included portal vein resection and reconstruction, hepatic artery resection and reconstruction (or arterialisation of the portal vein as an alternative), total hepatic vascular exclusion, in situ hypothermic perfusion and ex vivo (bench) hepatic resection¹⁰⁵⁻¹⁰⁸. These techniques are at the limits of what is currently feasible and are associated with significant

morbidity and mortality. Therefore these techniques should be reserved for carefully selected individuals with an otherwise poor prognosis.

1.5.4 Perioperative morbidity and mortality

In early hepatectomy series published in the 1980's, in hospital mortality was in the order of 5%, despite a highly selective approach to patient selection¹⁰⁹. This has progressively diminished despite more complex resections being undertaken in patients with more extensive disease⁵⁴. Perioperative mortality reported in large series of patients undergoing resection of CRLM is now typically between 1-3%^{25,54,110,111}. Though the data reported from the author's unit reports a mortality of 0.3%¹¹².

Unfortunately despite a near halving in perioperative mortality, in large series postoperative morbidity remains consistently high at around 41.6-45%^{25,54,113}. With severe complications (Dindo-Clavien¹¹⁴ Grade 3 and above) occurring in 14-29.7%^{25,54}.

Common causes of morbidity following hepatectomy include pulmonary complications (6.1-21.9%), cardiac complications (3-10%), biliary leak (4.8-8.9%), peri-hepatic collections (2.9-7.0%), PHLF (2.6-6%), and wound infections (3.4-5.9%)^{25,54,115}. However there is wide variation in reporting of complications, which may in part be due to subjective interpretation³⁴. For example in the case of a peri-hepatic abscess or bile leak, concurrent respiratory complication is common, though may not be included in morbidity

scores either due to a failure to identify it or exclusion based on the direct cause and effect relationship.

1.5.4.1 Factors associated with perioperative morbidity and mortality

Since the Dindo-Clavien¹¹⁴ classification allowed standardisation of the measurement of complications a number of studies have sought to elicit factors associated with poorer perioperative outcome, in the hope of better clarifying the population at risk of complications. These can largely be considered as factors associated with an individual's premorbid state, factors associated with the disease and prior treatments, and factors relating specifically to the intervention undertaken.

1.5.4.1.1 Patient Variables

Whilst there is debate about the relative impact of cardiopulmonary fitness on perioperative outcome, a number of other factors have been identified as being associated with increased perioperative risk including increasing age, impaired hepatic function, cirrhosis, hepatic steatosis, renal failure and medical comorbidity^{25,54,110,113,115-117}.

Given that we can only expect the number of older patients with increasing comorbidity to increase⁵, and with the worldwide increasing rates of obesity, these associations pose a threat to future perioperative outcomes. This makes the aspiration of improving perioperative outcomes challenging to deliver.

1.5.4.1.2 Treatment related variables

The only treatment related factor consistently identified, as being associated with an increased incidence of perioperative morbidity is the use of neoadjuvant chemotherapy.^{57,118,119}

Repeat hepatectomy has been associated with increased bile leaks, but not overall morbidity and mortality though, given an association with longer operating time¹²⁰ and increased blood loss,^{111,120} the absence of an association with increased complication may reflect the selective nature of patients considered for repeat hepatectomy.

The consequences of the newer liver directed therapies including Transarterial Chemoembolization (TACE) with irinotecan eluting beads (DEBIRI) and Selective Internal Radiation Therapy (SIRT) on postoperative morbidity and mortality are not yet clear.

1.5.4.1.3 Perioperative factors

The perioperative factors associated with increased perioperative morbidity and mortality have been extensively studied.^{25,54,111,118,121} The overarching theme of these studies suggest, as might be expected, that with increasing complexity and magnitude of surgery, there is an increase in perioperative morbidity and mortality. The key factors identified as being associated with poorer perioperative outcome are summarised in Table 1-4^{25,54,111,118,121}.

Table 1-4 Intraoperative factors associated with poorer perioperative outcome

Repeat hepatectomy
Major hepatectomy
Longer operating Time
Increased use of Pringle manoeuvre
Blood loss
Transfusion
Additional extrahepatic resection
Vascular resection
Bile duct resection
Hepatico-jejunostomy construction
Diaphragm resection

1.5.5 Survival

Overall survival for patients following hepatectomy for CRLM is reported between 36-58% with latter series tending to report better survival. Survival to 10 years is between 23-25%, with this seen effectively as cure^{122,123}. Identifying factors associated with either better or worse prognosis can aid treatment decisions, and allow a degree of individualised prognostication.

1.5.5.1 Predictors of survival

In a similar manner to perioperative outcomes factors associated with survival can be considered as patient factors, disease factors, and factors relating to the operative intervention. A number of scoring systems have been developed to aid in the prediction of survival,^{61,124,125} but changes in our understanding of disease biology, and better treatment mean that these are no longer as relevant in clinical practice.

1.5.5.1.1 Patient variables predictive of survival

Whilst age has been consistently identified as a predictor of worse perioperative survival, the same cannot be said for overall survival^{61,110,111,117}. Beyond the initial perioperative period, age does not have a significant effect on survival¹¹⁰.

Factors suggested to be associated with poorer overall survival include patients with higher ASA scores¹²⁶, sarcopenia (significant loss of muscle mass) and fatty liver disease^{61,127,128}. Though the role of fatty liver disease and sarcopenia appear related, the mechanism by which they affect survival is unclear. In a retrospective series, patients with fatty liver disease were more likely to have a lymph node positive primary tumour, higher CEA, more preoperative chemotherapy, larger metastases, and a positive hepatectomy resection margin¹²⁸. However given that chemotherapy is often given to treat those with less-favourable patterns of disease, and is a known cause of fatty liver disease, establishing cause and effect is more challenging¹²⁹.

This relationship is further complicated as fatty liver disease also serves as a surrogate marker for other comorbid conditions such as diabetes.

1.5.5.1.2 Tumour biology

After the initial perioperative period the biggest cause of death in these patients is related to the disease recurrence. This has been a major focus of research to establish disease related prognostication. A number of factors

have been identified and are summarised in Table 1-5. These factors often serve as surrogate markers of aggressive tumour biology, but even in these patients survival is achievable meaning further characterisation of tumour biology remains a research priority^{61,111,130-134}. Better understanding of the disease should allow improvements in targeted treatment and overall survival.

Table 1-5 Tumour related factors predicting poorer survival

Primary Tumour
Node positive primary tumour
Poorly differentiated primary tumour
Kras Mutation
Metastatic presentation
Extrahepatic metastatic disease
Increased number of metastases
Mucinous tumour
Invasion of surrounding hepatic structures by a metastases
Large Metastases (>5cm, and >10cm)
CRP>10
Elevated Neutrophil to lymphocyte ratio

1.5.5.1.3 Perioperative factors

In the perioperative management of patients with colorectal liver metastases factors have been identified that can affect long-term survival^{61,90,111,135,136}. These include a positive margin in a resected specimen, intraoperative blood loss, use of transfusion, and the development of postoperative complications^{61,111,130,135,137}. Methods to reduce complications could therefore have a significant effect on cancer survival.

Managing these patients outside an MDT environment also appears to negatively affect survival, possibly through inappropriate selection, delays to treatment and inappropriate use or failure to use additional therapies¹³⁶.

1.6 Enhanced recovery after surgery (ERAS)

Given the impact of perioperative outcomes on both healthcare costs, and long term survival following cancer surgery, strategies to minimise the consequences of surgery have been developed.

The seminal paper in the Lancet in 2003 from Kehlet paved the way for what would later be known as enhanced recover after surgery or ERAS¹³⁸. This was further described in 2005 which set out the components felt to be key to a successful ERAS programme¹³⁹.

Since this time the use of ERAS has proliferated across surgical disciplines, such as colorectal surgery¹⁴⁰⁻¹⁴², urological surgery¹⁴³, and vascular surgery¹⁴⁴, becoming the standard of care. They utilise a multimodal management strategy to improve perioperative outcome, and have been shown to reduce complications, hospital length of stay and hospital costs.¹⁴⁵

1.6.1 Components of ERAS

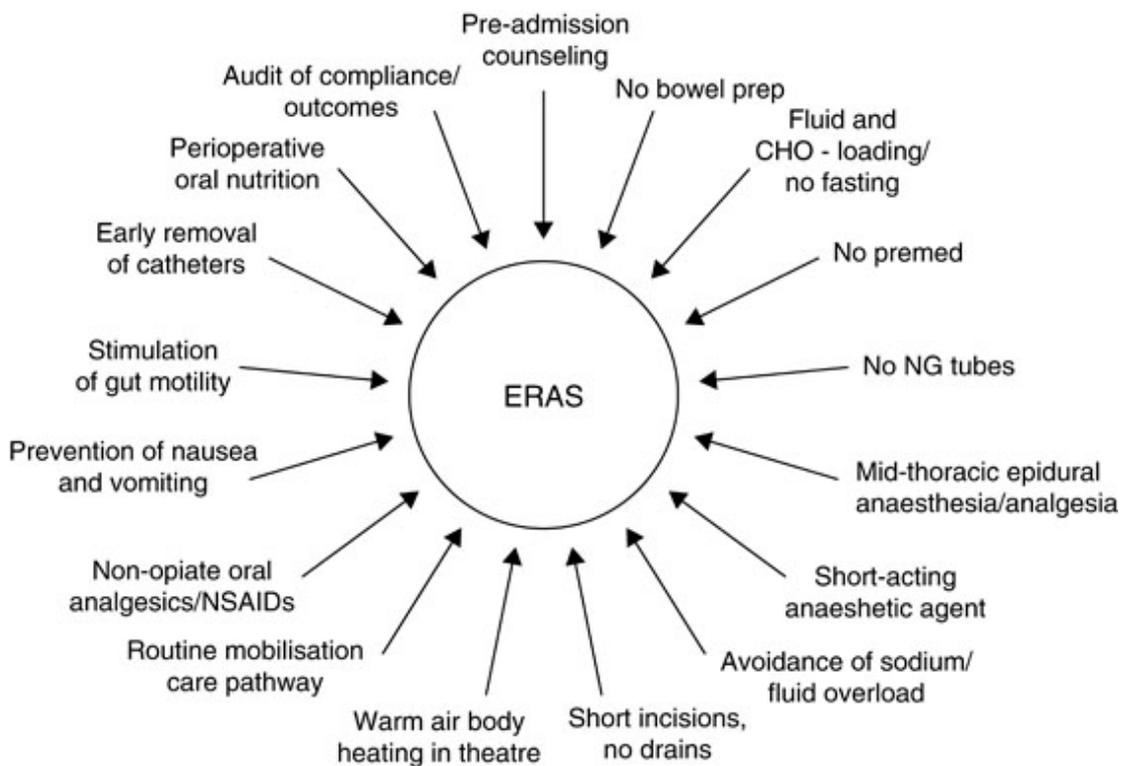
The four main principals of ERAS are^{139,141}:

1. Optimised preoperative assessment
2. Reducing the physical stress of surgery

3. Improved perioperative management
4. Early mobilisation

The individual components of a typical ERAS programme are shown in Figure 1-3¹³⁹. Given the success of ERAS, they are now considered as a standard of care in colorectal surgery¹⁴¹.

Figure 1-3 Components of an ERAS programme¹³⁹



1.6.2 ERAS in Liver surgery

Despite being a standard of care in colorectal surgery, the evidence for the use of ERAS in liver surgery is more limited with just six small published series identified in a recent systematic review¹⁴⁵. Since this systematic review only two other studies have been published. One, the only randomised trial

of ERAS versus standard care in liver surgery, included 160 patients (80 in either arm) ¹⁴⁶. This study demonstrated that ERAS was associated with shorter hospital stay (7 days versus 8 days $p=0.018$), and lower overall complications (30% vs. 47% $p=0.03$). There was no difference in the incidence of severe complications (Dindo-Clavien ¹¹⁴ grade III-IV). However this study was limited by stringent exclusion criteria, which included any resection greater than a hemihepatectomy, any hepatectomy with concomitant bile duct resection, repeat hepatectomy, patients greater than 65 years of age, any patient with “severe comorbidity”, and any patient with bilobar disease. . The applicability of this study to typical patients with CRLM who are typically over 65, frequently have significant comorbidity, and often have bilobar disease being treated with multiple hepatectomies is questionable. The applicability of this to our study population is further undermined given its concentration on primary liver cancer.

The other recent publication examining the role of ERAS in hepatectomy was a cohort study including 100 consecutive patients undergoing hepatectomy¹⁴⁷. This demonstrated that outcomes for patients managed within an ERAS programme were good, with 25% morbidity, and a median length of stay of 5 and 6 days for minor and major resections respectively. There was no postoperative mortality.

1.6.3 ERAS for patients undergoing hepatectomy for CRLM

The largest published series of ERAS in patients undergoing liver resection for colorectal metastases was completed during the course of this thesis at Aintree University Hospital¹¹². This study included consecutive patients undergoing hepatectomy for CRLM between February 2008 and September 2012. Cardiopulmonary exercise testing, which is not considered part of a standard ERAS programme, was introduced on 1st October 2009. Initially this was selective, and expanded to all patients from the 1st October 2011. This study demonstrated that ERAS was associated with short hospital length of stay (median 6 days), low overall morbidity (38.2%), and low severe complications (11%). Only 64.5% of patients were admitted to level 2 care postoperatively, and median length of stay in these patients was 1 day. There was only one in hospital death within the study representing a mortality of just 0.3%, much lower than other large series¹⁴⁸.

The findings from this study validate previous studies suggesting positive outcomes from ERAS^{145-147,149}. ERAS should now be seen as a standard of care following hepatectomy.

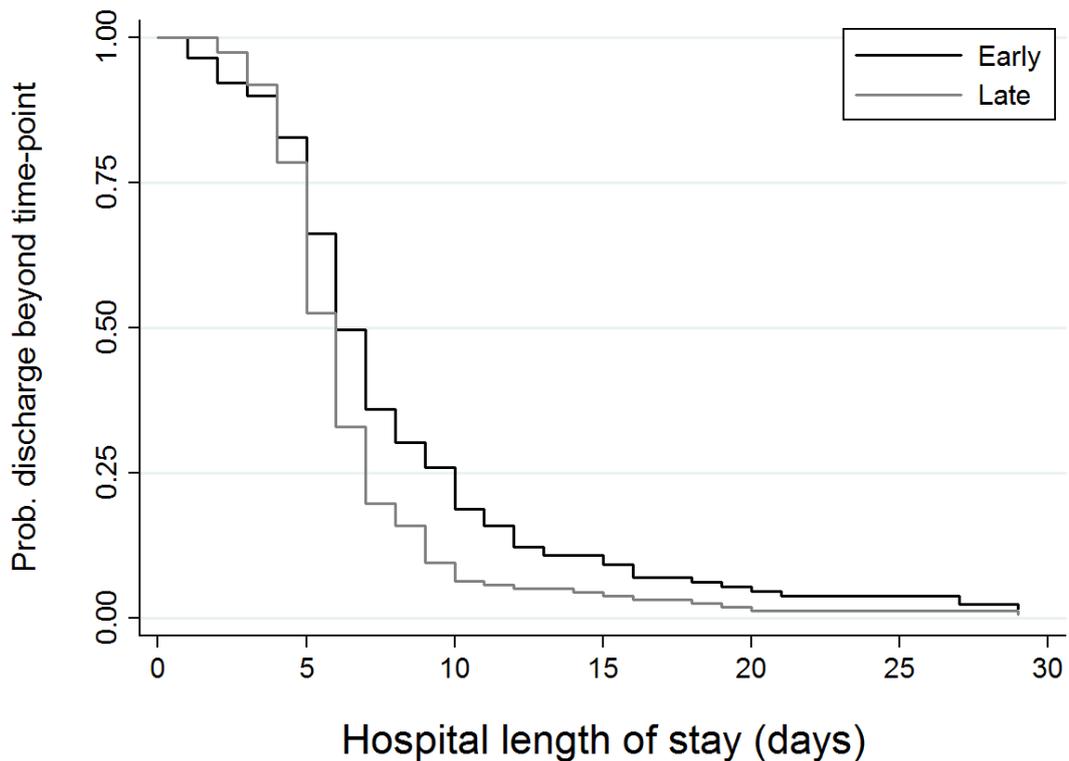
1.6.4 Evolution of ERAS

ERAS programmes are often seen as fixed entities with a defined management protocol, whereas in reality these programmes are fluid entities that mature as staff and patient awareness increases, as well as reflecting

developing local and national needs. Given the benefits of ERAS post hepatectomy the Aintree study sought to evaluate how outcomes changed as the ERAS programme matured¹¹².

The study cohort was divided into early and later cohorts that were compared. This demonstrated that as programmes mature, the length of stay reduced ($p < 0.01$). This reduction in hospitalisation was mainly due to a reduction in patients requiring prolonged admission (Figure 1-4)¹¹². The Kaplan-Meier curve (Figure 1-4) demonstrated that beyond 6 days, the length of stay curves separate. The probability of staying in hospital beyond 10 days was 25% for the early cohort compared to 7% for the latter cohort.

Figure 1-4 Kaplan Meir showing length of stay following hepatectomy in an ERAS programme



This is interesting as both overall and serious morbidity was not significantly different across the cohorts. This suggests that as ERAS programmes mature, there is a progressive minimisation of the consequences of complications on the length of hospitalisation. Given that complications are associated with poorer survival it would be of interest to see whether this progressive reduction in the impact of complications, led to changes in the impact of complications on survival.

Over this time period there was also a progressive reduction in the use of critical care admission (75.5% early cohort vs. 54.7% in the latter

cohort)($p < 0.0001$)¹¹². This reduction was thought to represent a growing confidence in the combination of anaesthetic review and CPET to risk stratify patients. The success of this stratification is further underlined by the absence of any patient triaged to level 1 care postoperatively subsequently requiring emergency critical care admission.

Taken in conjunction with other published studies, the findings of this work demonstrate that ERAS is feasible, and that the benefits accrue with time¹¹². The addition of CPET in the risk stratification, has likely contributed to the excellent perioperative outcomes, particularly in older patients where defining risk is harder¹⁴⁻¹⁹.

1.7 Rehabilitation and exercise therapy

Prior to the development of formalised ERAS, many have studied methods of improving recovery from surgical cancer treatment. Exercise has been a key area of interest for such studies, often delivered in as combinations of strength and cardiovascular training.

Specifically following cancer treatment exercise therapy has been used as part of survivorship programmes and has been shown to have a number of beneficial effects. Exercise is now an established method of improving recovery from surgery, and other cancer treatments¹⁵⁰⁻¹⁵⁴. Other benefits include improved strength, improved physical aerobic capacity, reduced

depression, and improved quality of life¹⁵⁰. It is also an established treatment for post cancer fatigue syndrome^{150,152,155-157}.

1.7.1 Exercise in metastatic colorectal cancer

Whilst there are accepted benefits in cancer survivors, a recent systematic review identified only 8 studies investigating the role of exercise therapy in metastatic cancer, and of these only 3 were randomised controlled trials¹⁵⁸. The metastatic disease in these studies was of varied origin, and only 3 trials included only patients with metastatic disease (Breast 2 Mixed 1). The review suggested that adherence was 75-85% and that the benefits of an exercise programme were similar to that in other populations with improved quality of life being the main outcome.¹⁵⁸. There has been no study of exercise intervention in patients with CRLM.

1.7.2 Delivering post treatment exercise therapy

The majority of cancer survivors are inactive, which is surprising given the purported benefits of exercise therapy¹⁵⁴, however this does emphasise the difficulties in delivering exercise therapy to this group. A number of barriers to increasing activity have been identified and can be summarised as physical, physiological, and institutional.

1.7.2.1 Physical barriers to exercise therapy

In the post-surgical setting many patients do not feel physically able to exercise, as a result of the cancer treatments they have endured. This

includes pain from surgical interventions and the consequences of intensive treatments such as radiotherapy, and chemotherapy^{153,154}. Inactivity during cancer treatment is also common and leads to physical deconditioning. Physical consequences of cancer therapy are summarised by the American college of sports medicine (Table 1-6)¹⁵³.

Table 1-6 Physical consequences of cancer therapy

	Surgery	Chemotherapy	Radiation
Second cancers		✓	✓
Fatigue	✓	✓	✓
Pain	✓	✓	✓
Cardiovascular changes: damage or increased CVD risk		✓	✓
Pulmonary changes	✓	✓	✓
Neurological changes:			
Peripheral neuropathy		✓	
Cognitive changes	✓	✓	✓
Endocrine changes			
Reproductive changes (e.g., infertility, early menopause, impaired sexual function)	✓	✓	✓
Body weight changes (increases or decreases)	✓	✓	
Fat mass increases	✓	✓	
Lean mass losses	✓	✓	
Worsened bone health		✓	✓
Musculoskeletal soft tissues: changes or damage	✓		✓
Immune system			
Impaired immune function and/or anemia		✓	✓
Lymphedema	✓		✓
Gastrointestinal system: changes or impaired function	✓	✓	✓
Organ function changes	✓		
Skin changes			✓

1.7.2.2 Physiological barriers to exercise therapy

Psychological disturbance is present in up to 50% of cancer patients, and in colorectal cancer nearly a quarter report depressive symptoms¹⁵⁹. Symptoms deteriorate over the course of cancer treatment¹⁶⁰. Consequently following treatment patients are more likely to be depressed, anxious and lacking in motivation. This represents a significant barrier to the introduction of exercise therapy.

A cancer diagnosis and treatment is also associated with the development of cancer related fatigue syndrome. This is a common complication of cancer diagnosis and treatment affecting up to 70% of patients¹⁶¹. The mechanism is poorly understood, but is probably multifactorial, including both physical and psychological components¹⁶¹. It results in disabling fatigue that prevents patients returning to pre-diagnosis levels of activity. Aerobic exercise has been established as a treatment for this condition, but the challenges of getting patients suffering cancer related fatigue to take up exercise are acknowledged¹⁶¹.

1.7.2.3 Institutional barriers to exercise therapy

Institutions providing cancer care predominantly focus on the delivery of safe and effective care. Care is concentrated in the immediate pre-treatment period, during treatment and in the early follow-up time period. Beyond this follow-up is of variable frequency but commonly diminishing. This lower visibility of the patient group post treatment, in conjunction with a lower institutional priority for exercise therapy, is suggested as one cause underlying the low levels of activity in cancer survivors¹⁵⁴.

1.8 Prehabilitation

Prehabilitation is defined as the process of enhancing the functional capacity of the individual to enable him or her to withstand a stressful event¹⁶². Given the benefits of ERAS, and post-treatment exercise therapy, pre-treatment optimisation and exercise therapy represents an attractive prospect that could augment the work of ERAS, and minimise some of the difficulties of post treatment rehabilitation.

Prehabilitation occurs before the development of many of the physical and psychological barriers to exercise therapy, which may develop with the initiation of cancer treatment. This should serve to increase the pool of patients able to participate, and could lead to reductions in the development of incapacitating physical consequences.

Prehabilitation could reduce the morbidity and mortality associated with treatment as accrue the benefits to physical and psychological functioning, that prehabilitation could theoretically deliver.

Exercise prior to treatment gives patients a defined goal that could translate into higher adherence and completion. It also serves to make the therapy visible to the clinicians involved in providing the cancer treatment, raising the awareness of exercise therapy, thus overcoming institutional barriers to exercise therapy.

1.8.1 Prehabilitation challenges

Despite the attractions of prehabilitation, there are a number of unique problems that must be addressed when developing prehabilitation programmes.

1.8.1.1 Defining fitness

One of the challenges to improving “fitness” is adequately defining what is meant by this concept. Traditionally employed measures of patient fitness such as ASA, performance status and questionnaires, lack the capacity to differentiate adequately, and are subjective. Assessment of fitness before and after a prehabilitation programme with such measures risks not detecting meaningful changes, or detecting changes related to attitude shift rather than a true change in fitness.

The relatively recent adoption of cardiopulmonary exercise testing has allowed accurate measurement and quantification of fitness in a reliable and repeatable fashion²⁹, and facilitates the adoption of prehabilitation programmes where fitness can be a measured outcome.

1.8.1.2 Patient group

The majority of cancer sufferers are sedentary¹⁵⁴. Patients with CRLM are often elderly (age >70), with associated comorbidities including heart disease, respiratory disease, and arthritic conditions⁵. This is in addition to metastatic colorectal cancer, where increasingly the metastatic disease is

detected at presentation, meaning that patients undergoing prehabilitation may have symptomatic primary tumours¹⁶³.

This poses a number of challenges for prehabilitation, and any programme must be appropriate for this challenging group of patients.

1.8.1.3 Time duration

One of the biggest challenges of any prehabilitation programme is the time constraints imposed by their cancer diagnosis. Timely treatment is essential to minimise the risk of progression, and the psychological input of having a cancer insitu. Current UK targets impose a 62-day time limit from the point of referral to the initiation of treatment, and 31 days from the decision to treat to the delivery of treatment. Given that during this time the establishment of the diagnosis must take place this leaves very little time to deliver a prehabilitation programme, and certainly more than 4-weeks is probably unachievable.

In addition to this, most patients being considered for surgical intervention for CRLM have a number of preoperative appointments and scans which will all detract from their time to partake in prehabilitation. So any prehabilitation programme must not be of a frequency that is likely to lead to low adherence.

1.8.2 Prehabilitation in practice

The majority of work on prehabilitation has been concentrated on joint replacement and orthopaedic surgery^{164,165}. Limited prehabilitation has been

undertaken prior to aortic aneurysm repair, lung resection, colorectal resection and resection of primary liver malignancy. The results are summarised below.

1.8.2.1 Prior to lung resection

There are just two published case series of prehabilitation before lung resection^{166,167}. The earlier study includes 19 patients recruited into an interventional study, where preoperative supervised exercise therapy was given for a median of 60 days¹⁶⁷. Of these, 17 patients completed the preoperative exercise therapy, with adherence of 88%. Only 12 completed the pre-surgical assessment of CPET and quality of life measures. Two patients died postoperatively and one was excluded following major complications. Only 9 of the original 19 patients completed prehabilitation and subsequent post-surgical assessment. Peak oxygen uptake (VO_2^{peak}) increased preoperatively in all patients, with correlation between improving fitness and improved pre-surgical fatigue scores.

The second exploratory study randomized 24 patients to either prehabilitation with strength and endurance training or to a chest physiotherapy programme prior to lung resection. They found a significant reduction in pulmonary complications and hospital length of stay in patients undergoing prehabilitation.¹⁶⁶

1.8.2.2 Prior to aortic aneurysm surgery

A randomised study examined the effect of a 6 week supervised exercise programme of patients' fitness prior to aortic aneurysm surgery¹⁶⁸. This study recruited 30 patients (20 intervention vs. 10 control), with 17 completing the exercise intervention, and 8 completing the control arm. Of note, one of the exercise participants suffered a cardiac arrest during the 7th exercise intervention. Two of the other withdrawals were for unrelated conditions, and the two withdrawals from the control arm were unexplained. Patients in the intervention group had a median increase in fitness of 10% (p=0.0007), with a suggested number needed to treat to produce clinically significant improvements of 4.4 patients. This study did not provide data on post-surgical outcome.

More recently 20 patients awaiting aortic aneurysm surgery partook in a prehabilitation study. When comparing these patients to baseline, they found post prehabilitation improvements in VO_2^{peak} (18.2 to 19.9 ml.kg⁻¹.min⁻¹), and VO_2 at AT(12.2 to 14.4 ml.kg⁻¹.min⁻¹)¹⁶⁹.

Both of these studies were limited by their small size and stopped short of recommending adoption of prehabilitation without further randomized evidence.^{168,169}

1.8.2.3 Prior to colorectal cancer surgery

In colorectal cancer surgery there are 3 reported randomised trials, and one case control series^{162,170,171}. The largest of these trials recruited 112 patients to either a home based cycling regime (58 patients), or a sham walking breathing arm (54 patients)¹⁶². There were 18 dropouts in the preoperative period, where the median exercise programme was 38 days. In this study they failed to demonstrate any benefit of exercise prehabilitation, with the walking group having better performance in the final 6 minute walk test prior to surgery, and the exercise arm actually deteriorating over the study period. The prime reason to explain this was the poor compliance with exercise intervention. This group went on to design a new prehabilitation programme combining exercise with cognitive therapy and nutritional support. This has been shown to improve fitness in the managed cohort, but is yet to be validated by a randomised trial.¹⁷⁰

A small-randomised study (14 intervention vs. 7 control) used a 4-week prehabilitation programme of constant level cycling 7 days per week¹⁷¹. There were two withdrawals from the study arm due to fatigue, and self-reported adherence to the programme in the remaining was 74%. This study failed to demonstrate significant differences in fitness in the prehabilitation arm, but it is likely this is an underpowered study given its size.

More recently two further studies have investigated prehabilitation in colorectal cancer patients. The first investigated the use of exercise therapy

in patients following neoadjuvant chemo-radiotherapy for rectal cancer, in the window before operative intervention ¹⁷². This non-randomized study compared patients electing to undergo prehabilitation with those declining to participate and measured CPET values at baseline and then 3 weekly from the completion of chemo-radiotherapy to surgery. The two groups were not comparable in terms of age, ASA status and CR-POSSUM predicted mortality. The intervention group were younger, with lower ASA status, and lower predicted morbidity and mortality. However, the groups had comparable VO_2^{peak} , and VO_2 at AT. Both groups had significant reductions in both these CPET values following chemo-radiotherapy, however the group undergoing prehabilitation recovered their VO_2^{peak} and VO_2 at AT to greater than baseline before surgery. Similarly to the vascular trials further larger studies have been recommended.

A further randomised study investigated the benefits of prehabilitation over rehabilitation in isolation in 77 patients prior to colorectal resection ¹⁷³. This study did not utilise CPET, but used the 6-minute walk test as an alternative, and demonstrated that patients not undergoing prehabilitation had a deteriorating 6-minute walk capacity prior to surgery. This lower capacity persisted through the postoperative period. At the completion of 8 weeks rehabilitation the prehabilitation group maintained a greater 6-minute walk capacity. They concluded that prehabilitation offered benefits above that of rehabilitation alone ¹⁷³.

Currently recruiting is the PREPARE-ABC trial, an NIHR funded trial¹⁷⁴. This trial seeks to establish the impacts of either a home or hospital supervised exercise program on perioperative morbidity and mortality in patients undergoing colorectal cancer surgery.

1.8.2.4 Prior to liver resection

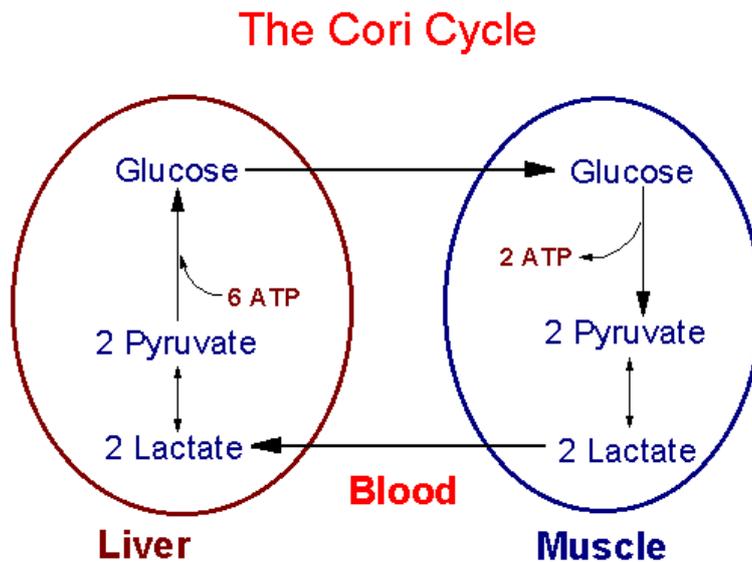
The only prehabilitation study in liver surgery focused on patients with chronic liver disease undergoing hepatectomy for hepatocellular carcinoma¹⁵⁹. This study recruited 51 patients (26 prehabilitation, 25 control) to a combined study of up to 1 month's prehabilitation with 6 months rehabilitative exercise therapy. Exercise variables were not reported preoperatively, and there was no difference in the perioperative outcomes, with morbidity very low at 10% overall, and no mortality. At 6 months postoperatively patients in the intervention arm had higher VO_2 at the AT and peak, lower fatty mass, higher platelet levels, and lower insulin resistance. Whilst the effect of prehabilitation on perioperative outcome was disappointing, the decrease in insulin resistance (measured using the HOMA-IR method of assessing insulin resistance¹⁷⁵) suggests a beneficial effect of exercise on glucose metabolism, possibly via modulation of hepatic gluconeogenesis.

1.9 Hepatic function and fitness

Hepatic gluconeogenesis is responsible for meeting the majority of the energy requirements of the human body. Hepatic gluconeogenesis utilises either hepatic glycogen stores, or lactate produced through anaerobic tissue respiration to produce glucose into the circulation (Figure 1-5). Only the liver and kidney are capable of producing glucose into the circulation, with the kidney only contributing in times of significant starvation¹⁷⁶. After 40 hours of fasting, hepatic gluconeogenesis from lactate (and other substrates) is responsible for 90% of the body's energy requirements¹⁷⁷.

There is limited work investigating links between gluconeogenic capacity and exercise performance¹⁷⁸. This is in part due to the inaccessibility of human liver tissue, and the challenges of measuring gluconeogenesis. An adequate model of hepatic functioning including gluconeogenesis could also aid the development of strategies to define a more accurate FLR.

Figure 1-5 Cori cycle



1.9.1 Gluconeogenesis in animal studies

The link between hepatic gluconeogenesis and endurance capacity was demonstrated in 1986 by John Alder¹⁷⁹. In this study trained and untrained rats had gluconeogenesis inhibited by 3-mercaptopicolinic acid (3-MPA), which led to a reduction in endurance capacity by 26% in trained animals and 32% in untrained animals. This was accompanied by a greater reduction in glycogen stores in the quadriceps muscles, suggesting that inhibition of hepatic gluconeogenesis led to faster reduction in muscle energy stores. Podolin confirmed this in 1996 by demonstrating that 3-MPA led to an 80% reduction in rats endurance time¹⁸⁰. It was also shown that older rats had less capacity for hepatic gluconeogenesis. The original hypothesis that this

could be due to dropping levels of phosphoenolpyruvate carboxylkinase (PEP-CK) was not confirmed.

In 2008, Hanson took a different approach by genetically manipulating the gluconeogenic pathway to study the effects. Introduction of the cDNA for the enzyme for α -skeletal actin gene promoter into a mice germ line led to the development of mice with a 100 fold increase in skeletal muscle PEP-CK. These mice had a 25-fold increase in endurance time, greater longevity, but were extremely aggressive¹⁸¹. This suggested that greater capacity for gluconeogenesis either in the liver or muscle contributes to greater endurance time, or fitness.

1.9.2 Gluconeogenesis in human studies

In human studies measuring gluconeogenic capacity in a similar way to animal studies has not been possible due to the risks associated with accessing hepatic tissue¹⁸². Thus studies have focussed on measuring in vivo levels of hepatic gluconeogenesis at rest, and during exercise using radiolabelled glucose studies^{178,182,183}.

These studies have demonstrated that after 4 hours of moderate exercise hepatic gluconeogenesis contributes in the order of 60% of overall glucose production, with the rest being produced through glycogen depletion¹⁸⁴. In the fasted state this increases progressively as glycogen stores are depleted. Negative feedback mechanisms serve to inhibit the tissue utilisation of

glucose and overall glucose production, prolonging the glycogen stores¹⁷⁶. In the normal physiological state glycogen stores can be preserved up until 60 hours, though beyond this hepatic gluconeogenesis produces almost all the energy utilised by the body. There are no studies of the rate of glycogen depletion in the post-surgical state where systemic energy requirements increased, but it is likely that hepatic gluconeogenesis will be of increasing importance¹⁸⁵.

The effect of fitness and exercise has been investigated, with endurance training associated with a two-fold increase in resting gluconeogenesis and threefold increase in gluconeogenesis during exercise¹⁸³.

The current conclusion of these studies is that hepatic gluconeogenesis plays an integral part in exercise^{178,183,186,187}.

1.9.3 Postsurgical outcomes

It has been well established that severe liver disease such as cirrhosis or acute hepatitis is associated with poorer surgical outcomes¹⁸⁸. Acute hepatitis is considered a contraindication to elective surgery¹⁸⁸. Surgical procedures in patients with cirrhosis have much higher morbidity and mortality¹⁸⁹. Early post cholecystectomy studies demonstrated mortality of 11-25% in patients with significant cirrhosis in contrast to 1.1% in those cirrhosis without impaired synthetic hepatic function¹⁹⁰. More recent studies have consistently demonstrated mortality is elevated in patients with cirrhosis

undergoing major abdominal surgery, with the severity of the cirrhosis correlating with the risk of mortality^{189,191,192}.

Reasons suggested for this trend are a hyper-dynamic circulation, a predisposition to anaesthetic related hypoxia, increased bleeding risk, increased susceptibility to bacterial infections, altered drug metabolism, poor wound healing, and pre-existing malnutrition^{188,189,193}.

Once outward clinical signs of liver disease are established the classification of the severity of the liver disease, as assessed by either the MELD or Child-Pugh score, directly correlates with the operative risk.^{188,193}

Whether better hepatic function in a patient with no outward signs of liver disease correlates to lower risk has not been tested. This has primarily been related to the inaccessibility of liver tissue and the challenges of developing a reliable model of hepatic function.

1.10 Ex vivo models of hepatic function

The gold standard for measurement of hepatic functioning and toxicology is *in vivo* testing. This, however, has significant challenges including animal welfare concerns, time constraints, cost, and most importantly the potential lack of applicability of animal studies to human treatment¹⁹⁴. These concerns were highlighted in the National Research Council report in 2007¹⁹⁵. A number of *in vitro* and *ex vivo* models of hepatic functioning have been

developed to help deal with the difficulties of in vivo models. All of these models have both advantages and disadvantages.

1.10.1 Immortalized Hepatic Cell lines

There are a number of immortalized liver derived cell lines, with the more recently developed hepatoma derived cell lines retaining expression of many liver-specific functions. The expression of liver specific functions is lower than that seen in primary hepatocytes, and the applicability of these cell lines for modelling hepatic function is limited further by the absence of interactions with other hepatic cell types ¹⁹⁶.

1.10.2 Primary Hepatocytes

Often seen as the gold standard for in vitro testing they can maintain functional activities in culture for up to 72 hours. There is a basic assumption that single cells of hepatocytes will behave in a similar manner to hepatocytes with the organ. Evidence has demonstrated that cells under traditional hepatocyte culture conditions undergo a series of morphological, gene expression and functional activity changes¹⁹⁶. There have been a number of approaches to preserve hepatic function with some success, but the results have varied between laboratories.

These variations are, in part, attributable to variation and challenges in the isolation of hepatocytes. The ideal methodology is yet to be established and standardised across laboratories ¹⁹⁷.

Primary human hepatocytes have a limited viability, thus meaning many laboratories rely on cryopreserved human hepatocytes for studies. These are purchased at considerable cost, and the quality of cells is variable on thawing.

1.10.3 3D culture systems

To help overcome the limited viability and loss of functionality demonstrated by primary human hepatocytes, 3D culture systems have been developed. This rapidly developing field involves the attempted artificial recreation of the complex micro-environment of the liver. 3D culture systems have evolved greatly over the last decade from formed hepatocyte spheroids to more advanced systems involving packed bed reactors and perfusion flow ^{197,198}. These complex systems represent the forefront of hepatocytes culture for hepatotoxicity studies, but all of these systems are complex to construct and maintain ¹⁹⁷.

1.10.4 Stem Cells

As previously mentioned supply of human hepatocytes is limited and labour intensive. This, in combination with the relatively short viability, has led to the desire to develop hepatocytes from stem cells. This has the aim of producing a reliable, robust and reproducible source of human hepatocytes for laboratory study. There has been some success in developing hepatocyte-like cells from human embryonic cells using supplemental media ^{199,200}.

Unfortunately, all differentiation protocols lead to highly variable functionality within the cell population developed, and cells lose functionality in a similar manner to isolated hepatocytes¹⁹⁷. These cells are also limited in a similar manner to primary hepatocytes, in the context of measuring hepatic function.

1.10.5 Liver slices

Slices of hepatic tissue, and the function of such slices have been studied for nearly 90 years²⁰¹. In particular, the technique was utilised in the 1960's and 1970's by a collection of groups including Hans Adolf Krebs to investigate carbohydrate metabolism within the liver²⁰¹⁻²⁰⁴. The technique utilizes slices of hepatic tissue in its entirety and has the advantages of containing all the cell types contained *in vivo* within the normal tissue structure¹⁹⁷.

One of the early limitations of hepatic slices was the variability of slice thickness and the challenge of producing slices thick enough to prevent too much structural damage to the hepatic cells (shearing forces) and thin enough to prevent early central necrosis within the cells from hypoxia. This difficulty was largely overcome with the development of the Krumdieck Precision Liver Slicer²⁰⁵. This began the modern era of precision cut liver slices.

Precision cut liver slices (PCLS) revolutionised the study of liver physiology and function. Whilst the majority of hepatic functions are derived from the hepatocytes, which make up around 80% of hepatic volume, their function is

known to be highly dependent on the communications with other cells within the liver. Thus PCLS are particularly useful in allowing study of hepatocytes within a complete liver model⁵⁸.

Whilst the liver slices model looks an attractive model of studying human hepatic function, there are a number of drawbacks. In a similar manner to the collation of human hepatocytes, it is relatively labour intensive.

The major limitation of slices remains the relative inaccessibility of human liver tissue. The majority of studies conducted using human liver slices utilise liver rejected on a quality basis for transplant. This by its very nature represents liver deemed to be of poor quality either due to disease, or problems with ischaemic time. Slicing has benefits over primary hepatocyte isolation in that cores of tissue can be taken from smaller liver samples, consequently making it easier to obtain when patients are undergoing resection²⁰⁶. This in itself presents further challenges particularly in minimising the time from resection to slicing and incubation, and optimising the technique.

Development of hepatic slicing as a viable model of hepatic functioning could allow, investigation of the links between fitness and hepatic functioning, better prediction of PHLF, and tailoring of perioperative treatment for the increasingly comorbid patients undergoing CRLM treatment.

Chapter 2: Aims and objectives

To further improve the care of patients undergoing surgical treatment of colorectal cancer liver metastases this research project has focused on the improvement of preoperative fitness, and the development of a viable in vitro model of hepatic function, to allow greater study of the effects of exercise on hepatic function.

2.1.1 Aim One

The first aim of the research programme is to develop an exercise programme that would be acceptable to the patient population, and deliverable in a time frame consistent with current treatment pathways.

2.1.2 Aim Two

Once this fitness programme has been developed this needs to be validated in the patient population to demonstrate that it is feasible to make a clinically relevant difference in patient fitness, within an acceptable time frame when patients are undergoing preoperative treatment and assessment.

2.1.3 Aim Three

Alongside this research area I intend to develop and a model of human hepatic function utilising PCLS. This should allow greater study of hepatic function and drug metabolism, opening doors to research areas and further improvement in the outcomes of patients treated for CRLM.

Chapter 3: Prehabilitation programme design and validation

3.1 Introduction

Designing a prehabilitation programme suitable for patients prior to major cancer surgery presents a number of challenges, and there is a paucity of literature. Supervised exercise programmes have delivered improvements in CPET variables in patients prior to aortic aneurysm^{168,169} and lung cancer surgery²⁰⁷. These used exercise programmes of 6 weeks or more, which is unlikely to be suitable for most major cancer pathways. Two randomised trials of prehabilitation before colorectal surgery failed to demonstrate significant improvements in CPET variables with 4 week home based programmes^{162,171}. This may have related to the adherence, and the home based nature of the intervention.

A cancer diagnosis is associated with fatigue and diminished physical capacity²⁰⁸. The cause is poorly understood but contributing factors include prior surgery, chemotherapy, direct cancer effects, and the psychosocial effects of a cancer diagnosis²⁰⁹. Exercise has been shown to be beneficial in the management of cancer related fatigue, can improve cardiovascular fitness, is associated with better quality of life and improved overall survival following a cancer diagnosis^{150,154,210,211}. Despite this there is a prevalence of

inactivity among both patients and survivors following a cancer diagnosis, meaning any prehabilitation programme must be suitable for a largely sedentary population^{154,210,211}.

Given these constraints the ideal prehabilitation programme prior to a major cancer operation is one that is suitable for the sedentary patient, who is likely to be elderly. This is particularly pertinent given that even in individuals volunteering to undertake exercise intervention studies, typical adherence is in the order of 74-86%, with a dropout rate in the order of 20%^{171,212-214}. Any prehabilitation programme should yield clinically significant improvements in fitness within a time period that would be acceptable for a preoperative cancer pathway. It should be easy to deliver in a cost efficient manner.

When examining the literature at the outset of this research it was felt that there was not a suitable validated exercise programme in use, and consequently the first task of this research was to design and validate such a programme.

3.2 Aim

The aim of this study was to design a prehabilitation exercise programme suitable for cancer patients, by demonstration of its efficacy in the healthy population.

3.3 Methods

The study was conducted with local research approval (11/H1005/3). All volunteer subjects gave informed consent before commencing programme.

3.3.1 Exercise programme

Given the success of hospital-based programmes and the failure of the home-based programmes in the preoperative setting, a hospital-based programme was used. Cycling was chosen as a modality most likely to be well tolerated by the patient group. The frequency of exercise sessions was set at three times per week. This was to balance the reduction in weeks training from prior studies, where frequency was less, whilst trying not to be so onerous as to discourage patients.

3.3.2 Design of exercise programme

The programme was designed within the exercise laboratory, using two individuals towards opposite ends of the fitness spectrum. It was designed to meet specific criteria, based on American College of Sports Medicine recommendations²¹⁵.

- An interval training exercise programme
- An exercise programme of an average intensity in excess of 60% VO_2^{peak}
- A peak intensity of a VO_2 of around 90% of VO_2^{peak}

The relative oxygen uptake at the anaerobic threshold (AT) was used to tailor the training programme to the individual. This variable is identifiable, independent of volition, and has been shown to correlate with both endurance capacity and perioperative outcome^{40,43,45}.

The length of the severe intensity component of the exercise programme increased gradually over the 4-week period to account for improving fitness, with consequent reduction in the light intensity sections. Two light sessions were included at the end of the first and last week, to allow recovery. These involved 3 bouts of 15 minutes cycling at light intensity. The design of the exercise programme was based on just one cardiopulmonary exercise test. The entire programme is summarised in tables 3-1 and 3-2.

Table 3-1 Overall exercise programme structure

	Duration	Wattage (as a percentage of workload achieved at anaerobic threshold)
Warm-up	7 minutes	50%
Interval session	30 minutes (6 x 5minute cycles)	High intensity – 120% Recovery intensity – 50%
Recovery	3 minutes	60%

Table 3-2 Length of interval intensities

	Length of high intensity portion of interval (seconds)	Length of recovery portion of interval (seconds)
Session 1+2	120	180
Session 4+5	130	170
Session 6+7	140	160
Session 8+9	150	150
Session 10+11	160	140

3.3.1 Delivery of exercise programme

The programme was delivered using an Optibike cycle ergometer (Ergoline, Bitz Germany). The ergometer utilises cards, which were programed at the initiation of the exercise programme.

Subjects sat upon the Optibike, and it was adjusted for comfort. They pedalled at 55-65 rpm for the duration of the exercise programme, with the resistance adjusting automatically as per the described programme.

3.4 Outcome variables

The aim was to achieve an increase of 1.5ml/kg/min in the Vo_2 at AT $ml.kg^{-1}.min^{-1}$. This was deemed clinically significant based on previous work in patients undergoing hepatobiliary surgery (our target population) ^{34,43,49}. Based on previous work³⁴ such an improvement in our patient population

would potentially transfer 30% towards routine ward care following surgery, as opposed to automatic critical care admission.

Secondary endpoints included other CPET variables identified as potentially predictive of perioperative outcome^{216,217}.

3.4.1 Assessment of fitness

All candidates underwent fitness assessment using CPET performed in a similar manner to our preoperative CPET programme, as discussed below³⁴.

3.4.2 CPET Testing

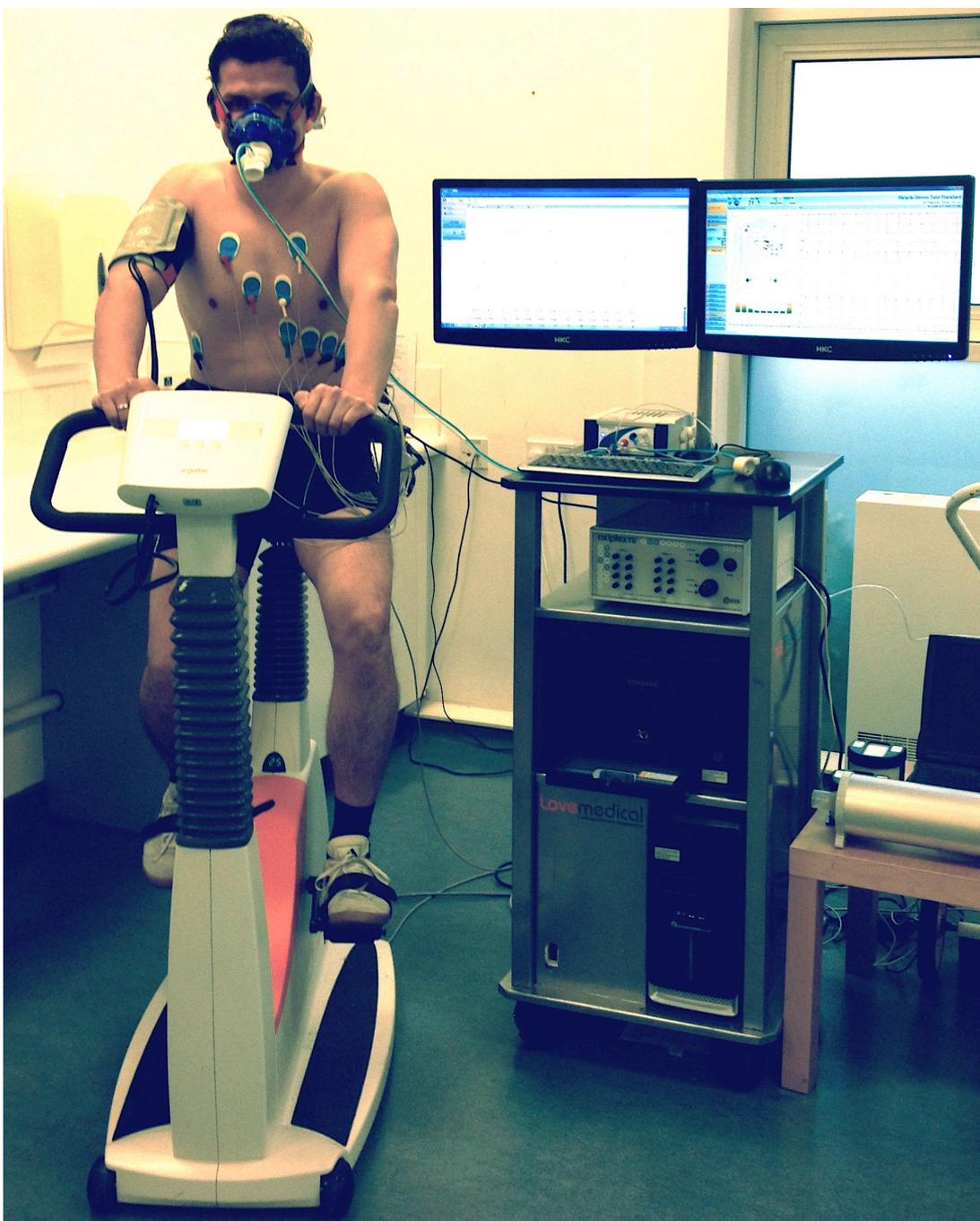
3.4.2.1 CPET equipment

CPET was conducted using an electromagnetically braked cycle ergometer (Ergoline 2000). A flow sensor (Geratherm Respiratory GmbH) was used to measure differences in flow stream pressures, which allowed a gas analyser to assess concentrations of O₂ and CO₂. The analysis was conducted using computer software (Blue Cherry version 1.1.4.0 – Geratherm Respiratory GmbH). Ambient temperature, pressure and humidity were recorded in real time (Ambi Stick - Geratherm Respiratory GmbH) and used within the computer software to aid in analysis.

The flow sensor was calibrated for flow (l/s) with a standard 3L syringe prior to each test. Two point gas calibrations for O₂ and CO₂, were also performed prior to each test, using standard, gravimetrically weighed, bottled calibration

gas of known concentrations (BOC gases). A typical CPET set-up is shown in figure 3-1.

Figure 3-1 Standard CPET setup



3.4.2.2 CPET Contraindications

Recommendations by CPET followed the American Thoracic Society/ American College of Chest Physicians recommendations²¹⁸ and by Jones and colleagues²¹⁹ were followed. All subjects were assessed for CPET contraindications (Table 3-3)²¹⁸.

Table 3-3 Contraindications to CPET

Absolute Contraindications	Relative Contraindications
Acute myocardial infarction	Left main coronary stenosis
Unstable angina	Moderate stenotic valvular heart disease
Uncontrolled arrhythmias causing symptoms or haemodynamic compromise	Severe untreated arterial hypertension at rest (systolic > 200mmHg, 120mm Hg diastolic)
Syncope	Tachyarrhythmia or brady-arrhythmia
Active endocarditis	Hypertrophic cardiomyopathy
Acute myocarditis or pericarditis	Significant pulmonary hypertension
Uncontrolled heart failure	Advanced or complicated pregnancy
Thrombosis of lower extremity	Electrolyte abnormalities
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary oedema	
Room air desaturation at rest <85% if no known lung pathologies	
Respiratory failure	
Acute non-cardiopulmonary disorder that may affect exercise performance	
Mental impairment leading to inability to co-operate	

3.4.2.3 CPET conduct

Patient demographics including name, date of birth, hospital identification, study number, gender, height (cms), and weight (kg) were entered into the software. Electrocardiography electrodes were placed in 12-lead positions and attached to the ECG analyser (AMEDTEC).

The ergometer position was adjusted according to patient preference.

An airtight seal around the facemask was achieved. A non-invasive blood pressure (BP) cuff was fitted, and an automated BP was measured at rest, and every 2 minutes during the test. Subjects were also monitored with continuous pulse oximetry.

Standard spirometry was performed before conduction of each test within the Blue cherry software.

The CPET test protocol has been published previously but is reported briefly below³⁴. The ramp incremental protocol was determined for each patient by using the formula by Wasserman and colleagues³². Subjects were instructed to pedal between 55 and 65 rpm for the duration of the test. The test protocol included four phases; an initial rest phase (three minutes), three minutes of unloaded cycling (zero watts), a subsequent ramp protocol (ideally 6-10 minutes), and 3-minute recovery period. The recovery period was extended as necessary to allow physiological parameters to return close to baseline levels, and exercise induced ECG changes to resolve.

The incremental exercise phase continued to volitional termination or until the below criteria were met:

- The subject stopped pedalling due to leg fatigue, dyspnoea, pain or light headedness
- The subject failed to maintain an RPM of greater than 40 RPM for more than 1 minute and does not respond to encouragement.
- Subject developed angina or the following ECG changes
- Development of 2mm ST depression if symptomatic or 4mm if asymptomatic or > 1mm ST elevation
- Development of a significant arrhythmias
- A fall in systolic pressure > 20mmHg from the highest value recorded during the test.
- Hypertension > 250mm Hg systolic; > 120 mm Hg diastolic
- Severe desaturation: SpO₂ < 80% accompanied by limiting hypoxaemia
- Or if a subject developed any of the following symptoms
 - Sudden pallor
 - Loss of coordination
 - Mental confusion

Ideally the exercise component of the test was 6-10 minutes. Following the exercise component there was a 5 minute recovery component during which the subject was observed until physiological variables including heart rate,

blood pressure, ventilation, and oxygen saturation, returned close to the baseline levels, and exercise induced ECG changes had resolved.

3.4.2.4 CPET evaluation and reporting

The clinician supervising the CPET, who was independent of the study, reported the test. Subsequently, the tests were re-evaluated by a physiologist blinded to clinical data including the time point at which the test was conducted. When interpreting the test the physiologist was informed of current medication that may affect the interpretation, including the use of beta blockade.

The estimated anaerobic threshold was determined using the V-slope method by 2 independent blinded assessors²²⁰.

3.4.3 CPET variables and definitions

A number of important physiological variables are recorded during CPET. Some definitions are included in the following table. Other variables recorded during a CPET include: heart rate (HR), blood pressure (BP), and oxygen saturation (SaO₂). All definitions are based on the work of Wasserman et al.³² Subjects were considered sedentary if they took part in no formal exercise during a typical week; formal exercise included commuting to work by bike.

Table 3-4 Cardiopulmonary exercise test definitions

Estimated Lactate Threshold ($\hat{\theta}_L$)	The exercise $\dot{V}O_2$ above which anaerobic high-energy phosphate production supplements aerobic high-energy phosphate production, Exercise above the $\hat{\theta}_L$ is reflected in the muscle effluent and central blood by an increase in lactate concentration, L/P ratio and metabolic acidosis.
Oxygen Pulse (O_2 pulse)	The oxygen uptake divided by the heart rate. This represents the amount of oxygen extracted by the tissues from the O_2 carried in each stroke volume. Can be calculated at $\hat{\theta}_L$ and at peak exercise.
Oxygen Uptake ($\dot{V}O_2$)	The amount of oxygen extracted from the inspired gas in a given period of time, expressed in ml or L per minute. This can often be expressed relative to the weight of an individual undergoing the test.
Peak Oxygen Uptake ($\dot{V}O_2$ at peak)	The highest oxygen uptake achieved during a maximum work rate test, calculated as the average $\dot{V}O_2$ in the last 30 seconds of exercise.
$\dot{V}O_2$ max	The $\dot{V}O_2$ at which there is a plateau in the $\dot{V}O_2$ despite increasing workload. A physiological maximum often not achieved in the patient population.
Work rate	The rate at which work is preformed in Watts.
Ventilatory Equivalents for CO_2 and O_2 ($\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$)	The ventilatory equivalents for CO_2 and O_2 are measurements of the ventilatory requirement for a given metabolic rate. Both can be calculated at $\hat{\theta}_L$ and at peak exercise.
Minute Ventilation (V_E)	The volume of gas exhaled divided by the time of collection in minutes.
Forced Expiratory Volume in 1 Second (FEV1)	Volume that has been exhaled at the end of the first second of forced expiration
Forced Vital Capacity (FVC)	The determination of the vital capacity from a maximally forced expiratory effort
FEV1/FVC	A calculated ratio of the proportion of a person's vital capacity that they are able to expire over one second

3.4.1 Measurement of $\dot{V}O_2$ kinetics

Measurement of $\dot{V}O_2$ kinetics was performed at the 3rd and 12th exercise sessions. This involved 3 bouts of 15 minutes of light intensity exercise. Initially cycling unloaded (0 watts) for 3 minutes before a workload of 60% wattage achieved at the anaerobic threshold was applied for 6 minutes, with a subsequent period of 6 minutes unloaded cycling (0 watts).

This was all done connected to the standard CPET equipment.

These data have not been analysed or included in this thesis. It was felt they would not add to the value of the research given the findings achieved.

These sessions were predominantly utilised as recovery exercise sessions.

3.4.2 Study Recruitment

Volunteer subjects were recruited from University Hospital Aintree. An open invitation was provided to staff across the Digestive Diseases Directorate (Gastroenterology and General surgery). No volunteers were excluded. The study was closed to recruitment once eleven volunteers had been recruited.

3.4.3 Statistical analysis

This was carried out using SPSS (Version 20, IBM 2011). The majority of the analysis utilized paired t-tests, based on the assumption that response to a prehabilitation programme across a population is likely to follow a normal distribution.

3.5 Results

3.5.1 Study Cohort

Eleven volunteer subjects were recruited with a median age of 54 years (IQR 44-56). The median BMI was 29.0 (IQR 28-32, and range 25.5-39.2). There were nine females and 2 males. Two subjects were current smokers, 2 ex smokers and 7 non-smokers. Other baseline characteristics are summarised in Table 3-5.

Table 3-5 Candidate demographics

Subject	Age	Sex	BMI	Smoking Status	PMH	Medication	Normal activity level
1	40	M	26.9	Non smoker	Nil	Nil	Sedentary
2	54	F	39.2	Non smoker	Nil	Nil	Sedentary
3	56	F	31.2	Non smoker	Nil	Nil	Sedentary
4	38	F	28.6	Non smoker	Nil	Nil	Sedentary
5	56	M	32.9	Smoker	Nil	Nil	Sedentary
6	46	F	28.6	Non smoker	Nil	Nil	2-3 times a week
7	42	F	25.5	Non smoker	Nil	Nil	2-3 times a week
8	46	F	37.0	Non smoker	Nil	Nil	Sedentary
9	59	F	26.7	X smoker	Nil	Nil	2-3 times a week
10	53	F	29.0	Non smoker	Hypertension	Propranolol	Sedentary
11	60	F	32.0	Smoker	COPD	Nil	Sedentary

3.5.2 Adherence

All eleven subjects completed the baseline and final CPET. Attendance at the exercise sessions was 96%, with 9 of the 11 subjects completing all of the exercise sessions.

3.5.3 Primary Outcome measure

There was a mean improvement in the relative O₂ uptake at the AT of 1.5 ml.kg⁻¹.min⁻¹ (95% CI 0.7 ml.kg⁻¹.min⁻¹ to -2.3 ml.kg⁻¹.min⁻¹) (p<0.01). Six subjects achieved improvements of greater than 2 ml/kg/min, with one patient achieving an improvement of 3.5 ml.kg⁻¹.min⁻¹. The remaining 5 subjects had differences of less than 1 ml.kg⁻¹.min⁻¹, with only one subject having a drop in the relative uptake at the anaerobic threshold. The changes in the relative O₂ uptake at the AT for all candidates are shown in Table 3-6.

Table 3-6 Changes in the anaerobic threshold

Subject	AT pre (ml/kg/min)	AT post (ml/kg/min)	Change (ml/kg/min)	% change
1	9.6	11.9	2.3	24
2	11.2	13.4	2.2	20
3	10.5	12.6	2.1	20
4	10	12.3	2.3	23
5	12.1	12.9	0.8	7
6	18.6	19.5	0.9	5
7	18.2	17.8	-0.4	-2
8	8.8	9.6	0.8	9
9	18	20.2	2.2	12
10	10.1	10.2	0.1	1
11	9.8	13.3	3.5	36
Overall	12.4	14.0	1.5 (95% CI 0.7:2.3)	12 (95% CI 6:19)

3.5.4 Effect on other variables

There was no significant change in the weight or BMI of subjects over the study period. The effect on other CPET variables is summarised in Table 3-7. There was a reduction in mean resting VO_2 of $1.4 \text{ ml.kg}^{-1}.\text{min}^{-1}$ (95% CI 0.3: $2.2 \text{ ml.kg}^{-1}.\text{min}^{-1}$) ($p=0.014$) representing approximately a 29% reduction in resting oxygen uptake. The increased VO_2 uptake at the anaerobic threshold was accompanied by a mean increase in the work rate at the AT of 19 watts (95% CI 12:26 watts) $p<0.01$). There was no significant change in heart rate at rest, anaerobic threshold or peak activity. There was an increase in peak VO_2 uptake of $1.8 \text{ ml.kg}^{-1}.\text{min}^{-1}$ (95% 0.6:3.0 $\text{ml.kg}^{-1}.\text{min}^{-1}$). There was no significant change in peak wattage. Given the significant

improvement in the mean oxygen uptake, it is not unsurprising that the O₂ pulse at both anaerobic threshold and peak activity improved given it is a derived variable.

Table 3-7 Changes in other CPET variables

Variable	Pre Training	Post Training	Change ml/kg/min (95% CI)	Mean Change %	Significance
Anaerobic Threshold (ml/kg/min)	12.4	14.0	1.5 (0.7:2.3)	+13%	0.001
Peak VO ₂ (ml/kg/min)	18.5	20.3	1.8 (0.6:3.0)	+10%	0.008
Resting VO ₂ (ml/kg/min)	4.5	3.2	-1.3 (-0.3:-0.4)	-29%	0.014
O ₂ Pulse at AT	9.1	10.1	1.0 (0.7:1.4)	+11%	0.000
Peak O ₂ Pulse	10.6	11.7	1.1 (-0.2:1.7)	+10%	0.001
Workload at AT (Watts)	73	92	19 (12: 26)	+26%	0.000
Peak Workload (Watts)	138	148	10 (-5:24)	+7%	0.17
Resting HR (BPM)	85	79	-6.2 (-13:1)	-7.3%	0.224
HR at AT (BPM)	114	114	0 (-8:7)	0%	0.938
Peak HR (BPM)	142	146	4 (-6:14)	2.5%	0.439

3.6 Discussion

This exercise programme delivered improvements in a variety of CPET variables in just 4 weeks. These improvements may be related to the high adherence achieved within this study, but also may in part be due to the lack of an underlying cancer diagnosis. This exercise programme is standardised and can be calculated based on the initial CPET, making it easily adaptable to the preoperative setting.

If this level of improvement in the anaerobic threshold could be achieved within the patient population it could represent a shift of 30% from a CPET assessed “high risk” (VO_2 uptake at AT of $<11 \text{ ml.kg}^{-1}.\text{min}^{-1}$) to a “low risk” group^{35,36}. This has the potential to reduce postoperative costs, and possibly perioperative morbidity.

The adherence of 96% achieved in this study was high in comparison to other studies, and this is likely to have contributed to the success of the programme^{162,168,171,207}. The underlying reason for this high adherence is likely to be multi-factorial. All subjects volunteered to partake in the exercise programme and consequently represent a highly motivated group. Some of the contribution for the high adherence may stem from the design of the exercise programme, as interval-based training programmes have been shown to have higher ratings of perceived enjoyment than constant load programmes²²¹. The underlying mechanism for this is difficult to distinguish

but is likely to relate to a combination of the varied exercise profile with the direct effects of high intensity exercise. Finally the study participants were without major health problems, and we would expect higher adherence in these healthy volunteers than the future intended preoperative cancer patient population.

The study has demonstrated that it is possible to devise a successful exercise programme referenced to a baseline CPET which is simple to calculate and easy to deliver. The use of the anaerobic threshold detected during cardiopulmonary exercise testing, is key to the designs for a number of reasons. All target patients undergoing major cancer resections are routinely assessed with CPET, and the AT derived is used to stratify the postoperative care. The AT has also been shown to correlate well with endurance capacity, and is detectable in most patients and thus is an attractive variable on which to base a standardised exercise programme^{30,45}.

The exercise programme has been based on the power produced at the anaerobic threshold. Power training has been suggested as a superior method of cycle training for elite athletes and with the advent of widely available power metres has become commonplace^{222,223}. Using power at the anaerobic threshold is an attractive value to base a training programme on owing to the ease with which a programme can be calculated, and delivered using pre-programmable cards. It removes the need for heart rate monitors, formerly a standard technique for assessing exercise intensity²²⁴.

This exercise programme delivered clinically significant improvements in fitness in just 4-weeks. In the preoperative setting two four-week programmes failed to deliver clinically significant improvements in CPET variables^{162,171}. These studies were of a higher frequency and both utilised home-based programmes, and both suggested adherence as a potential reason for failure. The success of the current programme is likely multifactorial including the high adherence, the interval nature of the programme, and the supervised nature of the exercise programme.

These findings are yet to be validated in a cancer patient population, but certainly provide cause for optimism. However, this must be tempered by the limitations of this study. This improvement was achieved in a population with an average fitness levels similar to the target patient population, however it must be noted there are a number of significant differing demographic variables which may prove significant when translating these findings into our target population. The study population here was younger, with a higher rate of female participants. None of the subjects had an underlying cancer diagnosis, with neither the associated paraneoplastic effects nor the concurrent treatment this may incur. This study also lacked a control arm, and it may be that fitness improvements seen within this cohort related to activity outside the prehabilitation programme, as there were no specific limitations placed on participants.

3.7 Conclusions

A standardised exercise programme based around the anaerobic threshold can deliver meaningful improvements in cardiopulmonary fitness. The feasibility of this training programme needs to be validated in the preoperative cancer population prior to randomised clinical trial assessing its impact on outcomes.

Chapter 4: Prehabilitation Trial

4.1 Introduction

Patients with lower CPET assessed oxygen uptake at the anaerobic threshold have been shown to have higher mortality, higher morbidity and longer hospital stay when undergoing major surgery^{40,43,49}. Specifically in HPB surgery, patients with lower fitness as assessed by CPET have higher rates of complications^{48,49,225}.

In cancer patients, postoperative rehabilitative exercise therapy has been shown to improve physical function, peak oxygen consumption and quality of life (QoL). There are, however, limitations. Following surgery, individuals may be fatigued, worried about the effects of exercise on the healing process, or anxious whilst awaiting adjuvant treatments^{226,227}. Postoperative rehabilitation also fails to add any of the benefits of exercise therapy to the immediate perioperative period¹⁶⁴. Preoperative exercise intervention, or prehabilitation, has been proposed as a more timely intervention in a patient's management pathway, as it may bring the benefits of exercise therapy to bear on the intended operative intervention^{162,164}.

Fitness is often considered as a static concept by the medical profession. It has, however, been demonstrated that many preoperative interventions have a detrimental effect on preoperative CPET. Preoperative chemotherapy in patients undergoing upper GI cancer resections led to a significant drop in

the anaerobic threshold, which in turn was associated with early mortality²²⁸. In colorectal cancer preoperative chemo-radiotherapy has been shown to be associated with significant reductions in CPET variables²²⁹. Indeed just a cancer diagnosis alone may be enough to precipitate a significant deterioration in fitness as suggested by the underlying mechanisms of cancer related fatigue syndrome¹⁶¹.

Prehabilitation aims to counter the negative impact of an underlying cancer and any neoadjuvant treatment, thereby improving preoperative fitness.

Currently no randomized study of prehabilitation has delivered improved preoperative fitness in a cancer population. The largest randomized trial of prehabilitation to date failed to demonstrate an advantage with a home-based exercise programme over a control arm of walking and breathing exercises¹⁶². A number of non-randomized studies have demonstrated that supervised exercise programmes of typically 6 weeks or more could deliver clinically relevant improvements in fitness^{168,172,207}. However, this delay is not always feasible when treating malignant disease. This randomized controlled study therefore sought to assess the feasibility of a 4-week supervised preoperative exercise programme in patients awaiting surgery for CRLM, assessing the impact on preoperative fitness and QoL.

4.2 Methods

4.2.1 Ethical approval

This prospective interventional randomized trial was conducted with full ethical approval that was granted by the Liverpool Central Research Ethics service with the registration number 11/H1005/3 (REC number) on the 12th April 2011 (IRAS ID: 65982) (Appendix 1.1).

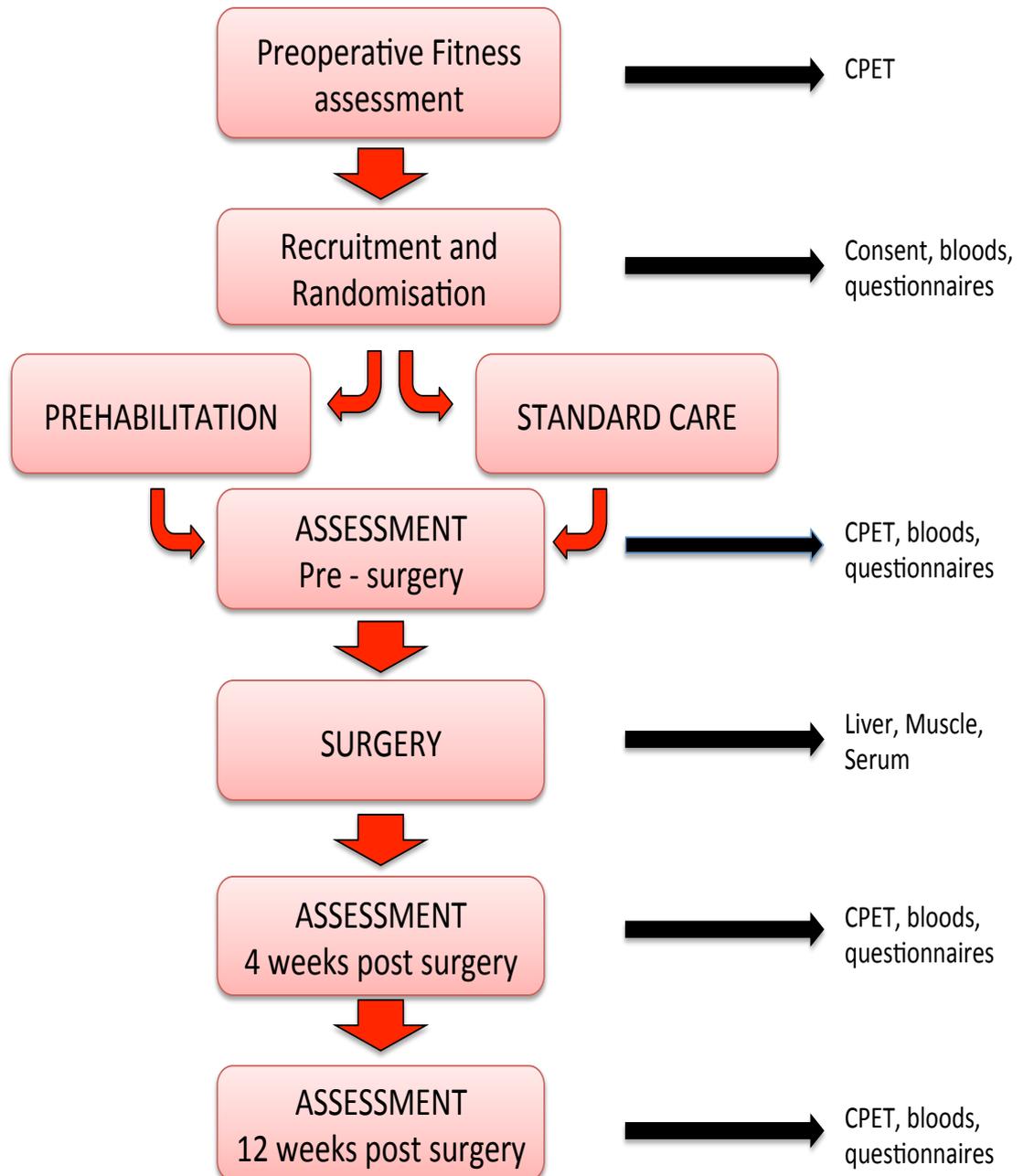
The study had Local Research approval and NHS sponsorship granted on the 12th April 2011 using the above listed REC number.

The study was listed on the open access clinical trials registry clinicaltrials.gov with the registration number NCT01523353.

4.2.2 Trial design

The study is summarised in the flow diagram below

Figure 4-1 Study Flow Diagram



4.2.3 Participants

All patients with CRLM being referred to the tertiary hepatobiliary service at Aintree University Hospital, Liverpool, UK were screened for potential eligibility. Eligibility criteria are summarized in Table 4-1. Potentially eligible candidates were given details of the study at the first clinic consultation (Patient Information leaflet Appendix 1.2). Patients were only then invited to participate once a decision to proceed to surgery had been made, and full informed consent was obtained. Ethical approval stipulated that recruitment to the study was not allowed to lead to a delay in surgical care. Consequently patients were only potentially eligible if the provisional operative date allowed at least 4 weeks for prehabilitation.

Table 4-1 Eligibility criteria

Inclusion Criteria	
1	Resectable CRLM
2	Age>18
3	Able to complete a cycle based exercise programme
4	Able to give informed consent
5	Adequate preoperative time to complete a cycle based exercise programme
Exclusion Criteria	
1	Known pre-existing chronic liver disease

4.2.4 Randomisation

Candidates were randomized to either a prehabilitation exercise programme or to standard care using a random number block randomization list created at trial outset, using Microsoft Excel 2010 (Microsoft, Washington). An individual independent of the study held this list. They were contacted via email to provide randomisation.

4.2.5 Primary outcome measure

The primary outcome measure of the study was change in the preoperative oxygen uptake at the anaerobic threshold following prehabilitation or standard care. An improvement of $1.5\text{ml.kg}^{-1}.\text{min}^{-1}$ was considered achievable¹⁶⁸ and clinically relevant. If delivered across a patient population¹¹² this could reduce the patients considered high risk (Vo_2 at AT $<11\text{ ml.kg}^{-1}.\text{min}^{-1}$) by 30%³⁵.

4.2.6 Secondary outcome measures

Secondary outcome measures included changes in the other preoperative CPET measures, and changes in QoL score, and Dukes activity Index (as discussed below). Data was also collected on operative intervention, perioperative outcomes, and subsequent postoperative progress. The study was not statistically powered to formally assess differences in perioperative or long-term outcome and these data are descriptive.

4.2.6.1 Quality of Life Assessment

Quality of life assessment was assessed using the RAND 36 – Short Form Health Survey ²³⁰ (RAND Corporation, Santa Monica, USA)(Appendix 1.5.1 page 230), and the EORTC QLQ-C30 questionnaire (Appendix 1.5.2 page 234) with the LMC-21(Appendix 1.5.3 page 235) bolt on questionnaire (EORTC, Brussels, Belgium). Patients completed questionnaires independently, with researchers available to explain any questions not fully understood by the candidates.

4.2.6.2 Activity Assessment

Activity was assessed using the Dukes Activity Index questionnaire (Appendix 1.5.4 page 237) ²³¹. Candidates completed questionnaires independently, with researchers available for assistance as necessary.

4.2.7 Blinding

Clinicians providing care were blinded to the intervention patients received, and blinded to the results of all but the baseline CPET test. This blinding included anaesthetists, surgeons, nurses and staff reporting the CPET tests.

4.2.8 Sample size

Preliminary data suggested that the target population had a mean oxygen uptake of 12.0 ml.kg⁻¹.min⁻¹ (SD 2.04). To demonstrate an increase of 1.5 ml.kg⁻¹.min⁻¹, with a power of 0.8, and a type I error probability of 0.05, 30 subjects randomised equally to either prehabilitation or standard care were

required. Assuming an attrition rate of 25%²⁰⁷, a total recruitment of 38 patients was calculated. Analysis was conducted on an intention to treat basis.

4.2.9 Interventions

The prehabilitation programme is described in detail earlier (Chapter 3.3.1 page 64). Briefly it consisted of 12 interval exercise sessions over a 4-week period²³². The sessions included a warm up and warm down, and 30 minutes of interval training alternating between moderate (<60% VO_2^{peak}) and vigorous intensity exercise (>90% VO_2^{peak})²³³. The sessions were delivered using a cycle ergometer (Optibike Ergoline GmbH, Bitz, Germany). The exercise programme was personalized to candidates following a standardized equation based on their work rate at their anaerobic threshold on the baseline CPET test.

No restrictions were placed on candidates in either arm of the study, and they were encouraged to follow clinical advice on exercise prior to surgery.

4.2.10 Cardiopulmonary Exercise Testing

The methodology for performing cardiopulmonary exercise test assessment has been previously described in Chapter 3^{34,216}.

Evaluation of anaerobic threshold, AT, was undertaken independently by two experienced assessors, blinded to each other's assessments, with disagreement resolved by a third assessor.

Patient were considered high risk if their Vo_2 at AT was less than $11 \text{ ml.kg}^{-1} \cdot \text{min}^{-1}$ ³⁵. High risk patients were routinely admitted to critical care postoperatively, and had increased intraoperative monitoring and support¹⁴⁸.

4.2.11 Blood tests

Blood was collected at each assessment and processed under standard clinical laboratory conditions within the clinical laboratories at University Hospital Aintree. This was to exclude the presence of significant anaemia, or overt hepatic dysfunction that may affect CPET variables.

4.2.12 Activity

Activity levels were assessed with the Dukes Activity Status Index.²³¹

4.2.13 Statistical methods

Continuous normal data was analysed using a t-test, and the Mann-Whitney was used for continuous data with a non-normal distribution. Categorical data was analysed using the X^2 test, or Fischer's exact as appropriate. All statistical tests were conducted using SPSS (version 20.0, IBM, 2011).

4.3 Results

4.3.1 Study conduct

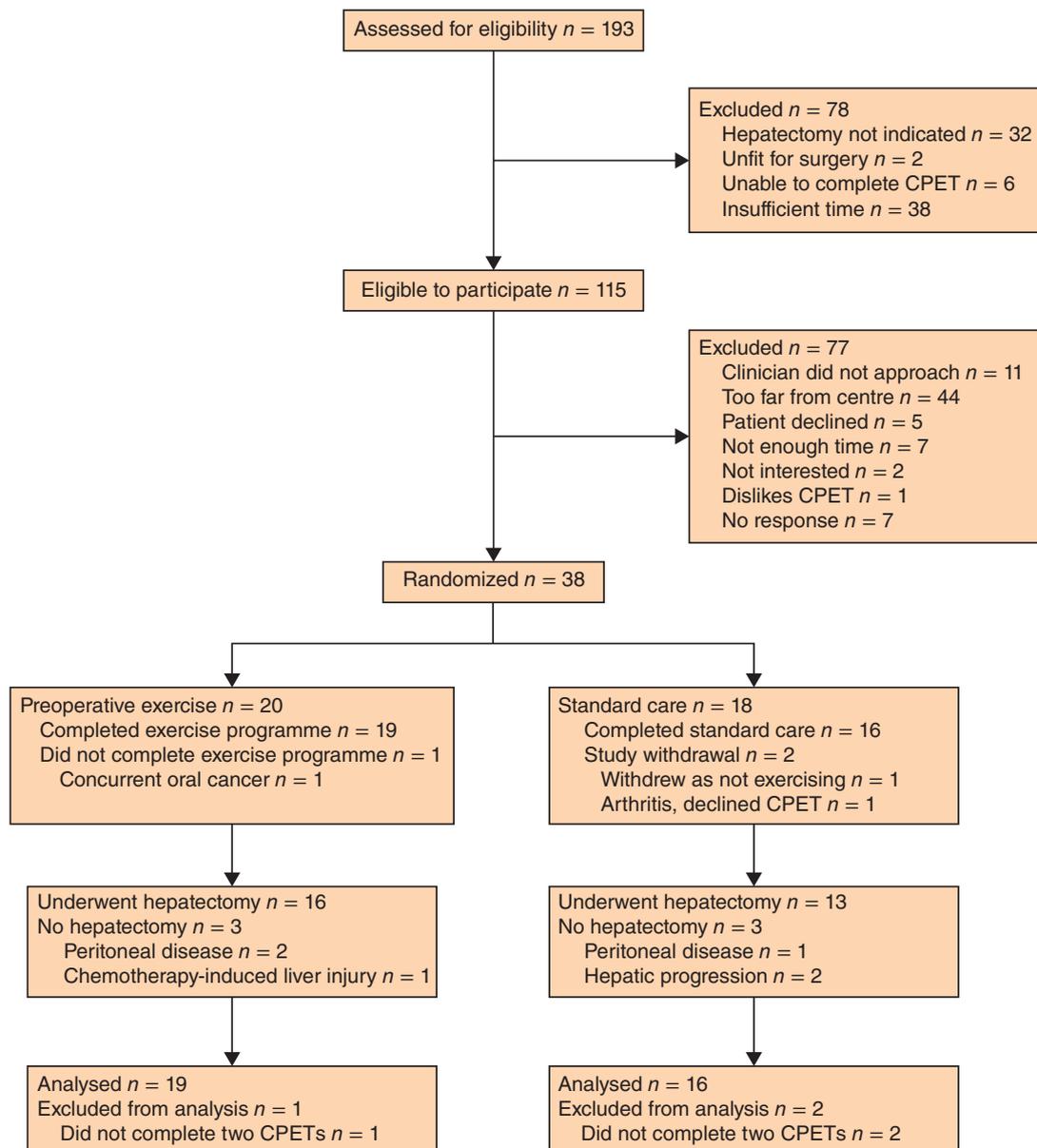
4.3.1.1 Study time period

The study opened to recruitment on the 1st July 2011, recruiting the first patient on the 14th July 2011. The study recruited its 38th patient on the 18th February 2013 and closed to recruitment at that point. Active follow up was completed on the 20th June 2013. Surveillance for recurrence and survival from the date of liver surgery is on going and will be for 10 years, as per the current clinical standard of colorectal liver metastasis follow-up.

4.3.1.2 Study recruitment and preoperative progress

The recruitment and study progress is summarised in the consort diagram (Figure 4-2).

Figure 4-2 Consort diagram showing study recruitment



4.3.1.3 Reasons for ineligibility

Consecutive patients referred to supra-regional MDT with CRLM were screened for eligibility. Of the 193 patients screened for eligibility, only 115 were deemed potentially eligible. In 38 patients there was insufficient time to complete an exercise intervention before a provisional operation date. Other reasons are listed in Table 4-2.

Table 4-2 Reasons for study ineligibility at screening

Hepatectomy not appropriate treatment	32
<i>Rapidly progressive disease on chemotherapy</i>	7
<i>Percutaneous ablation</i>	3
<i>SIRT</i>	1
<i>No evidence of metastases</i>	6
<i>Palliative DEB-Tace</i>	1
<i>Declined surgery</i>	2
<i>Irresectable disease at assessment</i>	12
Insufficient time to deliver prehabilitation	38
Unfit for surgery	2
Unable to perform CPET	6
<i>Severe Arthritis</i>	4
<i>Recent pulmonary embolism</i>	1
<i>Necrotic wound post APR</i>	1

4.3.1.4 Reasons for failure to recruit

There were 11 potentially eligible patients identified through screening who were not approached to join the study. This was predominantly in the early to mid portion of the study, and solely related to one clinician within the unit who failed to mention the study to patients at first consultation.

Of the 104 approached 66 declined to partake in the study. Of these 66, 44 patients (66.7%) declined the study due to the distance and travelling involved. Other reasons included 5 (7.5%) with anxiety, 7 (10.6%) with limited time due to work commitments, 2 (3%) with no interest in exercise, and 1 who did not want to undertake further CPET due to claustrophobia from the CPET mask. In 7 patients (10.6%) no reason was given.

4.3.1.5 Randomisation and subsequent withdrawal

Thirty-eight patients were consented and randomised into the study. Twenty patients were randomised to the prehabilitation intervention, and 18 to standard care. One patient randomised to standard care withdrew from the study 2 hours following recruitment. This was before the results of randomisation were available and before completion of baseline quality of life questionnaires and blood tests. This was due to the development of arthritic pain hours after the completion of preoperative CPET and the desire to avoid further CPET assessment. Due to an incomplete baseline assessment, and subsequent withdrawal from the entire study, this patient was excluded from the study and not included in any analysis.

Two other patients withdrew from the study, one in each arm. One patient in the prehabilitation arm was diagnosed with concurrent oral cancer, and underwent urgent radical neck dissection. One patient on the standard care arm withdrew as a direct result of being randomised to standard care. Both these patients are included in the baseline demographic analysis, but excluded from the analysis beyond this.

One further patient in the standard care arm completed the preoperative component of the study but did not undergo any surgical intervention. This was as a result of a scan arranged following completion of the preoperative component due to worsening abdominal pain demonstrating rapidly progressive hepatic disease with new extrahepatic disease. They were referred for second line palliative chemotherapy.

4.3.1.6 Surgical intervention and follow-up

Overall 34 of 37 patients who underwent initial assessment had surgical intervention. Laparotomy only was carried out in 5 patients (3 Prehabilitation 2 Standard care) for the reasons shown in Figure 4-2. This was not significantly different between study arms. This rate of futile laparotomy in study patients (14.7%) was higher than seen in the overall cohort of patients undergoing resection of CRLM during the study period (4.4%) ($p < 0.05$)²³⁴.

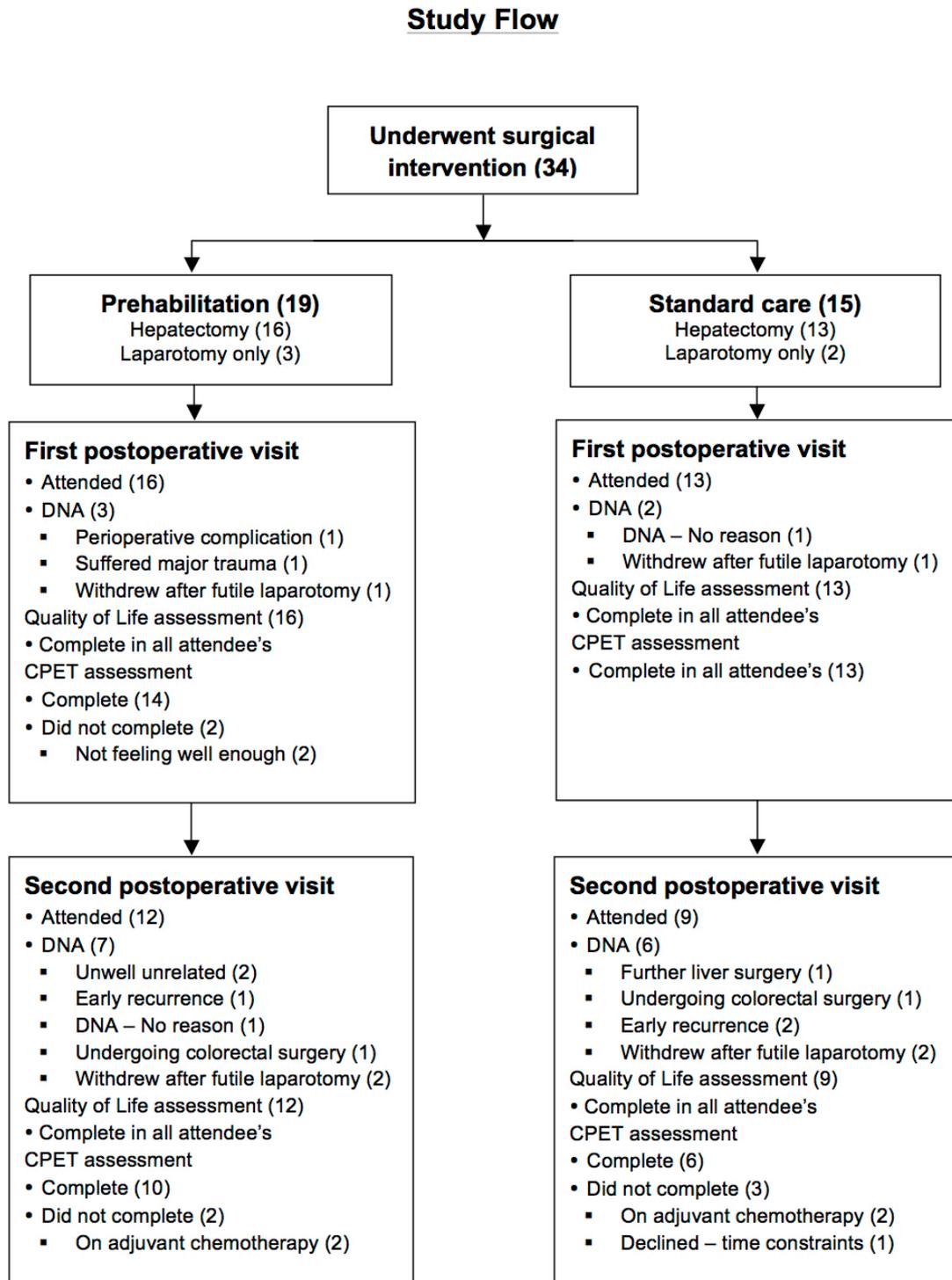
Hepatectomy was performed in 16 patients in the prehabilitation arm, and 13 in the standard care arm. The number of patients undergoing surgical

intervention, and subsequent follow-up assessment is summarised in Figure 4-3.

There was no significant difference in attendance rates at either the first or second postoperative visit between the study arms. Of the 34 patients who underwent surgery, 31 attended the 1st postoperative visit (17 Prehab, 14 Standard Care). Of the 31 patients who attended their 1st post-operative visit 22 attended the 2nd visit at 12 weeks.

In patients attending the visits, there was no significant difference in the desire to undergo postoperative CPET (26 at 1st postoperative visit, 16 at second postoperative visit).

Figure 4-3 Study flow for patients undergoing surgical intervention



4.3.2 Study cohort characteristics

4.3.2.1 Patient characteristics

The individual patient characteristics are summarised in the appendix (Appendix 1.4 page 226). The overall demographics for the study group are summarised in table 4-3. There was no significant difference in characteristics across the two groups but the median age of patients recruited into the study is lower than would typically be seen in our patient group, illustrated by the publication of study units data (Appendix 1.6 page 238)¹¹².

Table 4-3 Demographics of study cohort

	Study cohort (37)	Prehab (20)	Standard Care (17)	P value
Median Age (IQR)				
At cancer diagnosis*	60(53-69)	60(55-64)	60(51-70)	0.918
At study recruitment	62(54-69)	61(56-66)	62(53-72)	0.916
Sex				
Male	26	13	13	0.495
Female	11	7	4	
Recruitment BMI**	29.5(4.1)	29.7(4.2)	29.3(4.2)	0.748
Smoking Status				
Smoker	6	2	3	0.75
X-smoker	6	3	3	
Non smoker	25	15	11	
Comorbidities				
Cardiovascular	18	10	8	1.00
Respiratory	7	3	4	0.68
Diabetes	4	2	2	1.00
Renal Disease	1	1	0	1.00
CNS	5	2	3	0.64
Musculoskeletal	6	4	2	0.67
Depression	2	1	1	1.00
Prior cancer diagnosis	7	5	2	0.42
Prior cancer surgery	5	4	1	0.35
None	4	1	3	0.33
Medication				
Cardiovascular	16	8	8	0.75
Diabetic	2	1	1	1.00
Anticoagulation	11	7	4	0.50
Respiratory	2	2	0	0.50
Nil	5	1	4	0.16

*median(IQR)

**mean(standard deviation)

4.3.2.2 Primary presentation and treatment

The details of the primary presentation and treatment are summarised below.

There were no significant differences between cohorts.

Table 4-4 Primary presentation and management of study cohort

	Study cohort (37)	Prehab (20)	Standard Care (17)	P value
Primary Site				
Right	6	2	4	0.58
Left	9	6	5	
Rectal	21	12	8	
Emergency presentation				
Yes	9	3	6	0.251
No	28	17	11	
Presenting Symptoms				
Obstruction	4	0	4	0.251
Rectal Bleeding	9	5	4	
Anaemia	7	4	3	
Change in Bowel habit	12	8	4	
Bowel Cancer Screening	4	3	1	
Other symptoms	4	2	2	
Unavailable	1	0	1	
Synchronous presentation				
Yes	18	8	10	0.330
No	19	12	7	
Surgical strategy for synchronous presentations				
Colorectal surgery first	12	5	7	0.330
Liver surgery first	5	2	3	
Joint resection	1	1	0	
Perioperative treatment				
None	16	7	9	0.51
Adjuvant radiotherapy	1	0	1	1.00
Long course Chemo-radiotherapy	9	6	3	0.46
Neoadjuvant systemic chemotherapy	6	4	2	0.67
Adjuvant chemotherapy	9	5	4	1.00

4.3.2.3 Primary surgery and outcomes

The surgical treatment of the primary malignancy and complications of treatment are summarised below. There were no significant differences between groups.

Table 4-5 Primary surgery and outcome

	Study cohort (37)	Prehab (20)	Standard Care (17)	P value
Primary Surgery				
Right hemicolectomy	6	2	4	
Left hemicolectomy	5	2	3	
Sigmoid colectomy	5	5	0	
Anterior resection	16	8	8	0.91
APR	1	1	0	
Other resection	3	1	2	
Primary unresected	1	1	0	
Covering ileostomy	9	4	6	0.45
Laparoscopic approach				
Yes	6	3	3	
No	27	15	12	0.56
Converted	3	1	2	
En-bloc resection of other metastatic colorectal disease	2	2	0	0.49
Post operative Complications				
Yes	15	8	7	
No	16	9	8	0.99
Unknown	4	2	2	
Re-operation				
Yes	1	1	0	1.00

4.3.2.4 Primary Histology

The histology of the primary tumours is summarised in Table 4-6. Again there were no significant differences between groups.

Table 4-6 Primary histology

	Study cohort (37)	Prehab (20)	Standard Care (17)	P value
Dukes Stage				
A	2	2*	0	0.33
B	9	4	4	
C1	16	7	9	
C2	6	5	1	
Unavailable	6	3	3	
T stage				
1	0	0	0	0.25
2	8	5	3	
3	16	8	8	
4	8	6	2	
Unavailable	5	1	4	
N stage				
0	10	6	4	0.51
1	9	4	5	
2	12	8	4	
Unavailable	6	2	4	
Differentiation				
None				0.66
Well	1	1	0	
Well/Moderate	8	3	5	
Moderate	11	7	4	
Poor	3	2	1	
Unavailable	12	6	6	
Mucinous tumour	2	1	1	1.00
3Vascular invasion				
Yes	12	7	5	0.79
No	14	8	6	
Unavailable	11	5	6	
K ras status				
Wild-type	11	6	5	1.00
Mutant	4	2	2	
Unavailable/Not done	22	12	10	

* One post conversion neoadjuvant chemotherapy for liver synchronous disease, and one post rectal radiotherapy.

4.3.2.5 Metastatic presentation

The patient characteristics surrounding the metastatic presentation are summarised in Table 4-7. There was a trend towards lower disease free interval within the Standard Care Arm (Log Rank significance 0.09) (Figure 4-4). Primarily this was powered by a greater proportion of patients presenting synchronously within the standard care arm (8 of 17 standard care versus 7 of 20 prehabilitation)

Figure 4-4 Chart showing difference in time to metastasis detection.

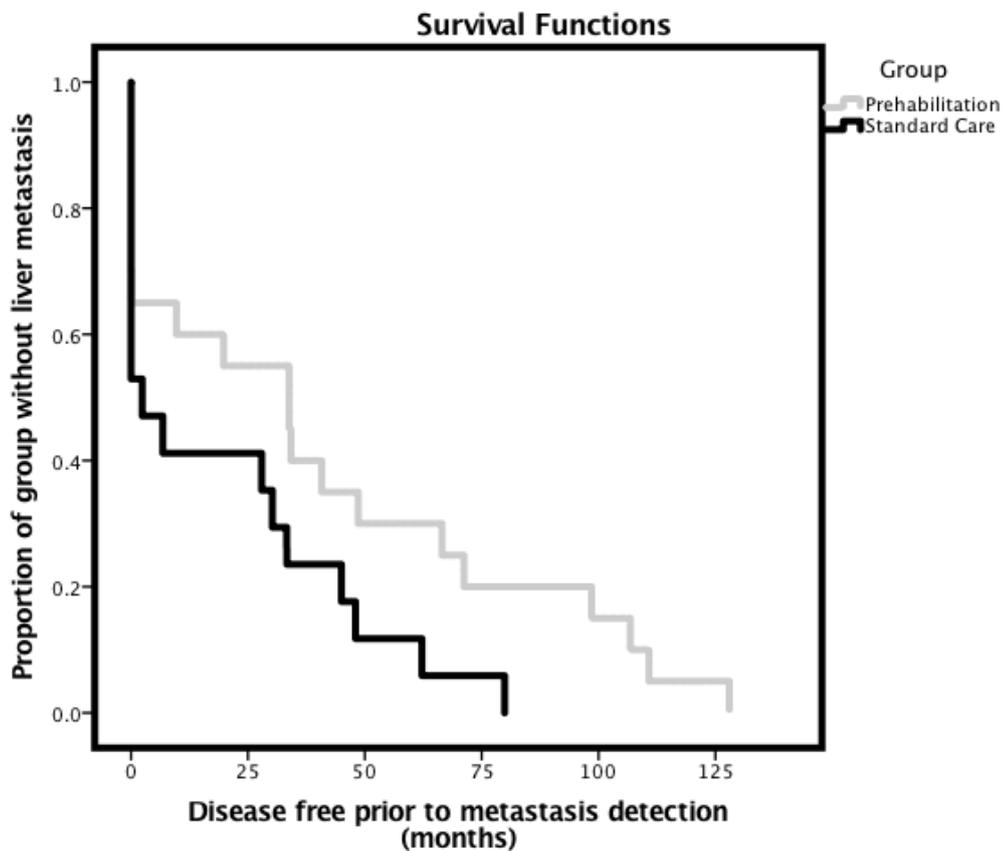


Table 4-7 Summary of metastatic presentation

	Study cohort (37)	Prehab (20)	Standard Care (17)	P value
Time from primary to metastases				
Synchronous	15	7	8	
>0-12 months	3	2	1	
>12-36 months	7	4	3	N/A
>36-60 months	4	2	2	
>60 months	8	5	3	
Mode of detection				
Staging CT	17	7	10*	
Surveillance CT	16	9	7	0.21
Climbing CEA	3	3	0	
Incidental on ultrasound	1	1	0	
Previous metastatic disease/local recurrence treatment				
Lung resection	1	1	0	
Anastomotic recurrence	1	1	0	N/A
Hepatectomy	2	1	1	
Prior primary colorectal cancer	1	0	1	
Other concurrent metastatic disease on presentation scans				
Lung	4	1	3	
Pelvic recurrence	2	1	1	
Splenic	1	0	1	N/A
Ovarian	1	0	1	
Wound	2	1	1	
Portal node	1	0	1	
Preoperative hepatic disease				
Bilobar metastases	13	5	8	0.19
Isolated metastases	9	5	4	
2-3 metastases	8	5	3	0.16
4-6 metastases	9	2	7	
7 or more	3	3	0	
Maximum size >5cm	13	7	6	1.00
Maximum size >10cm	0	0	1	1.00

* One on staging for secondary primary colorectal cancer.

4.3.3 Baseline outcome variable comparisons

This section describes the baseline scores of the variables to be used as outcomes within the study.

4.3.3.1 Baseline CPET variable comparison

Baseline CPET characteristics were similar in both the prehabilitation group and standard care group (Table 4-8). The only difference between cohorts was a lower ventilatory equivalent of oxygen at peak exercise, in the prehabilitation group.

Table 4-8 Baseline CPET variable comparison. Values shown as mean (standard deviation). P value shown for comparison between cohorts.

CPET variable	Overall	Prehab	Standard Care	P value
Patients included in analysis	37	20	17	N/A
FEV1	3.00 (0.8)	2.91 (0.78)	3.10 (0.88)	0.50
FVC	4.14 (1.03)	3.99 (0.99)	4.32 (1.09)	0.34
FEV1/FVC	72.4 (7.8)	72.8 (6.9)	72.1 (9.0)	0.81
Resting relative O ₂ uptake (ml/kg/min)	3.6 (0.6)	3.6 (0.6)	3.6 (0.8)	0.96
Resting absolute O ₂ consumption (l/min)	0.306 (0.070)	0.305 (0.062)	0.308 (0.081)	0.91
Resting HR (bpm)	85 (16)	87 (17)	81 (15)	0.26
Relative O ₂ uptake at AT (ml/kg/min)	11.3 (1.6)	11.3 (1.5)	11.4 (1.8)	0.74
Absolute O ₂ uptake at AT (l/m)	0.965 (0.231)	0.953 (0.220)	0.979 (0.249)	0.74
O ₂ Pulse at AT	9.1 (2.8)	8.7 (2.5)	9.6 (3.1)	0.34
Ventilatory equivalent of O ₂ at AT	28.1 (4.6)	26.7 (3.8)	29.6 (5.1)	0.06
Ventilatory equivalent of CO ₂ at AT	30.1 (4.3)	30.0 (4.0)	31.8 (4.6)	0.22
Work rate at AT (watts)	65 (16)	64 (16)	66 (16)	0.68
HR at AT (bpm)	109 (18)	113 (20)	105 (15)	0.20
Relative O ₂ uptake at peak	18.0 (3.1)	17.6 (2.3)	18.6 (3.9)	0.37
Absolute O ₂ uptake at peak (l/min)	1.535 (0.402)	1.491 (0.349)	1.587 (0.464)	0.48
O ₂ Pulse at peak	11.2 (3.4)	10.7 (3.0)	11.8 (3.8)	0.37
Ventilatory equivalent of O ₂ at peak	41.0 (7.2)	38.7 (6.3)	43.7 (7.4)	0.03
Ventilatory equivalent of CO ₂ at peak	33.6 (4.4)	32.4 (4.1)	35.0 (4.3)	0.08
Work rate at peak (watts)	131 (33)	124 (27)	139 (39)	0.19
HR at peak (bpm)	141 (23)	143 (22)	138 (24)	0.50
HR response to AT(bpm)	25 (11)	26 (12)	24 (9)	0.67
HR reserve (bpm)	56 (17)	56 (18)	57 (18)	0.87

4.3.3.2 Baseline quality of life score comparison

The quality of life scores based on SF36 are summarised in Table 4-9, with those from EORTC (with Liver Metastasis Component (LMC) addition) summarised in Table 4-10. At baseline there were no statistically different findings between cohorts.

Table 4-9 Baseline SF 36 values

	Study cohort (37)	Prehab (20)	Standard Care (17)	Cohort Diff.	95% Confidence Interval		Sig.
					lower	upper	
Physical Function	76	70	84	+13	-3	29	0.10
Role-Physical	47	46	49	+2	-26	31	0.87
Body Pain	70	65	77	+12	-8	30	0.21
General Health	63	63	63	+1	-13	+14	0.93
Vitality	55	52	59	+7	-10	23	0.44
Social Functioning	72	65	80	+16	-3	34	0.09
Role Emotional	72	70	74	+4	-21	30	0.73
Mental Health	78	75	82	+7	-5	18	0.22
Overall Physical Health	62	59	66	+7	-9	23	0.37
Overall Mental Health	68	64	72	+7	-7	21	0.31
TOTAL SF36 Score	67	63	71	+7	-7	22	0.29

Table 4-10 Baseline EORTC (including LMC bolt on) Values

Global Health Status	Study cohort (37)	Prehab (20)	Standard Care (17)	Cohort Diff	95% Confidence Interval		P value
					lower	upper	
Global Health Status	66	70	60	-10	-26	5	0.19
Physical Functioning	86	84	88	4	-10	17	0.59
Role Functioning	81	83	77	-6	-25	13	0.51
Emotional Functioning	84	84	84	0	-13	12	0.96
Cognitive Functioning	88	84	91	6	-9	22	0.39
Social Functioning	81	81	82	2	-16	20	0.86
Fatigue	26	25	31	5	-13	23	0.54
Nausea and vomiting	6	8	3	-5	-14	4	0.30
Pain	18	21	14	-8	-24	9	0.37
Dyspnoea	10	9	10	2	-16	19	0.85
Insomnia	25	26	27	1	-21	23	0.94
Appetite loss	10	14	13	-2	-20	17	0.87
Constipation	7	5	8	3	-8	14	0.57
Diarrhoea	11	5	19	13	-2	29	0.08
Financial Difficulties	16	19	10	-9	-28	10	0.34
LMC Eating	6	5	9	4	-6	15	0.44
LMC Pain	15	15	14	-1	-13	10	0.82
LMC Fatigue	31	30	35	4	-18	27	0.70
LMC Social	15	16	13	-4	-18	11	0.59
LMC Anxiety	34	32	39	7	-12	26	0.47
LMC Weight-loss	6	7	10	3	-12	19	0.65
LMC taste	13	16	17	1	-21	23	0.94
LMC dry mouth	24	21	27	6	-17	29	0.60
LMC neuropathy	29	25	31	7	-15	29	0.54
LMC Jaundice	2	0	4	4	-4	12	0.28

4.3.3.3 Baseline activity

Baseline activity was assessed using the Dukes activity status index (Appendix 1.5.4 page 237)²³¹.

4.3.3.3.1 Baseline Dukes activity questionnaire

At recruitment there was a difference in the number of people reporting an inability to run a short distance with a greater proportion of the standard care arm reporting being capable of running a short distance (16 of 17 (94%) of standard care versus 12 of 20 (60%) Prehab) (p=0.02). Other than this the overall activity status was largely similar across the groups, including the overall Dukes activity score.

Table 4-11 Baseline comparison of Dukes activity index with percentage capable of achieving questioned activity

	Overall	Prehab (20)	Standard Care (17)	P value*
Eat dress, bathe or use the toilet	100	100	100	ns
Walk indoors, such as around their house	100	100	100	ns
Walk 200 yards on level ground	95	90	100	0.49
Climb a flight of stairs or walk up a hill	97	95	100	1.00
Run a short distance?	76	60	94	0.02
Do light work around the house like dusting or washing dishes	100	100	100	ns
Do moderate work around the house like vacuuming sweeping floors or carrying groceries?	97	95	100	1.00
Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	78	70	88	0.24
Do yard work like raking leaves, weeding or pushing a power mower?	84	85	82	1.00
Have sexual relations?	62	60	65	1.00
Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a ball?	70	65	76	0.50
Participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?	49	55	41	0.52
Overall Dukes score**	46	44 (16.5)	48 (10.4)	0.32

*Fisher's exact test

** Independent t test (Standard Dev)

4.3.4 Exercise programme compliance

Adherence to the exercise programme was excellent with 18 of 19 patients who completed the programme completing 100% of exercise sessions. One patient missed 2 exercise sessions when they developed large bowel obstruction due to their primary tumour and spent 4 days in hospital undergoing colonic stenting. Overall adherence to the exercise programme was 99.1%.

One patient in the exercise arm discontinued smoking as they felt it was making them more “short of breath” during the exercise sessions. They have remained abstinent in the postoperative period.

4.3.5 Effect of prehabilitation on CPET variables

4.3.5.1 Single arm analysis of change in CPET variables within prehabilitation group

One patient was excluded from the analysis, as they did not complete a second CPET test. This left 19 patients included in the analysis, which is summarised in Table 4-12. Within the group there was a significant improvement in the O₂ pulse at the AT, the relative and absolute O₂ uptake at peak, the peak work rate, the heart rate reserve AT. There were also a trend towards improved values in resting HR, relative O₂ uptake at the AT, absolute O₂ uptake at the AT, work rate at the AT, and peak O₂ pulse.

Response to the training programme was variable, which can be seen by the generalised widening of the standard deviations for a variety of the CPET variables. For example the relative O₂ uptake at the AT increased by an average of 1 ml.kg⁻¹.min⁻¹, however this ranged from a -3.7 ml.kg⁻¹.min⁻¹ (26% decrease) to a 6.7 ml.kg⁻¹.min⁻¹ (70%) increase. Overall, 7 patients increased by 1.5 ml.kg⁻¹.min⁻¹ or more, 1 decreased by 1.5 ml.kg⁻¹.min⁻¹ or more, and 11 patients either increased or decreased by less than 1.5 ml.kg⁻¹.min⁻¹. Similar variation in response to the prehabilitation programme was seen in a series of other key variables, and these are summarised in Table 4-13.

Table 4-12 Single arm comparison of CPET variables in prehabilitation group. Shown as mean (standard deviation), and mean change (95% CI for mean)

CPET variable	Baseline (19)	Post Prehab (19)	Change (95% CI)	P value
FEV1	2.95 (0.76)	2.95 (0.76)	0.00 (-0.16:0.16)	0.97
FVC	4.05 (0.98)	4.10 (0.95)	0.048 (-0.17:0.27)	0.67
FEV1/FVC	72.5 (7.0)	71.9 (7.7)	-0.6 (-2.3:1.2)	0.51
Resting Relative O ₂ uptake (ml.kg ⁻¹ .min ⁻¹)	3.6 (0.58)	3.6 (0.55)	-0.0 (-0.3:0.2)	0.74
Resting absolute O ₂ consumption (l/min)	0.309 (0.061)	0.308 (0.078)	-0.002 (-0.027:0.024)	0.90
Resting HR (bpm)	88 (17)	84 (16)	-4 (-8:1)	0.09
Relative O ₂ uptake at AT (ml.kg ⁻¹ .min ⁻¹)	11.2 (1.5)	12.2 (2.4)	1.0 (-0.2:2.1)	0.09
Absolute O ₂ uptake at AT (l/m)	0.964 (0.220)	1.06 (0.328)	0.098 (-0.009:0.205)	0.07
O ₂ Pulse at AT	8.8 (2.5)	9.6 (2.9)	0.8 (0.1:0.5)	0.03
Ventilatory equivalent of O ₂ at AT	26.8 (3.9)	27.0 (4.0)	0.1 (-1.5:1.7)	0.87
Ventilatory equivalent of CO ₂ at AT	29.8 (4.0)	30.0 (4.0)	0.1 (-1.0:1.2)	0.82
Work rate at AT (watts)	65 (16)	73 (23)	8 (-1:16)	0.08
HR at AT (bpm)	114 (21)	112 (17)	-1 (-6:4)	0.61
Relative O ₂ uptake at peak (ml.kg ⁻¹ .min ⁻¹)	17.6 (2.3)	19.4 (3.8)	2.0 (0.4:3.6)	0.02
Absolute O ₂ uptake at peak (l/min)	1.507 (0.351)	1.683 (0.490)	0.177 (0.031:0.322)	0.02
O ₂ Pulse at peak	10.7 (3.0)	11.6 (3.0)	0.8 (-0.1:1.7)	0.08
Ventilatory equivalent of O ₂ at peak	38.7 (6.5)	38.4 (5.8)	-0.2 (-1.9:1.4)	0.76
Ventilatory equivalent of CO ₂ at peak	32.2 (4.2)	32.3 (3.6)	0.1 (-1.0:1.1)	0.91
Work rate at peak (watts)	125 (26)	138 (35)	13 (7:19)	0.00
HR at peak (bpm)	144 (22)	146 (22)	2 (-2:6)	0.31
HR response to AT(bpm)	26 (13)	28 (12)	2 (-2:6)	0.26
HR reserve (bpm)	56 (18)	62 (20)	6(1:10)	0.03

Table 4-13 Summarising variation in response of key CPET variables in prehabilitation group

	Mean	Std. Deviation	Min	Max	Range
Relative O ₂ uptake at AT (ml.kg ⁻¹ .min ⁻¹)	1.00	2.46	-3.70	6.70	10.40
Relative O ₂ uptake at peak (ml/kg/min)	2.0	3.3	-2.6	10.8	13.4
O ₂ Pulse at AT	0.8	1.4	-1.5	3.8	5.3
O ₂ Pulse at peak	0.8	2.0	-2.5	5.2	7.7
Work rate at AT (watts)	8	18	-18	48	66
Work rate at peak (watts)	13	14	-2	50	52

4.3.5.2 Single arm comparison of CPET variables within the standard care group

One patient was excluded from the analysis, as they did not complete a second CPET test. This left 16 patients included in the analysis, which is summarised in Table 4-14.

Other than a minor reduction in the FEV1 (-0.08 litres), and heart rate at the anaerobic threshold (3 bpm) there was no statistically significant difference between CPET variables pre and post conduction of standard care. There was a trend towards a lower anaerobic (both relative and absolute) threshold following standard care.

There was not the same variation in outcome seen in the prehabilitation arm, as evidenced by the largely similar standard deviations pre and post standard

care (Table 4-15). Focusing on the relative O_2 uptake at the anaerobic threshold, no patient improved by $1.5 \text{ ml.kg}^{-1}.\text{min}^{-1}$ or greater, 4 patients deteriorated by $1.5 \text{ ml.kg}^{-1}.\text{min}^{-1}$ or more, and 12 patients changed their AT by less than $1.5 \text{ ml.kg}^{-1}.\text{min}^{-1}$.

Table 4-14 Single arm comparison of CPET variables in standard care group. Shown as mean (standard deviation), and mean change (95% CI for mean change)

CPET variable	Baseline (16)	Post Standard Care (16)	Change (95% CI)	P value
FEV1	3.10 (0.88)	3.12 (0.83)	-0.08 (-0.15:-0.00)	0.04
FVC	4.32 (1.01)	4.31 (1.01)	-0.11 (-0.26:0.04)	0.15
FEV1/FVC	72.1 (9.0)	72.6 (9.6)	-0.1 (-1.9:1.7)	0.94
Resting Relative O ₂ uptake (ml.kg ⁻¹ .min ⁻¹)	3.6 (0.8)	3.8 (0.8)	0.1 (-0.4:0.6)	0.65
Resting absolute O ₂ consumption (l/min)	.308 (0.81)	.319 (0.73)	.008 (-0.036:0.051)	0.72
Resting HR (bpm)	81 (15)	79 (19)	-2 (-6:3)	0.40
Relative O ₂ uptake at AT (ml.kg ⁻¹ .min ⁻¹)	11.4 (1.8)	11.0 (2.1)	-0.5 (-1.2:0.1)	0.09
Absolute O ₂ uptake at AT (l/m)	.979 (0.249)	0.942 (0.262)	-0.038 (-0.090:0.014)	0.14
O ₂ Pulse at AT	9.6 (3.1)	9.6 (3.3)	-0.1 (-0.7:0.5)	0.77
Ventilatory equivalent of O ₂ at AT	29.6 (5.1)	28.8 (4.2)	-0.8 (-2.2:0.6)	0.26
Ventilatory equivalent of CO ₂ at AT	31.8 (4.6)	31.4 (3.4)	-0.3 (-1.8:1.1)	0.63
Work rate at AT (watts)	66 (16)	64 (19)	-3 (-10:4)	0.42
HR at AT (bpm)	105 (15)	101 (17)	-3 (-6:-1)	0.02
Relative O ₂ uptake at peak (ml.kg ⁻¹ .min ⁻¹)	18.6 (3.9)	18.7 (4.1)	0.0 (-1.3:1.2)	0.96
Absolute O ₂ uptake at peak (l/min)	1.587 (0.464)	1.603 (0.464)	0.006 (-0.107:0.118)	0.91
O ₂ Pulse at peak	11.8 (3.8)	12.1 (3.8)	0.2 (-0.6:0.9)	0.64
Ventilatory equivalent of O ₂ at peak	43.7 (7.4)	42.7 (8.0)	-1.1(-3.5:1.2)	0.32
Ventilatory equivalent of CO ₂ at peak	34.9 (4.3)	34.5 (4.7)	-0.5 (-2.4:1.4)	0.57
Work rate at peak (watts)	138 (39)	140 (39)	0 (-5:6)	0.92
HR at peak (bpm)	138 (24)	136 (26)	-2 (-7:3)	0.41
HR response to AT(bpm)	24 (9)	22 (9)	-2 (-5:2)	0.34
HR reserve (bpm)	57 (18)	57 (17)	0 (-4:4)	0.87

Table 4-15 Summarising variation in response of key CPET variables in standard care group

	Mean	Std. Deviation	Min	Max	Range
Relative O ₂ uptake at AT (ml.kg ⁻¹ .min ⁻¹)	-0.5	1.2	-2.5	1.3	3.8
Relative O ₂ uptake at peak (ml.kg ⁻¹ .min ⁻¹)	-0.3	2.4	-5.3	4.5	9.8
O ₂ Pulse at AT	-0.1	1.1	-1.7	1.9	3.6
O ₂ Pulse at peak	0.2	1.4	-3.3	2.7	6.0
Work rate at AT (watts)	-3	13	-30	22	52
Work rate at peak (watts)	0	11	-26	14	40

4.3.5.3 The effect of prehabilitation on CPET variables: comparison between study arms.

The differences achieved in key CPET variables are summarised in Table 4-16. The primary outcome is highlighted in red, and demonstrates that a four-week cycle based interval-training programme is capable of delivering a 1.5 ml.kg⁻¹.min⁻¹ shift in the anaerobic threshold (p-0.023). This represents a 14% shift from the baseline value, and just short of one standard deviation for our patient population. This shift was accompanied by a significant improvement in the absolute O₂ uptake at the anaerobic threshold of 0.136 litres (14%) (p-0.024), and an improvement of 13 watts (10%) at peak exercise (p-0.005).

There were also a number of non-significant trends in favour of the prehabilitation group including a 10% improvement in O₂ pulse at the AT (p-0.05), a 15% improvement in the work rate at AT (p-0.06), an 11% improvement in the relative O₂ uptake at peak (p-0.05), a 11% improvement in the absolute O₂ uptake at peak (p=0.07), and a 3 bpm (5%) improvement in the HR reserve.

There was no change in the FEV1, FVC, resting O₂ uptake, resting HR, or ventilatory equivalents of CO₂ and O₂.

Table 4-16 Summary of differences in change of CPET variables between cohorts following intervention. Primary outcome variable highlighted (Red)

CPET variable	Mean difference following		Difference between cohorts (95% CI)	P value
	Prehab	Standard Care		
FEV1	0.00	-0.08	0.21 (-0.04:0.06)	0.17
FVC	0.048	-0.11	0.36 (-0.10 :0.81)	0.12
FEV1/FVC	-0.6	-0.1	3.8 (-4.6: 12.2)	0.36
Resting Relative O ₂ uptake (ml.kg ⁻¹ .min ⁻¹)	-0.0	0.1	-0.2 (-0.7 :0.4)	0.56
Resting absolute O ₂ consumption (l/min)	-0.002	0.008	-0.009 (-0.056: 0.0376)	0.67
Resting HR (bpm)	-4	-2	-2 (-8: 4)	0.53
Relative O ₂ uptake at AT (ml.kg ⁻¹ .min ⁻¹)	1.0	-0.5	1.5 (0.2:2.9)	0.02
Absolute O ₂ uptake at AT (l/m)	0.098	-0.038	0.136 (0.020:0.252)	0.02
O ₂ Pulse at AT	0.8	-0.1	0.9 (0.0:1.8)	0.05
Ventilatory equivalent of O ₂ at AT	0.1	-0.8	0.9 (-1.2: 3.0)	0.39
Ventilatory equivalent of CO ₂ at AT	0.1	-0.3	0.5 (-1.3:2.2)	0.60
Work rate at AT (watts)	8	-3	10 (-1: 22)	0.06
HR at AT (bpm)	-1	-3	2 (-4:8)	0.47
Relative O ₂ uptake at peak (ml.kg ⁻¹ .min ⁻¹)	2.0	0.0	2.0 (0.0:4.0)	0.05
Absolute O ₂ uptake at peak (l/min)	0.177	0.006	0.171 (-0.012:0.354)	0.06
O ₂ Pulse at peak	0.8	0.2	0.7 (-0.5:1.9)	0.26
Ventilatory equivalent of O ₂ at peak	-0.2	-1.1	0.9 (-1.8:3.6)	0.50
Ventilatory equivalent of CO ₂ at peak	0.1	-0.5	0.6 (-1.4:2.5)	0.57
Work rate at peak (watts)	13	0	13 (4:22)	<0.01
HR at peak (bpm)	2	-2	4 (-2:11)	0.19
HR response to AT(bpm)	2	-2	4 (-1:9)	0.14
HR reserve (bpm)	6	0	3 (0:12)	0.07

4.3.6 Effect of exercise intervention on quality of life

As described earlier, one candidate in each study arm was excluded from the analysis, as they had only baseline quality of life assessments. The SF-36 questionnaire, must be interpreted by considering that a shift of 10 points is needed to be deemed clinically relevant. Thus meaning that statistically significant shifts may occur that are not deemed clinically relevant.

4.3.6.1 SF-36 single arm analysis

When considering changes in the quality of life assessed by the SF-36 questionnaire, first it is worth considering the arms in isolation to establish whether significant changes have occurred. The results are summarised in tables 4-17 and 4-18. Within the prehabilitation arm a clinically relevant positive change was seen in 5 of the eight domains, of which “Role-physical”, “Vitality”, “Social functioning” and “Role-emotional” were statistically significant (table 4-17). Clinically relevant and statistically significant positive differences were found in the overall physical health, overall mental health, and overall SF-36 score (table 4-17). Overall, there were positive shifts in all domains with the exception of the “general health” domain that remained unchanged.

In the standard care arm no clinically relevant changes in scores were observed, and the only statistically significant change was a negative shift in the “mental health” domain (Table 4-18) this approached clinical relevance.

Though this change failed to reach the shift of a score of 10 deemed clinically significant.

Table 4-17 Change in SF 36 values prehabilitation (Paired T test)

	Baseline (19)	Post Prehab (19)	Change	95% Confidence Interval		Sig.
				lower	upper	
Physical Function	73	81	8	2	14	0.014
Role-Physical	49	68	20	1	38	0.039
Body Pain	68	80	12	-1	26	0.077
General Health	64	66	2	-6	10	0.616
Vitality	54	66	12	4	20	0.005
Social Functioning	66	83	17	6	28	0.005
Role Emotional	70	89	19	0	38	0.045
Mental Health	76	83	7	2	12	0.009
<i>Overall Physical Health</i>	61	72	11	4	17	0.003
<i>Overall Mental Health</i>	66	77	11	5	18	0.003
<i>TOTAL SF36 Score</i>	65	77	12	5	19	0.002

Table 4-18 Change in SF 36 vales post-standard care (Paired t test)

	Baseline (16)	Post Standard Care (16)	Change	95% Confidence Interval		Sig.
				lower	upper	
Physical Function	83	85	2	-5	10	0.535
Role-Physical	47	48	2	-21	25	0.887
Body Pain	75	78	3	-5	11	0.475
General Health	65	67	3	-5	11	0.493
Vitality	58	64	6	-3	16	0.175
Social Functioning	79	80	1	-16	18	0.926
Role Emotional	77	73	-4	-24	16	0.672
Mental Health	83	77	-6	-11	0	0.049
<i>Overall Physical Health</i>	65	68	3	-4	10	0.360
<i>Overall Mental Health</i>	72	72	0	-9	9	0.989
<i>TOTAL SF36 Score</i>	71	72	1	-7	9	0.828

4.3.6.2 SF-36 Prehabilitation versus standard care comparison

The results of a comparison between the two study arms are summarised in table 4.19. Clinically relevant changes in favour of prehabilitation were observed in 4 of the 8 domains (“Role-physical”, “Social Functioning”, “Role-emotional” and “mental health”), though only the changes observed in the mental health domain was statistically significant.

Clinically relevant changes were also observed in the overall mental health and overall SF-36 score, with the prehabilitation arm contributing to an 11% improvement in overall SF-36 score ($p=0.028$).

Across all the 8 SF-36 domains prehabilitation seemed to consistently contribute to improvements in QoL, though statistical significance was not observed. A larger study would be needed to confirm if prehabilitation can deliver improvements in these domains.

Table 4-19 Difference in SF36 scores across the two cohorts following exercise intervention or standard care

	Prehab (19)	Standard Care (16)	Difference	95% Confidence Interval		Sig.
				lower	upper	
Physical Function	8	2	5	-3	14	0.223
Role-Physical	20	2	18	-10	46	0.199
Body Pain	12	3	10	-7	26	0.240
General Health	2	3	-1	-12	11	0.902
Vitality	12	6	6	-6	17	0.333
Social Functioning	17	1	17	-2	36	0.085
Role Emotional	19	-4	23	-3	50	0.083
Mental Health	7	-6	12	5	20	0.001
<i>Overall Physical Health</i>	11	3	8	-2	17	0.103
<i>Overall Mental Health</i>	11	0	12	1	22	0.037
<i>TOTAL SF36 Score</i>	12	1	11	1	21	0.030

4.3.6.3 Single arm comparison of EORTC and LMC scores

In a similar manner to the SF-36 analysis, first each arm was considered in isolation (tables 4.20 & 4.21).

Globally there were minimal changes in the EORTC scores. Improvements were seen in the prehabilitation arm in the physical functioning domain, and

both fatigue domains. There were also trends towards improved scores in the domains global health status, pain, appetite loss, and dry mouth.

In the standard care arm there was an improvement in the domain global health status. However, there was deterioration in the domain cognitive functioning. There were a number of trends towards improvements in the domains fatigue, dyspnoea, and financial difficulties.

4.3.6.4 EORTC prehabilitation versus standard care comparison

The results of a comparison between the two study arms are summarised in Table 4-22. This summarises the difference from baseline to post prehabilitation or standard care, and also gives the overall difference between the two study arms given that positive and negative changes occurred. There were no statistically significant differences between the two study arms.

Table 4-20 Differences in the EORTC score (including LMC bolt on component) for the patients undergoing prehabilitation

	Baseline (19)	Post Prehab (19)	Change	95% Confidence Interval		Sig.
				lower	upper	
Global Health Status	70	76	6	-1	13	0.069
Physical Functioning	84	90	6	0	13	0.049
Role Functioning	83	87	4	-6	13	0.448
Emotional Functioning	84	80	-4	-15	7	0.447
Cognitive Functioning	84	89	4	-7	16	0.426
Social Functioning	81	86	5	-8	19	0.420
Fatigue	25	15	-11	-21	0	0.049
Nausea and vomiting	8	4	-4	-11	4	0.331
Pain	21	14	-7	-15	1	0.088
Dyspnoea	9	7	-2	-15	12	0.79
Insomnia	26	18	-9	-21	3	0.135
Appetite loss	14	4	-11	-21	0	0.055
Constipation	5	2	-4	-9	2	0.163
Diarrhoea	5	2	-4	-11	4	0.331
Financial Difficulties	19	11	-9	-22	4	0.172
LMC Eating	5	3	-3	-11	6	0.506
LMC Pain	15	12	-4	-12	5	0.420
LMC Fatigue	30	19	-12	-22	-2	0.023
LMC Social	16	11	-6	-16	4	0.235
LMC Anxiety	32	29	-3	-13	7	0.529
LMC Weight-loss	7	4	-4	-13	6	0.429
LMC taste	16	7	-9	-21	3	0.135
LMC dry mouth	21	11	-11	-21	0	0.055
LMC neuropathy	25	21	-4	-19	12	0.650
LMC Jaundice	0	0	0	n/a	n/a	n/a

Table 4-21 Differences in the EORTC score (including LMC bolt on component) for the patients undergoing standard care

	Baseline (16)	Post Standard Care (16)	Change	95% Confidence Interval		Sig.
				lower	upper	
Global Health Status	62	69	7	0	14	0.048
Physical Functioning	88	88	0	-11	11	1
Role Functioning	80	84	4	-7	16	0.433
Emotional Functioning	84	84	1	-8	9	0.885
Cognitive Functioning	92	88	-4	-9	0	0.041
Social Functioning	83	88	4	-1	10	0.104
Fatigue	27	21	-7	-14	0	0.057
Nausea and vomiting	3	4	1	-1	3	0.334
Pain	14	19	4	-5	14	0.334
Dyspnoea	11	4	-7	-14	1	0.082
Insomnia	22	20	-2	-20	16	0.792
Appetite loss	7	2	-4	-14	5	0.334
Constipation	9	2	-7	-17	4	0.189
Diarrhoea	20	13	-7	-24	11	0.424
Financial Difficulties	11	4	-7	-14	1	0.082
LMC Eating	7	4	-2	-7	3	0.334
LMC Pain	15	12	-3	-9	3	0.301
LMC Fatigue	32	21	-10	-22	2	0.084
LMC Social	32	5	-7	-15	1	0.095
LMC Anxiety	38	31	-7	-21	6	0.266
LMC Weight-loss	4	7	2	-3	7	0.334
LMC taste	11	4	-7	-23	9	0.384
LMC dry mouth	29	24	-4	-18	9	0.499
LMC neuropathy	33	29	-4	-21	12	0.582
LMC Jaundice	4	0	-4	-14	5	0.334

Table 4-22 Difference in EORTC (including LMC bolt on) scores across the two cohorts following exercise intervention or standard care

	Prehab (19)	Standard Care (16)	Diff.	95% Confidence Interval		Sig.
				lower	upper	
Global Health Status	6	5	1	-9	12	0.776
Physical Functioning	6	0	6	-5	18	0.284
Role Functioning	4	2	1	-13	16	0.843
Emotional Functioning	-4	-5	1	-16	17	0.927
Cognitive Functioning	4	-8	13	-2	27	0.081
Social Functioning	5	0	5	-12	22	0.533
Fatigue	-11	-11	1	-14	16	0.937
Nausea and vomiting	-4	1	-5	-13	3	0.258
Pain	-7	4	-11	-23	0	0.059
Dyspnoea	-2	-6	4	-11	20	0.564
Insomnia	-9	-8	0	-23	22	0.968
Appetite loss	-11	-10	0	-18	18	0.99
Constipation	-4	-6	3	-7	13	0.581
Diarrhoea	-4	-6	3	-13	19	0.732
Financial Difficulties	-9	-6	-3	-18	13	0.735
LMC Eating	-3	-5	3	-8	14	0.636
LMC Pain	-4	-3	-1	-11	10	0.889
LMC Fatigue	-12	-15	3	-13	19	0.72
LMC Social	-6	-8	2	-11	14	0.773
LMC Anxiety	-3	-10	7	-9	23	0.391
LMC Weight-loss	-4	-4	1	-15	16	0.933
LMC taste	-9	-13	4	-17	25	0.72
LMC dry mouth	-11	-4	-6	-22	10	0.423
LMC neuropathy	-4	-4	1	-21	22	0.951
LMC Jaundice	0	-4	4	-4	12	0.282

4.3.7 Effect of prehabilitation on activity

4.3.7.1 Effect of prehabilitation on Dukes activity status index

The changes in Duke's activity index comparing baseline to post prehabilitation or standard care are summarised in tables 4.23 and 4.24.

Within the prehabilitation arm there was very little change, with only a trend towards an increased belief that study participants could undertake moderate recreational activity and greater Dukes score. In the standard care arm there was again little difference. Given the findings of the single arm analysis more detailed analysis was not undertaken.

Table 4-23 Prehabilitation arm changes in Dukes activity index from baseline to post intervention (19 patients).

	Baseline	Post Prehab	change	Sig.
Eat dress, bathe or use the toilet	19	19	0	N/A *
Walk indoors, such as around their house	19	19	0	N/A *
Walk 200 yards on level ground	18	18	0	N/A *
Climb a flight of stairs or walk up a hill	19	19	0	N/A *
Run a short distance?	12	15	+3	0.25*
Do light work around the house like dusting or washing dishes	19	19	0	N/A *
Do moderate work around the house like vacuuming sweeping floors or carrying groceries?	19	19	0	N/A *
Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	14	14	0	N/A *
Do yard work like raking leaves, weeding or pushing a power mower?	17	19	+2	0.50*
Have sexual relations?	12	14	+2	0.61*
Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a ball?	13	18	+5	0.07*
Participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?	11	13	+2	0.72*
Overall Dukes score**	45.6 (14.5)	51.0 (11.9)	4.8 *** (-1.6: 11.2)	0.13

*McNemar test

** Independent t test (Standard Dev)

*** 95% Confidence Interval

Table 4-24 Standard care arm changes in Dukes activity index from baseline to immediately before surgery (16 patients)

	Baseline	Post Prehab	change	P value*
Eat dress, bathe or use the toilet	16	16	0	N/A
Walk indoors, such as around their house	16	16	0	N/A
Walk 200 yards on level ground	16	16	0	N/A
Climb a flight of stairs or walk up a hill	16	16	0	N/A
Run a short distance?	15	15	0	N/A
Do light work around the house like dusting or washing dishes	16	16	0	N/A
Do moderate work around the house like vacuuming sweeping floors or carrying groceries?	16	16	0	N/A
Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	14	14	0	N/A
Do yard work like raking leaves, weeding or pushing a power mower?	13	14	+1	1.00
Have sexual relations?	10	13	+3	0.25
Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a ball?	13	13	0	N/A
Participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?	8	8	0	N/A
Overall Dukes score**	48.5 (10.7)	50.3 (9.9)	+1.7 (-4.2 : 7.7)	0.550

*McNemar test

** Independent t test (Standard Dev)

*** 95% Confidence Interval

4.3.8 High risk cohort subset analysis

An unplanned subset analysis was carried out to consider changes occurring in patients deemed “high risk” with an oxygen uptake at the anaerobic threshold of $<11 \text{ ml.kg}^{-1}.\text{min}^{-1}$.

4.3.8.1 Changes In CPET values in the high risk cohort

Within the high-risk cohort there were significant changes in the CPET values. This is despite limited patient numbers (9 prehabilitation, 7 standard care). Prehabilitation was associated with a significant improvement in both the relative and absolute oxygen uptake at the AT. There was also an increase in the work rate at the AT, and improved ventilatory equivalents of both oxygen and carbon dioxide at peak exercise (Table 4-25).

Table 4-25 CPET changes in high-risk cohort

CPET variable	Mean difference after intervention		Difference between cohorts (95% CI)	P value
	Prehab (9)	Standard Care (7)		
FEV1	0.09	-0.33	0.42 (-0.28 : 1.12)	0.22
FVC	0.137	-0.547	0.684 (-0.308 : 1.676)	0.16
FEV1/FVC	0.2	-9.1	9.4 (-9.7 : 28.4)	0.31
Resting Relative O ₂ uptake (ml.kg ⁻¹ .min ⁻¹)	0.1	0.3	-0.1 (-0.6 : 0.4)	0.56
Resting absolute O ₂ consumption (l/min)	0.010	0.026	-0.016 (-0.058 : 0.027)	0.44
Resting HR (bpm)	-4	-2	-2 (-12 : 9)	0.75
Relative O ₂ uptake at AT (ml.kg ⁻¹ .min ⁻¹)	1.9	-0.4	2.3 (0.3: 4.2)	0.03
Absolute O ₂ uptake at AT (l/m)	0.151	-0.024	0.175 (0.015 : 0.335)	0.03
O ₂ Pulse at AT	1.2	0.0	1.2 (-0.1 : 2.4)	0.06
Ventilatory equivalent of O ₂ at AT	1.3	-1.3	2.5 (-0.5 : 5.6)	0.10
Ventilatory equivalent of CO ₂ at AT	0.4	-0.8	1.2 (-1.1 : 3.5)	0.29
Work rate at AT (watts)	13	-6	19 (5 : 33)	0.01
HR at AT (bpm)	1	-4	5 (-4 : 13)	0.23
Relative O ₂ uptake at peak (ml.kg ⁻¹ .min ⁻¹)	2.8	0.3	2.5 (-1.3 : 6.2)	0.18
Absolute O ₂ uptake at peak (l/min)	0.234	0.037	0.197 (-0.124 : 0.519)	0.21
O ₂ Pulse at peak	1.4	0.5	0.8 (-0.9 : 2.6)	0.31
Ventilatory equivalent of O ₂ at peak	0.3	-4.2	4.6 (0.3 : 8.9)	0.04
Ventilatory equivalent of CO ₂ at peak	0.9	-2.7	3.6 (1.1 : 6.0)	0.01
Work rate at peak (watts)	13	-1	14 (-1 : 30)	0.07
HR at peak (bpm)	1	-5	6 (-4 : 15)	0.20
HR response to AT(bpm)	5	-2	7 (-2 : 15)	0.13
HR reserve (bpm)	4	-3	7 (-2 : 17)	0.12

4.3.8.2 Changes in Quality of Life in the high risk cohort

When comparing the SF-36 values between cohorts there was a clinically relevant improvement in the mental health domain of 10 (95% CI 8:29) in favour of prehabilitation ($p < 0.01$) (Table 4-26). There was also trend towards improved role-physical (+36 (95% CI -2:74)). Though confidence intervals are very wide for the role-physical domain, so caution must be exercised in the interpretation.

Table 4-26 Changes in SF 36 values within high-risk cohort

	Prehab (9)	Standard Care (7)	Difference	95% Confidence Interval		Sig.
				lower	upper	
Physical Function	8	3	5	-12	23	0.51
Role-Physical	25	-11	36	-2	74	0.06
Body Pain	17	9	8	-26	41	0.63
General Health	4	3	2	-16	19	0.85
Vitality	11	10	1	-17	18	0.95
Social Functioning	17	-6	22	-16	60	0.23
Role Emotional	19	5	14	-33	60	0.54
Mental Health	8	-10	18	8	29	0.00
<i>Overall Physical Health</i>	13	3	10	-5	24	0.16
<i>Overall Mental Health</i>	12	0	11	-9	31	0.25
<i>TOTAL SF36 Score</i>	13	1	13	-5	30	0.14

4.3.9 Perioperative outcomes

4.3.9.1 Surgical interventions

The surgical interventions undertaken are summarised in Table 4-27. There were no statistically significant differences between the cohorts. Specifically there was no difference between the incidence of major hepatectomy, or minor hepatectomy (prehab 38%, standard care 31%), those cases where additional non-hepatic procedures were undertaken (prehab 16%, standard care 13%), or the number of lesions undergoing treatment (median 3 in both groups).

Table 4-27 Extent of surgical intervention

	Prehab (19)	Standard Care (17)	P value
Hepatic Procedure			
No surgery	0	4	
Open and Close	3	2	
No hepatic intervention	1	0	
Right Hemihepatectomy	1	2	
Left hemihepatectomy	2	0	
Right hemihepatectomy + multiple metastectomy	2	1	N/A
Left hemihepatectomy + multiple hepatectomy	0	1	
Left lateral sectionectomy	0	1	
Metastectomy	4	4	
Multiple metastectomy	5	1	
Multiple metastectomy + Ablation	1	1	
Extended right hemihepatectomy + caudate lobectomy	1	0	
Hepatectomy Extent			
Major	6	4	0.90
Minor	10	9	
Additional Procedure			
Yes	3	2	
No	16	13	1.00
Additional Procedures (excluding gallbladder)			
Bile Duct reconstruction	1	0	
Right hemicolectomy	1	0	
Incisional hernia repair		1	N/A
Excision of wound metastasis	1	1	
Portal vein ligation		1	
Segments involved in treatment*	3 (1:5)	3 (1:4)	0.682
Lesions Treated*	3 (1:4.25)	3 (1:7)	0.693

*Median and IQR

4.3.9.2 Comparison of perioperative outcomes between study arms

The main perioperative outcomes analysed by group are summarised in Table 4-28. Whilst statistically there is no significant difference in perioperative outcomes across the cohorts, all the patients who suffered a readmission were part of the prehabilitation group (4 vs 0; 21% vs 0%). The reasons for readmission included 1 abdominal dehiscence, 2 patients developed bilomas requiring percutaneous drainage, and one patient developed significant hepatic insufficiency and pedal oedema.

Table 4-28 Comparison of perioperative outcomes across cohorts

	Study cohort (34)	Prehab (19)	Standard Care (15)	P value
Critical Care Admission *	12 (36%)	8 (42%)	4 (27%)	0.48
Complication*				
All Grades	15 (44%)	9 (47%)	6 (40%)	0.47
Grade 3&4	4 (12%)	3 (16%)	1 (7%)	0.40
Complications				
Total	26	10	13	
Bile Leak/Biloma	2	2	0	
Hepatic Insufficiency	4	1	3	
Atrial fibrillation	1	1	0	
Pacemaker malfunction	1	1	0	
Respiratory Infection	4	1	3	
Wound Infection	2	2	0	
Ileus	1	0	1	
Renal Impairment	1	1	0	
Abdominal Dehiscence	1	1	0	
Postoperative confusion	2	0	2	
Nausea and vomiting	2	0	2	
UTI	1	0	1	
Thrombocytopenia	1	0	1	
Critical care length of stay**	1 (1:2)	1 (1:2)	1.5 (1:2)	1.00
Length of stay**	5 (4:6.5)	5 (4:6)	5 (4.5:7)	0.584
Readmission*	4 (12%)	4 (21%)	0 (0%)	0.113

* Shown as median and percentage ** Shown as median and IQR

4.3.10 Assessments post surgery

Exploratory data were collected for patients post operatively. Unfortunately the data is confounded by varied surgical interventions, varied postoperative course and limited numbers. This means beyond attendance data, meaningful conclusions cannot be drawn. Consequently this data is not presented.

4.4 Discussion

4.4.1 Preoperative CPET values

The study met its primary objective of detecting a difference $\geq 1.5 \text{ ml.kg}^{-1}.\text{min}^{-1}$ in the Vo_2 at AT when comparing a prehabilitation programme to standard care.

The significant difference seen in the study is in part due to an unexpected deterioration in CPET values in the standard care arm. In the standard care arm no patient had a significant improvement in Vo_2 at AT ($\text{ml.kg}^{-1}.\text{min}^{-1}$) and 4 had deterioration in excess of $1.5 \text{ ml.kg}^{-1}.\text{min}^{-1}$. Overall there was a non-significant trend towards worse Vo_2 at AT ($\text{ml.kg}^{-1}.\text{min}^{-1}$) ($p=0.09$). This would be in keeping with the literature on cancer related fatigue syndrome suggesting deteriorating physical conditioning is a key contributor to that syndrome¹⁶¹.

This is a previously unpublished finding, and raises the question about timing of any preoperative CPET test. Many of the large series examining CPET tests fail to report the timing of the CPET test in relation to surgery^{34,43,49,229}, and given that we have seen significant deterioration in CPET values in just 4 weeks of standard care adds another potential confounding factor to the literature. It may be that a CPET test conducted 4 weeks prior to surgery suggesting a patient is low risk, may in fact be inaccurate by the time of

surgery, meaning a patient gets inappropriately labelled as low risk and managed as such.

The improvements in the workloads achieved at both the AT and peak exercise suggest improvements in skeletal muscle mass. Nearly 20% of patients undergoing colorectal liver metastasis resection are identified as having sarcopenia, a factor associated with higher complications, higher cost and earlier cancer recurrence^{127,235,236}. If prehabilitation could attenuate this, it could lead to lower costs of surgery, with better long term outcomes and disease free survival, vastly improving the cost efficacy of our treatments. Unfortunately this was not explored in this study and would be a focus for future research.

The variation in response to the standardised exercise programme is interesting and in keeping with the theory of “responder/non responder” based on genetic markers²³⁷. It should not be suggested that an absence of a VO_2 response means that the exercise has failed to yield benefit. In the prehabilitation arm nearly 40% of patients responded to the exercise programme in terms of the Vo_2 at AT, but looking at the “non-responders” it may be that if they were left without prehabilitation their Vo_2 values would have deteriorated, as was seen in a number of patients on standard care.

Interestingly the group deemed high risk, appeared to have arguably some of the biggest improvements in CPET Values. This would suggest that this group, at highest risk have the most to gain from prehabilitation. In the era of

limited health resource these patients should form the focus of further research and intervention.

Other benefits of exercise including improved muscle bulk, improved insulin resistance and improved preoperative psychological status²³⁸⁻²⁴¹. All can contribute to an improved perioperative outcome. These were not studied in this thesis and would warrant further exploration.

4.4.1 Preoperative QoL

Clinically and statistically significant improvements in quality of life were detected using the SF-36 questionnaire. This was not anticipated at the outset of the study as it was not possible to power the study on available data, and the absence of any correlating results in the EORTC questionnaires probably represents an under-powering for that particular outcome measure.

The improvement in quality of life was in part related to improved physical functioning but the majority of the improvement was in improved mental health, in particular emotional and social functioning. This finding of improved emotional and social functioning is in keeping with other studies of exercise in cancer sufferers^{242,243}. It is however interesting that a four week programme of just 12 sessions can achieve similar improvements to programmes typically of much longer duration.

The improvements in QoL are almost certainly related to the actual participation in the exercise programme. In comparison to the CPET values that deteriorated across the control arm, the QoL (SF-36) values were largely unchanged, suggesting that the QoL was independent of physical fitness. This would suggest that improvements in physical fitness do not necessarily correlate with improved QoL but participation in the exercise programme itself seemed to be key. This is similar to previous work²⁴⁴, but the mechanism for this improvement is not clear and remains a focus for further work. Perhaps this could be examined by a study comparing prehabilitation against a sham arm of social interaction alone.

Prehabilitation offers an opportunity to improve the preoperative education that could have multifactorial benefits beyond that of the improved physical fitness alone. Preoperative exercise intervention provides an opportunity to educate patients. The exercise was supervised by a number of staff with differing levels of knowledge of the surgical intervention proposed. Staff were allowed to answer patient questions, and it may be that some of the improved QoL seen is due to improved preoperative education and reduced anxiety levels. Lower preoperative anxiety, is associated with better postoperative gut motility and improved wound healing^{139,245-248}.

Life expectancy for patients with colorectal liver metastasis is increasing with a reported 5-year survival of 10% in patients treated with only palliative intent²⁴⁹. Consequently, quality of life and not just length of life is becoming

ever more important. The improvement in preoperative quality of life in this study should be seen as a significant achievement, given this is often a challenging time for patients. However the longer-term effect was not explored and this would need to be assessed, as this may be a short-lived change.

Prehabilitation fits well with the principals of living with and beyond cancer (LWBC), a concept of trying to improve quality of life and both physical and social functioning for patients undergoing cancer treatment, and in their life after treatment²⁵⁰. Exercise has been seen to be a key component of LWBC, with poor exercise levels identified and seen as a major focus for improving outcomes²⁵⁰⁻²⁵².

The presence of preoperative psychological disturbance may be associated with poorer long-term survival in colorectal cancer¹⁵⁹. In our study we found significant improvements were achieved in particular in the mental health of patients undergoing prehabilitation. The impact of this on long-term life expectancy could be examined in future studies.

4.4.2 Recruitment

The recruitment rate was lower than seen in previous prehabilitation studies^{168,170,173}, distance to travel being the greatest barrier to recruitment. This barrier became apparent during the trial and was in part due to the tertiary nature of the disease. This meant asking patients to travel for up to 3 hours

three times a week in addition to hospital appointments, with no funding for travel expenses incurred. Accepting this barrier, recruitment was acceptable, with a number of patients willing to travelling 90 minutes each way to attend exercise sessions and assessments. In future studies making prehabilitation accessible locally would likely improve recruitment and make it applicable to the majority of patients.

The cohort recruited to the trial were younger than a typical demographic of patients with CRLM ¹¹². This clearly demonstrates a recruitment bias in favour of younger patients. Younger patients are reported to have more advanced disease at presentation and higher recurrence rates so this may have contributed to the selection of a cohort with biologically aggressive disease ²⁵³.

Interestingly, two factors anticipated to be significant barriers to recruitment did not materialise at the level expected. Around 12% of patients were excluded purely on the basis of inadequate time to deliver the exercise programme before the provisional surgery date, suggesting that the exercise programme in use in this study could be delivered within current UK cancer pathways. Given that much of the population presenting with liver metastases are elderly, few could not participate as a result of being physically unable to cycle. This absence of physical limitation as a barrier would fit with our previous experience of CPET in the population ³⁴.

4.4.3 Study Cohort

Whilst importantly there were no differences in any baseline characteristics between study arms, it is worth considering the effect recruitment bias may have had on the overall cohort within the study.

The presence of a cohort with more aggressive tumour biology is supported by baseline characteristics with nearly half of patients presenting with synchronous disease, and 6 patients having a colorectal primary in situ during the trial. This is higher than would be expected in a typical cohort of patients presenting with liver metastases¹⁶⁰. A number of candidates had already undergone resection of other site disease, and several had multi-site disease. The patients also had a greater preponderance to an advanced primary than seen in other studies¹⁶⁰.

Patients with a metachronous presentation had an unexpectedly high rate of complications following their primary surgery at approximately 50%. This high complication rate is not explainable by emergency presentations as the rates of emergency presentations are fairly typical in our study cohort¹⁴². Complications have been implicated in disease recurrence following colorectal resection and hepatectomy for CRLM^{238,254}. This relationship warrants further exploration.

4.4.4 Preoperative study progress

Study completion and attendance was high in comparison to other studies^{162,169,173,207}. In particular the adherence of 99.1% is excellent, suggesting that the exercise intervention is acceptable to the recruited patient group; and that the study cohort were highly motivated. This given the relatively low recruitment rate raises the question of selection bias, and may temper the results, and mean the results do not translate in wider practice.

Other contributory factors to the high adherence include the supervised nature of the exercise, and the interval nature of training. Other supervised exercise programmes have been successful^{168,172,207} in comparison to home based prehabilitation programmes which have failed to yield significant fitness improvements^{162,171}. Interval-based training programmes have been shown to have higher ratings of perceived enjoyment than constant load programmes; meaning adherence is likely to be higher.²²¹

There was a relatively high rate of failure to progress to hepatectomy, with 5 patients being irresectable at laparotomy, 3 for peritoneal disease, 1 for advancing hepatic disease, and one for extensive chemotherapy induced liver injury (patient required 70% hepatectomy). This is much higher than expected given our own published data²³⁴. Whilst given the small numbers this could be chance, it could also suggest that the overall cohort had aggressive tumour biology.

4.4.4.1 Preoperative Activity

Activity did not objectively increase in the prehabilitation group compared with the standard care group. It may be that the Dukes activity index was not an adequate tool to evaluate activity, and that with the proliferation of electronic activity monitors this could be better assessed in future studies.

4.4.5 Perioperative outcomes

There is no statistically significant difference in perioperative outcomes or complication rates between the study arms. This however is limited by the small numbers and confounded by the differing extent of surgical intervention.

There was no difference in length of stay, however there were three readmissions with complications from the prehabilitation study arm. A larger study would be needed to assess any differences observed, but given that in large series of hepatectomy using ERAS the median length of stay is already reduced to 6 days any benefit would be limited¹¹².

4.4.6 Postoperative study progress

Due to a multitude of factors there was a relatively high attrition rate following the active study period, which has limited conclusions drawn from the postoperative period. In particular 3 patients failed to undergo any surgical intervention, and then a further 5 patients did not undergo hepatectomy. These patients undergoing a laparotomy only were not excluded from the

study, and were eligible to partake in follow-up. By the second postoperative visit a number of patients had started to undergo further treatment including surgery (3 patients), and chemotherapy (8 patients), this limited attendance and completion of CPET tests, and could have confounded QoL measures.

Reassuringly the vast majority of patients attending the 6-week visit were physically capable of completing a CPET test. This was a point of concern during trial design, with clinicians involved in the trial design concerned that patients were unlikely to be physically capable. The high compliance rate suggests that if anything we underestimate the capacity of patients to recover from major surgery. A larger study could utilise tests from 6 weeks to measure how quickly patients recover following surgery.

4.5 Conclusions

This randomized study has demonstrated that in patients prior to hepatectomy for CRLM, prehabilitation appears to be feasible. It leads to a significant improvement in preoperative relative oxygen uptake at the anaerobic threshold, and a variety of other CPET variables. It also improves preoperative quality of life. This study was not powered to assess the affect of prehabilitation on postoperative outcome, and now its feasibility can be demonstrated future studies should be constructed to explore this further.

Chapter 5: Human liver slices as a model of hepatic function

5.1 Introduction

Patients with impaired hepatic function (cirrhosis), have poorer post surgical outcomes¹⁸⁸. Given that patients with better cardiopulmonary fitness have better post surgical outcomes, it could be postulated that patients with better CPET fitness have better hepatic function. Being able to correlate these factors would help allow tailoring of intervention and therapy. This could help reduce PHLF, thereby improving the safety profile of hepatectomy for CRLM.

There is some evidence to support this correlation in animals, possibly mediated by an improvement in gluconeogenic capacity¹⁷⁹. Unfortunately due to inaccessibility and limitations in the current models of hepatic functioning this relationship has not been adequately explored in humans¹⁸². A number of different models of hepatic functioning have been developed¹⁹⁷. The most common of these is primary human hepatocyte collection and incubation, which is often seen as the gold standard for toxicology studies¹⁹⁷. This technique has a number of limitations, most notably the absence of other cells and the hepatic matrix, which is important for cellular function. One alternative method of hepatic function study is the use of human liver slices.

These have the advantage of containing all hepatic cells within the structure of the liver⁵⁸.

Human liver slices are not a widely used model of study, primarily due to limited access to hepatic tissue, and their relatively time consuming production^{255,256}. The prime source of liver for hepatic slicing is from rejected transplant specimens, or from the edge of resected liver. Both of these sources are associated with prolonged time to slicing, which in conjunction with a variable operative trauma, contributes to the variability of function seen in samples²⁵⁶. This variability has also contributed to a failure in widespread uptake of the technique.

Liverpool University is home to the MRC Centre for Drug Safety Science, and the Liverpool Hepatobiliary Centre. The Liverpool Hepatobiliary Centre is a high volume, internationally recognised cancer resectional centre. The MRC Centre for Drug Safety Science is the UK's leading centre for investigation of drug safety science. A close collaboration between the centres has already led to a system for collection of primary hepatocytes from liver resection specimens²⁵⁷.

Liver slices are seen as a potential solution to the reducing frequency of samples large enough for primary hepatocytes, primarily as a result of increasing parenchymal preserving surgery. Human liver slices can be collected from the margin even of metastectomy samples.

The aims of this component of the thesis are to develop a model of hepatic function based on human liver slices and demonstrate it is feasible at the University of Liverpool.

5.2 Methods

5.2.1 Consent

The research was performed with full ethical approval (Appendix 1.1), and all candidates were consented for donation of tissue samples.

5.2.2 Sample Collection

5.2.2.1 Liver sample collection

Following appropriate patient information and informed consent, hepatic tissue cores were produced within the operating theatre to minimise warm ischemia time. Following removal from the abdomen the hepatic resection specimen was immediately placed on a sterile surface. Cores of tissue (diameter - 8mm) were collected manually using the technique described by *Fischer et al 1995*²⁵⁸. These were placed in ice cold pre-oxygenated Krebs-Henissett Buffer than had been pre-oxygenated with 95%O₂/5%CO₂ and transported to the laboratory.

Separately a sample of liver tissue and tumour tissue was collected using a scalpel from the resection specimen. These were placed in separate Eppendorf tubes and immediately frozen in liquid nitrogen before transfer to -80°C freezer (Sanyo Upright ultra low freezer MDFU72VC).

5.2.2.2 Muscle

The operating surgeon collected a small sample of skeletal muscle (2-4g) from the anterior abdominal wall. This was immediately snap frozen in liquid nitrogen, before transfer to a -80°C freezer (Sanyo Upright ultra low freezer MDFU72VC).

5.2.2.3 Serum

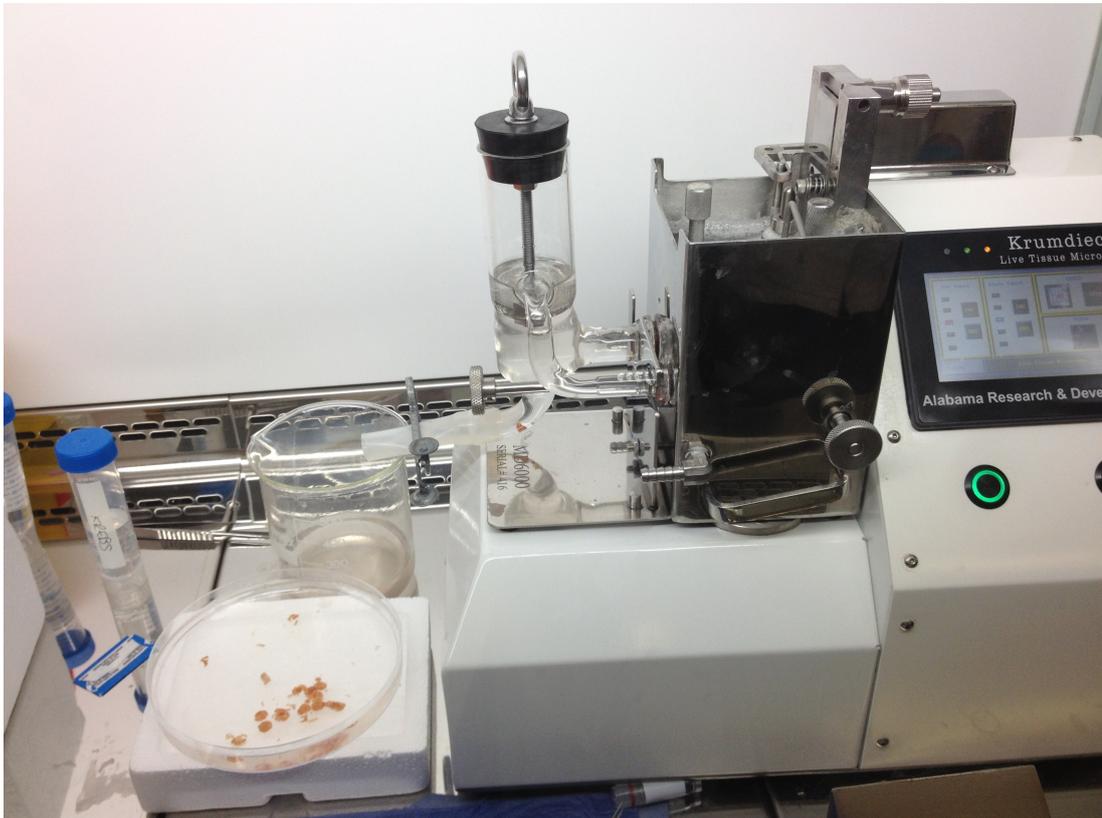
Blood was taken using standard phlebotomy technique at all study time points (baseline, post prehab/standard care, post op visit 1, post of visit 2). This was spun at 4°C, 13,000 rpm for 10 minutes, following which the serum was removed using a pipette and placed in an Eppendorf tube and stored at -80°C.

5.2.1 Production of hepatic slices

The ideal thickness of liver slices to facilitate uptake of oxygen and substrates during incubation has previously been established as 240 μm ²⁵⁹⁻²⁶¹.

The Krumdieck MD6000 slicer (Alabama Research and Development, Munford, USA)(Figure 5-1) was used to generate hepatic slices using the method described by *De Graaf et al* with the slicer set to 240 μm ⁵⁸.

Figure 5-1 Krumdiek MD6000slicer in use.



5.2.2 Incubation

All culture and media changes were conducted under sterile conditions. Slices for incubation were immediately transferred to 12 well plates containing 1.5 ml of the incubation medium, as per Dogterom 1993²⁶². This was pre-incubated for 90 minutes to allow for cells traumatised during the slicing period to die, and other cells to restore potassium and ATP levels²⁶⁰. At this point slices were transferred using fine forceps to pre-warmed, pre-prepared 12 well plates containing 1.5ml of incubation medium at 37°C. Media changes were conducted at 24 hours as per deGraff⁵⁸. Slices were

harvested at baseline, immediately following pre-incubation, then following pre-incubation at 1,2,4,12,24,48, and 72 hours.

5.2.3 Viability assessment

Viability was assessed with ATP and mitochondrial function.

5.2.3.1 ATP assessment

Samples were placed in round-bottomed 2ml Eppendorfs containing ATP collection solution. These were snap frozen in liquid nitrogen until time of ATP analysis.

Samples were defrosted on ice, before tissue disruption with a microbead beater and centrifuged at 13,000 rpm, for 3 minutes at 4°C to form a pellet cell debris and a supernatant. The pellet was then dissolved in 1ml of 0.5 M NaOH (> 2h, 60°C), for subsequent protein estimation

ATP analysis was carried out using the CellTiter-Glo Luminescent Cell viability assay (Promega, Madison, USA). The ATP standards were prepared using Adenosine 5'-triphosphate disodium salt, (Sigma-Aldrich, Gillingham, UK). All values were expressed in relation to the protein content of the slice.

5.2.3.2 Mitochondrial activity assessment

Mitochondrial activity was measured on the day of the incubation by the Resazurin test A 12 well plate for conduct of the assay was made up and placed in an incubator prior to the experiment. Each well contained 1350 µL

of Krebs buffer, which was allowed to equalise with the incubator temperature prior to the assay.

At the selected time point a slice was transferred into one of the wells on the assay plate, and 150 μ L (10% of total well volume) of Resazurin solution (Sigma-Aldrich, Gillingham, UK) was added.. The plate was incubated for 90 minutes, following which the slice was placed in a round-bottomed 2ml Eppendorf and snap frozen in liquid nitrogen for future estimation of protein content.

To measure fluorescence, 100 μ L of the study solution was added to a 96-well black plate, running samples in triplicate. A plate reader at 560nm then read this.

5.2.3.3 Protein assessment

Total protein concentration was determined using the method described by Lowry et al (1951)²⁶³.

5.2.4 Functional assessment

5.2.4.1 Albumin production

Following a 4-hour incubation, albumin concentration in the incubation medium was assessed using the Human ELISA Quantification Kit (Bethyl Laboratories, Cambridge Bioscience, Cambridge UK).

5.2.4.2 Glucose Production

Slices were removed from incubation media and incubated in Krebs-Henseleit Buffer (KHB) without Glucose. At 90 minutes supernatant was removed and glucose concentration estimated using the Glucose Oxidase estimation kit (Sigma-Aldrich, Gillingham, UK).

5.2.1 Solutions used in laboratory analysis

There are a number of solutions used within the study and their production methodology and composition is described below.

5.2.1.1 Liver collection and transport media

Cores of Liver tissue were collected using 1x HEPES solution (Fisher Scientific UK, Loughborough).

5.2.1.2 Incubation media

This was made up using phenol-free Williams E media (Sigma-Aldrich, Gillingham, UK) supplemented with 2 mM glutamine (Sigma-Aldrich, Gillingham, UK), penicillin-streptomycin (100 U/mL penicillin; 100 µg/mL streptomycin; invitrogen), 100 nM dexamethasone (Sigma-Aldrich, Gillingham, UK) and 1 X soln. ITG-S (Life-Technologies, Carlsbad, USA). All concentrations are final concentrations.

5.2.1.3 Standard Krebs-Henseleit Buffer

A 10× concentrated KHB stock solution (10× KHB) was produced. First 3.67 g $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ was dissolved in 0.5 litres of ultrapure water. Then 3.73 g KCl, 69 g NaCl, 2.71 g $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ and 1.63 g KH_2PO_4 were dissolved in a separate 0.5 litres of ultrapure water. Subsequently, the 2 solutions were mixed together and stored at 4 °C (stable for 6 months)⁵⁸.

On the day of the slice experiment, 2 litres of KHB was prepared by dissolving 4.2 g NaHCO_3 , 9.9 g d-glucose monohydrate and 4.76 g HEPES in about 0.8 litres of ultrapure water at 4 °C. Following this 200 ml 10× KHB, and 1 litre of ultrapure water at 4 °C were mixed. This was kept at 0–4 °C on melting ice, and oxygenated with 95% O_2 /5% CO_2 for at least 30 minutes before use. The pH was measured and standardised to pH 7.4.

5.2.1.4 Krebs-Henseleit Buffer without Glucose

KHB buffer without glucose was prepared in a similar manner to standard KHB (Chapter 5.2.1.3), except that instead of d-glucose monohydrate, L-lactate (Sigma-Aldrich, Gillingham, UK) was added to a final concentration of 20mM/l.

5.2.1.5 ATP collection

To prepare 500 ml of the ATP collection solution, 0.372 g EDTA was dissolved in 100 ml of ultrapure water. The pH was adjusted with 5 M NaOH to obtain a pH of 10.9. Ultrapure water was added to the solution to obtain a

volume of 130 ml. This was supplemented with 370 ml ethanol (96%). This solution can be stored at 4 °C for approximately 3 months.

5.2.1.6 ATP dilution solution

To prepare 1 litre of the ATP dilution solution, 900ml of ultrapure water was combined with 100 ml of the ATP collection solution. This can be stored for 1 month at 4 °C.

5.2.2 Histological analysis

Slices were stored in 10% neutral buffered formalin solution (Sigma-Aldrich, Gillingham, UK). One patient who underwent full 72-hour culture was randomly selected for analysis.

The slices were processed and paraffin embedded by trained pathology staff at Leahurst School of Veterinary Science, Neston, UK.

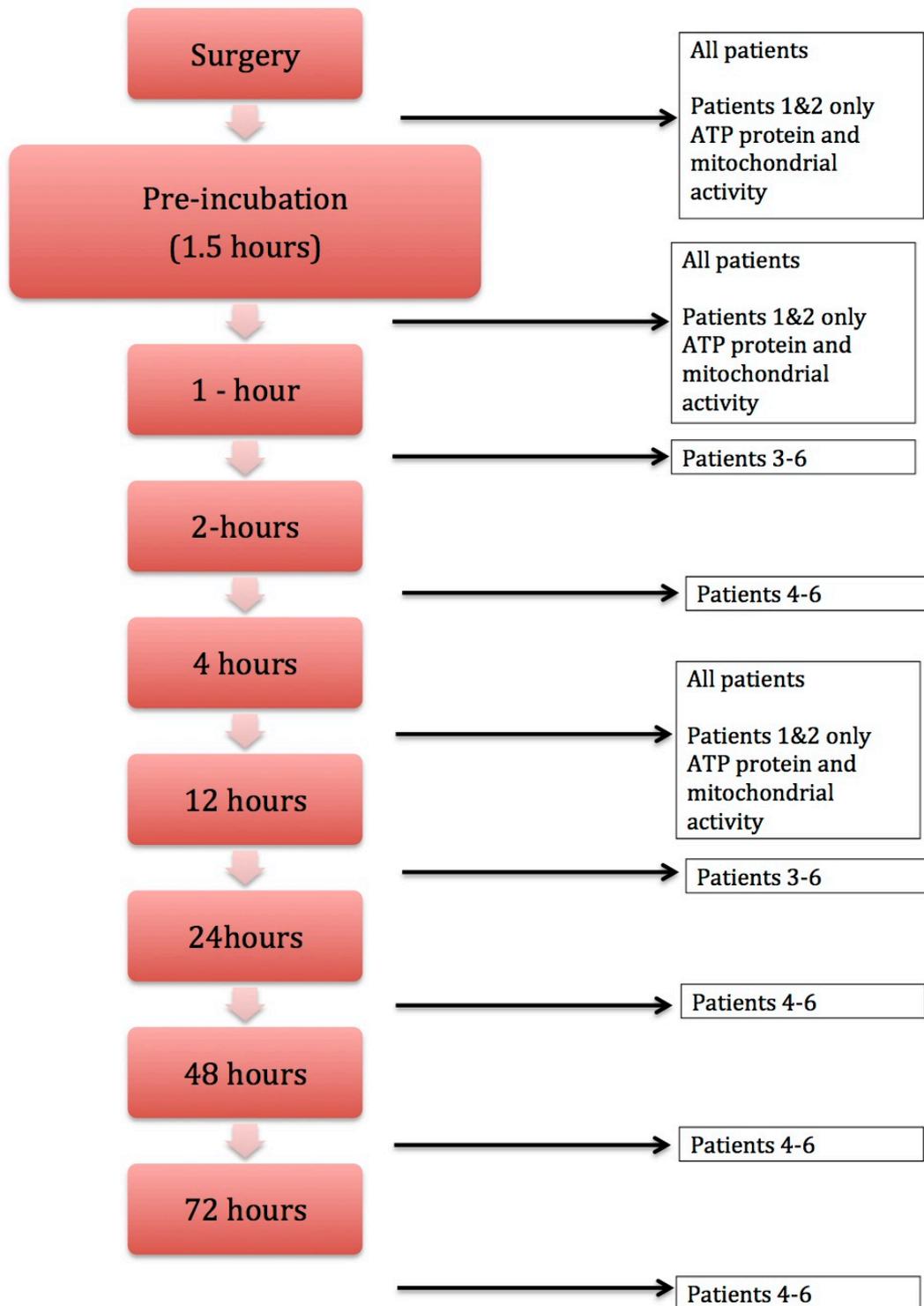
Slices were then sent to a histopathologist for analysis using standard techniques.

5.2.3 Study conduct

Samples were analysed from a variety of different time points. The overall pathway is summarised in Figure 5-2.

There was limited quantity of available tissue from patient 3 which curtailed the experiments that could be performed.

Figure 5-2 Tissue collection points



5.3 Results

5.3.1 Patient Demographics

After method development six patient samples underwent hepatic slicing. The slices obtained were used for a variety of experiments. Patient demographics are summarised in Table 5-1. There were three men and three women, aged 47 – 76. Three had undergone prior chemotherapy, two as neo-adjuvant for their hepatic resection; this was completed at 44 weeks, 20 weeks and 7 weeks respectively prior to hepatic resection. All 3 received a standard chemotherapy regimen with oxaliplatin and capecitabine. Five of the patients had underlying metastatic colorectal cancer, and one had hepatocellular carcinoma without evidence of cirrhosis. Patients had little comorbidity, though patients 5 and 6 self reported poor (patient's subjective assessment) recent activity levels, with patient 5 struggling for many months with chronic pelvic sepsis, and patient 6 suffering from chronic fatigue syndrome.

Steatosis was present in all patients histologically. Patient 4 had evidence of sinusoidal obstruction, thought to relate to the size of his hepatic tumour (13cm HCC). No patients had any chronic liver disease or cirrhosis.

Table 5-1 Demographics of patients undergoing slicing

Variable	Patient					
	1	2	3	4	5	6
Sex	Male	Female	Male	Male	Female	Female
Age	62	54	76	74	58	47
Comorbidities	Hypertension	Hypothyroid	Hypertension Gastritis	Hypertension Asthma	Hypertension Hypothyroid Pelvic sepsis post anterior resection	ME Depression
Reason for Hepatectomy	CRLM	CRLM	CRLM	HCC	CRLM	CRLM
Medication	Lisinopril Bendroflumethiazide	Thyroxine	Amlodipine Lansoprazole	Amlodipine Perindopril Seritide Salbutamol	Tramadol Amlodipine Thyroxine	Fluoxetine
Prior Chemotherapy	NO	Yes	No	No	Yes	Yes
Time finished before surgery (Weeks)	N/A	20	N/A	N/A	44	7
Chemotherapy agents (cycles)	N/A	6 cycles Oxaliplatin Capecitabine	N/A	N/A	6 cycles Oxaliplatin Capecitabine	6 cycles Oxaliplatin Capecitabine
Histological evidence of liver damage	Steatosis	Steatosis	Minimal Steatosis	Mild Sinusoidal dilatation	Mild steatosis and portal inflammation	Normal

5.3.1.1 Preoperative blood tests

Preoperative blood results are summarised in Table 5-2. No patient was anaemic. Patient two had an elevated platelet count, thought to be a post inflammatory response to an episode of bowel obstruction, treated by the insertion of a colonic stent two weeks prior to hepatic resection. No patient had biochemical evidence of renal impairment or hepatic impairment.

Table 5-2 Preoperative blood tests of patients

Variable	Patient					
	1	2	3	4	5	6
Hb (g/dL)	13.3	13.5	14.9	14.3	13.0	12.7
WCC (10 ⁹ /L)	12.6	11.2	6.9	7.2	5.9	8.4
Plt (10 ⁹ /L)	238	561	225	346	197	402
Urea (mmol/L)	5.1	5.0	5.1	4.4	6.6	4.4
Creatinine (umol/L)	97	68	107	66	76	67
Albumin (g/L)	44	45	49	47	46	44
Bilirubin (umol/L)	30	4	9	7	5	5
ALT (u/L)	16	23	22	15	22	20
Alkaline Phosphatase (u/L)	72	119	93	138	176	151
INR	1.0	1.0	1.0	1.1	1.0	1.1
Prothrombin Time (seconds)	10.9	10.9	10.8	11.3	10.9	11.4
APPT (seconds)	27.9	N/A	28.9	N/A	25.3	N/A

5.3.1.2 Patient CPET values

All patients had undergone cardiopulmonary exercise testing and their results are summarised in Table 5-3. Patients 4, 5 and 6 were of lower fitness levels (AT <11 than patients 1, 2 and 3 (AT >11). All CPET variables for these patients were markedly depressed throughout.

Table 5-3 CPET values

		Candidate					
		1	2	3	4	5	6
Days before surgery of test		9	1	55	69	50	9
Height (cm)		182	165	165	176	160	166
Weight (kg)		104	64	81	83	53	77
BMI (kg/m ²)		31.6	23.5	29.8	26.9	20.9	27.9
REST	VO2/KG (ml/kg/min)	3.2	3.8	4.0	4.0	4.6	3.1
	Absolute VO2 l/min	0.33	0.24	0.32	0.33	0.25	0.24
	o2 pulse	3.5	3.0	3.5	5.0	2.5	2.3
	VE/Vo2	28.7	33.8	34.7	33.5	35.4	42.3
	VE/VCO2	38.9	35.2	37.8	39.8	40.8	39.6
	HR	93	81	92	67	98	102
	RER	0.74	0.96	0.92	0.84	0.87	1.04
AT	VO2/KG (ml/kg/min)	11.6	12.4	12.0	8.8	9.6	6.1
	Absolute VO2 l/min	1.21	0.79	0.97	0.73	0.51	0.47
	o2 pulse	10.5	7.0	8.4	8.6	4.9	4.5
	VE/Vo2	28.4	29.6	31.7	32.3	35.4	27.4
	VE/VCO2	34.1	30.0	34.4	36.4	37.9	29.1
	Wattage	70	60	58	62	20	32
	HR	115	114	116	87	105	105
	RER	0.83	0.99	0.90	0.88	0.94	0.94
VO2 peak	VO2/KG (ml/kg/min)	15.9	19.4	16.8	11.3	14.8	14.0
	Absolute VO2 l/min	1.65	1.24	1.36	0.94	0.79	1.08
	o2 pulse	11.5	7.9	9.8	11.0	6.2	7.5
	VE/Vo2	38.1	50.6	38.3	32.5	36.8	39.8
	VE/VCO2	33.2	36.0	34.8	36.5	31.9	31.7
	Wattage	166	108	104	76	68	116
	HR	144	158	139	84	127	144
	RER	1.15	1.41	1.10	0.89	1.16	1.26
Delta HR1	HR response to AT (bpm)	22	33	24	20	7	3
Delta HR 2	HR reserve (bpm)	51	77	47	*	29	42

*Developed AF at peak exercise, patient also on beta-blockade.

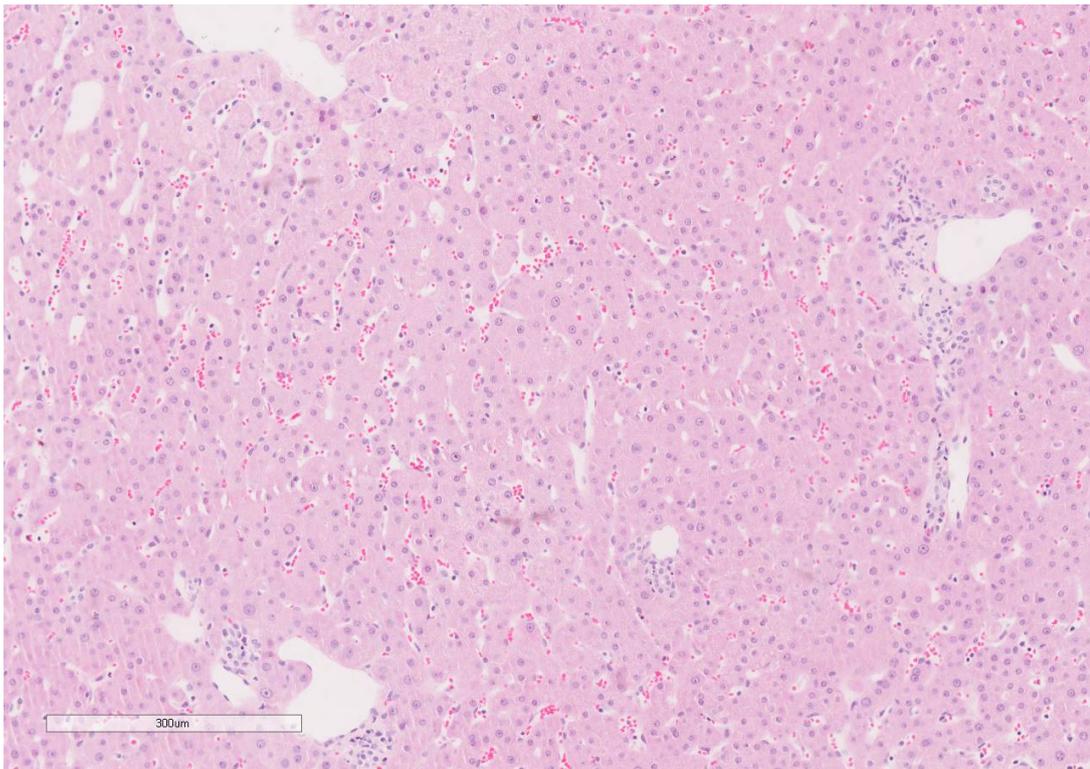
5.3.2 Histological analysis

Histological analysis of slices was conducted on one patient (patient 4) over a full time course.

5.3.2.1 Initial histological analysis

All three slices demonstrated liver tissue with portal tracts. The hepatocytes were normal, with lightly eosinophilic finely granular cytoplasm and minimal nuclear pleomorphism. There was no evidence of steatosis or cholestasis. Slight sinusoidal congestion; in keeping obstruction due to tumour, was evident. The portal tracts were normal.

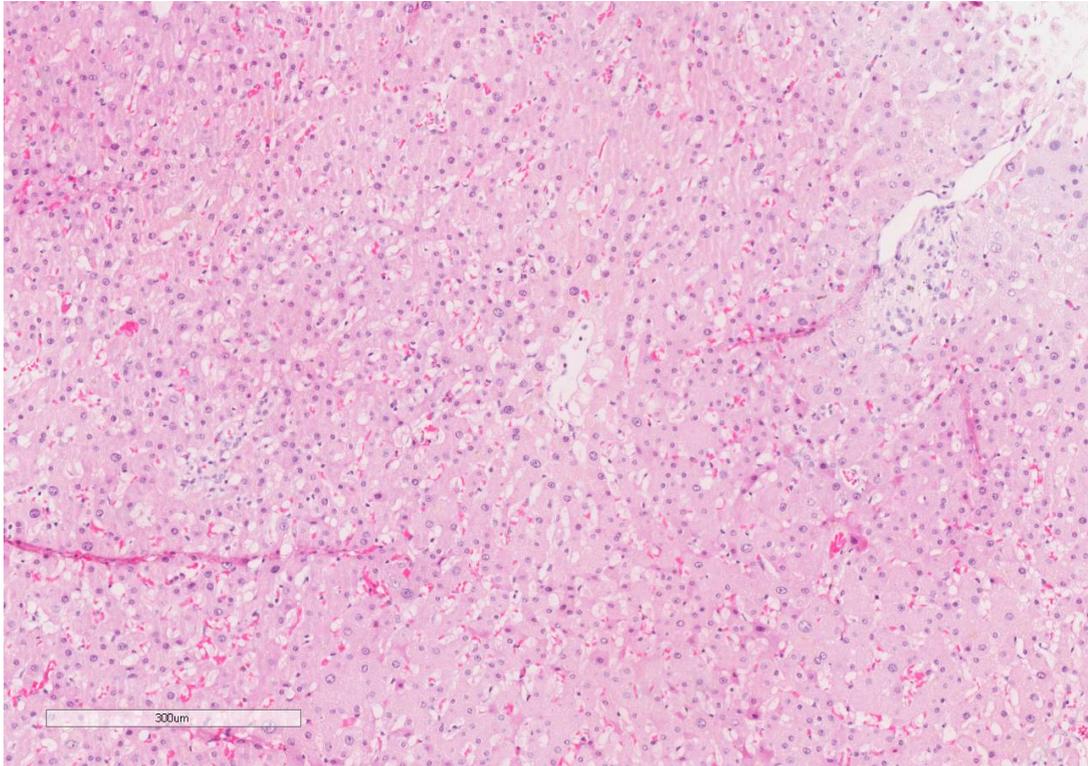
Figure 5-3. H+E stain of liver slice at x110 magnification demonstrating normal hepatic structure with slight sinusoidal congestion.



5.3.2.2 Post pre-incubation until 4 hours

Following pre-incubation the slices all retain normal architecture, with no histological change. By one hour there are very occasional acidophilic hepatocytes (represents dying hepatocytes)(<1 per $\times 4$ field), which gradually increase in frequency to 4 hours. By 4 hours acidophilic hepatocytes are counted at 2-6 per $\times 10$ field. By 2 hours there is very slight enlargement of some hepatocytes, which is similar up until 4 hours. Sinusoidal dilatation starts to develop at 2 hours. In one of the slices at 4 hours this has progressed to sinusoidal congestion. This is the slice with the most evidence of other inflammatory change including acidophilic hepatocytes. At four hours there is evidence of increasing eosinophilic granular change to the cytoplasm in all slices.

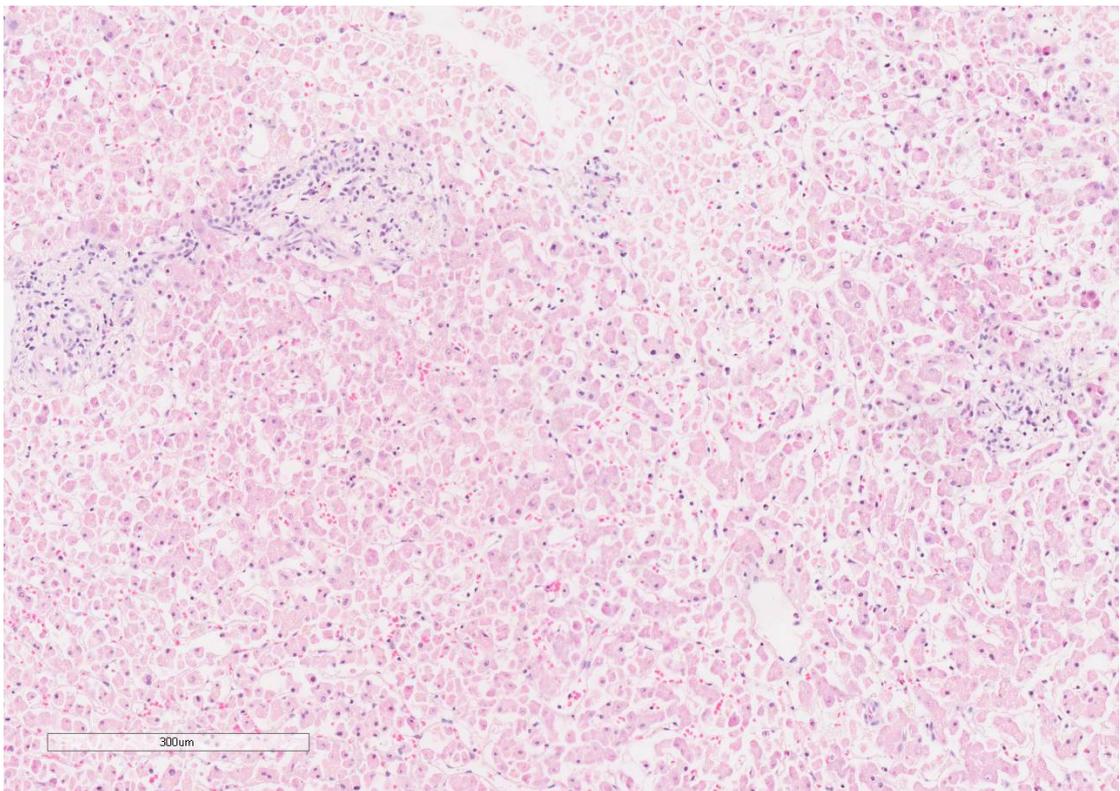
Figure 5-4 H+E stain of liver slice 4 hours post incubation at x110 magnification, demonstrating increasing eosinophilic granular change.



5.3.2.3 12-24 hours following pre-incubation

At 12 hours there is significant histological change with a loss of cohesiveness of hepatocytes, and evidence of nuclear pyknosis. There is evidence of individual hepatocyte necrosis/apoptosis. These changes are progressive by 24 hours, with zones of enlarged vacuolated hepatocytes developing. These hepatocytes contain enlarged nuclei. These changes occur mainly in the peri-portal areas. In non-portal areas cellular morphology is preserved with minimal cytoplasmic and nuclear changes.

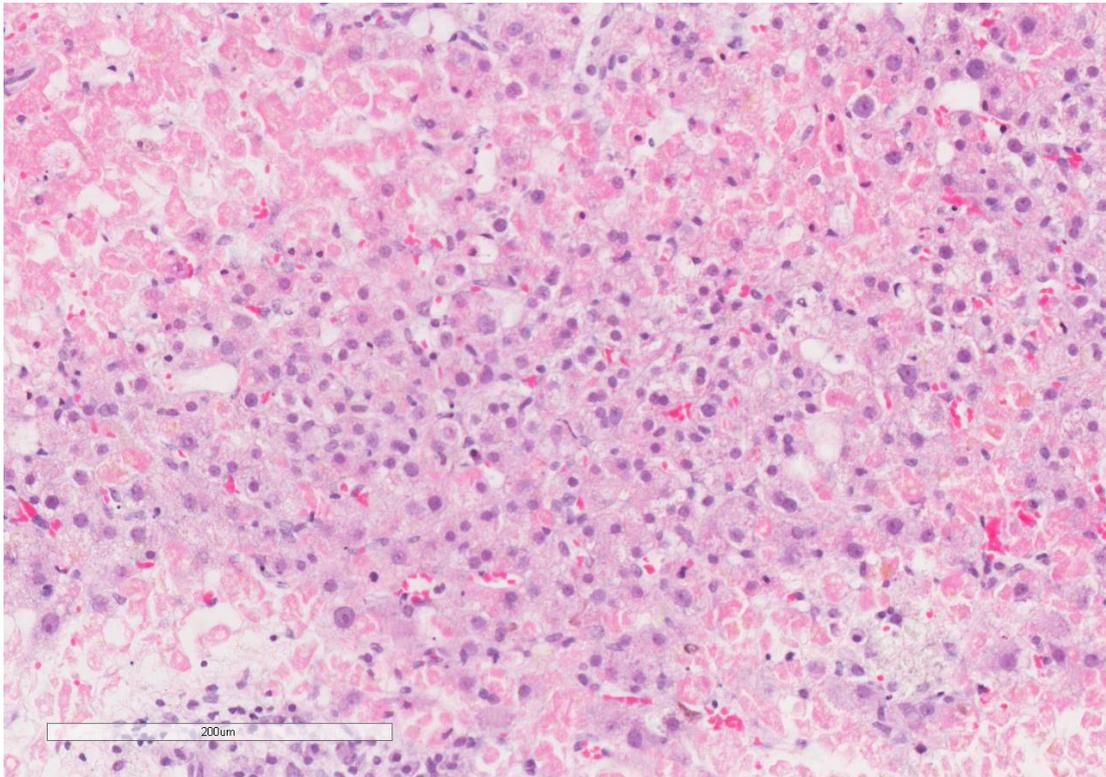
Figure 5-5 +E stain of liver slice 24 hours post incubation at x110 magnification demonstrating some peri-portal hepatocyte necrosis but preservation of cellular morphology elsewhere.



5.3.2.4 48-72 hours post pre-incubation

At 48 hours the inflammatory changes seen at 24 hours have progressed, with increasing numbers of necrotic hepatocytes. There are, however, still sections of viable hepatocytes, though within these sections there are occasional ballooned hepatocytes. The necrotic changes are predominantly centred around the portal tracts. These changes are progressive at 72 hours with increasing necrotic hepatocytes, though even at 72 hours there remain sections of viable hepatocytes.

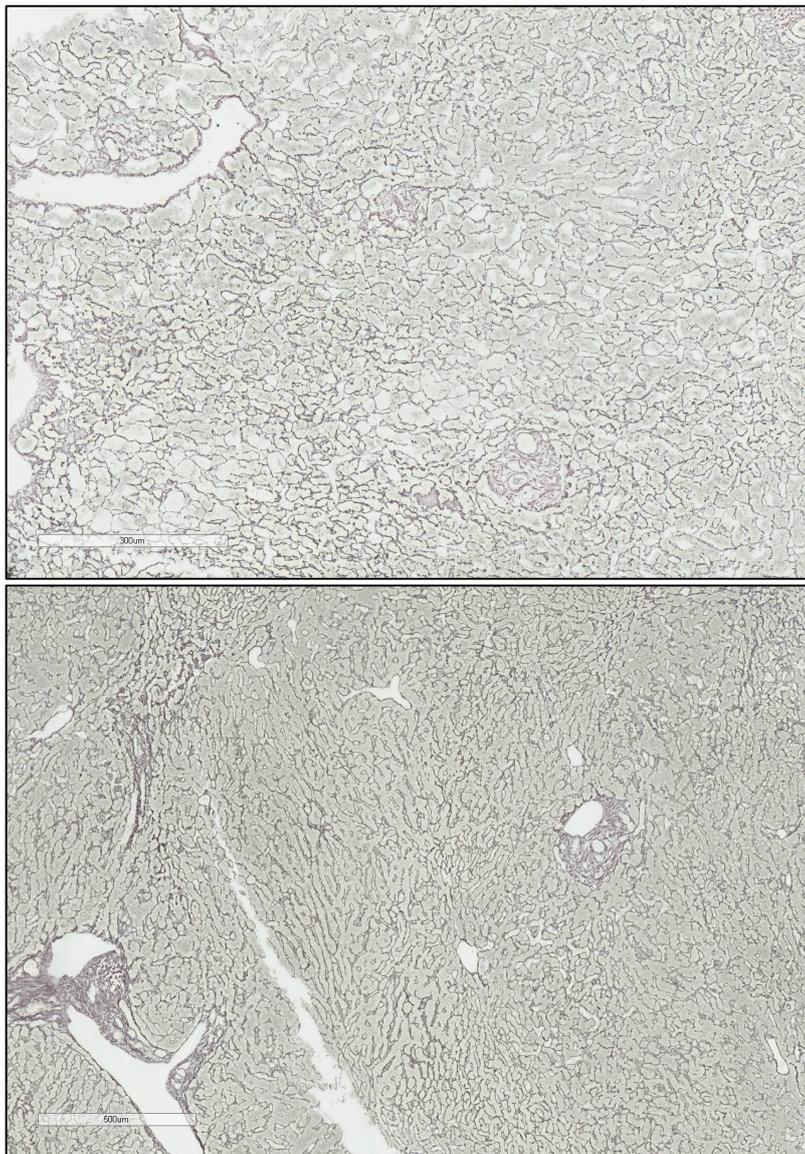
Figure 5-6 +E stain of liver slice 72 hours post incubation at x110 magnification demonstrating preservation of viable hepatocytes.



5.3.2.5 Histological assessment of intracellular matrix

The cellular matrix was assessed using reticulin staining. This demonstrated good preservation of the extracellular matrix.

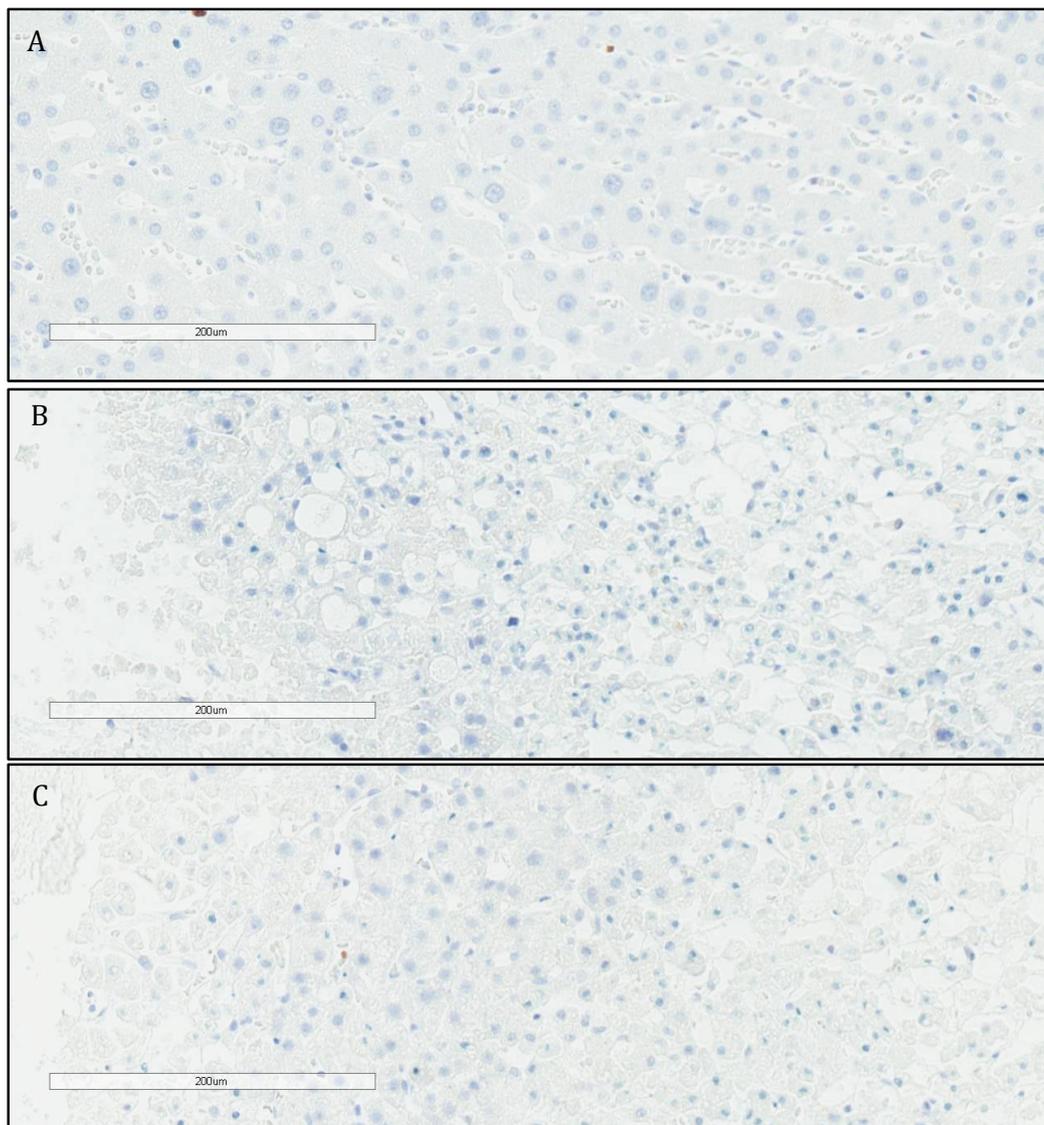
Figure 5-7 Reticulin staining of initial slice (Top) at x90 magnification and at 72 hours (Lower) at x50 magnification demonstrating good preservation of the extracellular matrix.



5.3.2.6 Ki 67 Staining

Cellular proliferation was assessed using Ki 67 and Vimentin staining. There was little demonstrable increase in cellular proliferation during the course of the incubation. The Ki67 stains are shown below to illustrate this.

Figure 5-8 Vimentin staining of liver slices at x225 magnification demonstrating no increase in Ki-67 over the course of the incubation.



A - Initial, B - 24 hours, C - 72 hours

5.3.3 Viability Assays

5.3.3.1 ATP

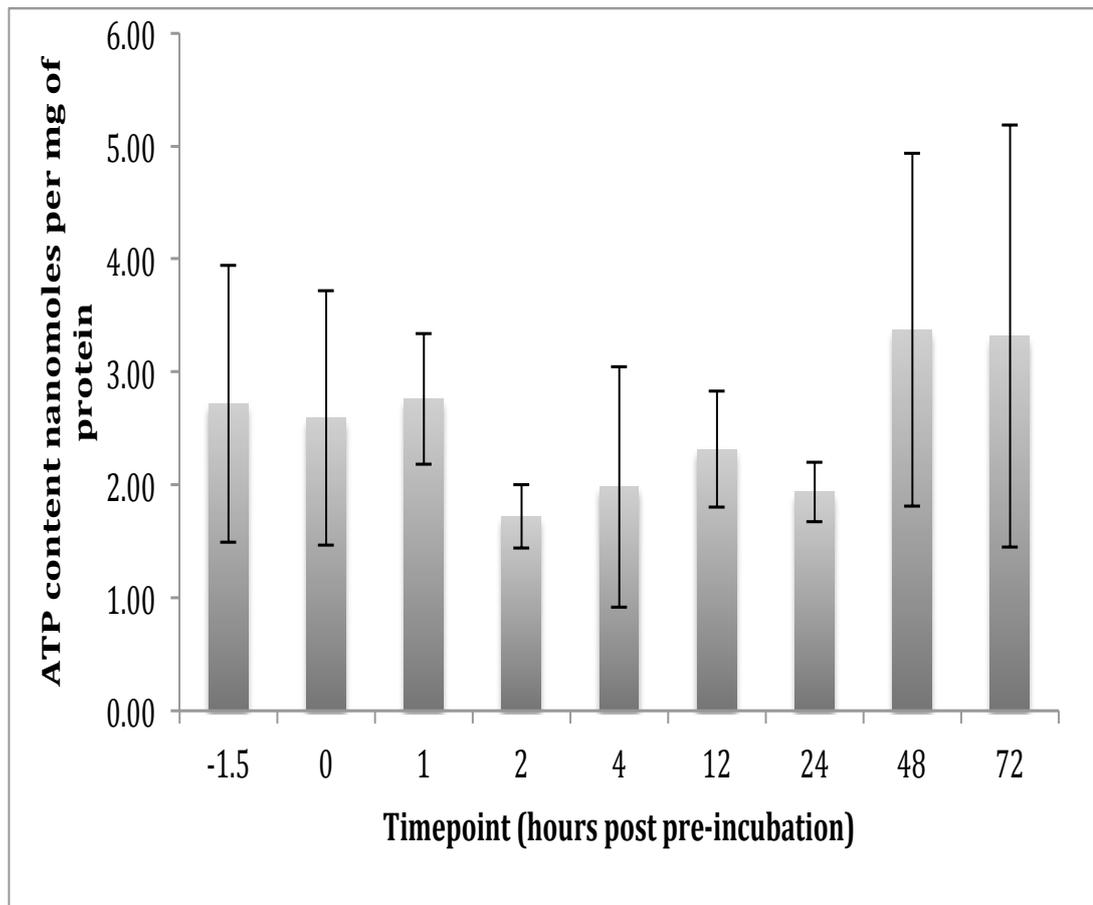
ATP was measured at baseline, immediately following pre-incubation, and then at 1, 2, 4, 12, 24, 48 and 72 hours following pre-incubation. Patients 1 and 2 only had one slice run at time points baseline, following pre-incubation, and at 4 hours. Patient 3 had 3 slices taken at time-points baseline, following pre-incubation, and then at 4 and 24 hours. Patients 4 - 6 had 3 slices run at each time point. Results are expressed relative to the protein content of the slices, as nanomoles ATP per mg protein. An ATP ratio of 2 nanomoles per mg of protein has previously been reported as representing viability⁵⁸. Mean ATP at baseline was 2.72nm/mg (SD 1.23), Patients 1-4 had values typically in excess of 2nm/mg. Patients 5 and 6 had values significantly below this threshold, with a mean ATP content of 1.48 nm/mg protein (SD 0.52 nm/mg protein). Despite this suggested non-viability, as can be seen from the other assays, these slices appeared to retain viability and preservation of function through to 72 hours.

ATP content was preserved throughout the incubation period, with no discernable reduction relative to protein content (Figure 5-9 & Table 5-4). This suggests preservation of viable cells during the time-course.

Table 5-4 ATP content of slices, expressed relative to protein in nanomoles per mg of protein.

Time Point		Patient					
		1	2	3	4	5	6
initial	Slice 1	3.81	2.59	3.24	4.06	1.61	1.14
	Slice 2			2.04	4.21	2.14	0.74
	Slice 3			2.34	4.95	1.95	1.28
Post Pre Incubation	Slice 1	3.88	3.16	1.47	3.84	1.81	2.68
	Slice 2			1.64	4.18	1.55	1.83
	Slice 3			1.29	3.15	0.94	1.15
1 HR	Slice 1				3.35	1.76	2.29
	Slice 2				3.49	1.33	3.61
	Slice 3				2.39	3.18	3.42
2HR	Slice 1				2.34	0.98	1.47
	Slice 2				1.03	1.76	2.28
	Slice 3				2.39	1.46	1.76
4 HR	Slice 1	4.05	1.78	1.59	2.84	1.17	1.05
	Slice 2			1.63	1.05	0.88	1.29
	Slice 3			2.10	1.90	0.96	1.76
12 HR	Slice 1				4.07	2.11	2.27
	Slice 2				2.02	1.78	2.17
	Slice 3				2.47	1.61	2.33
24 HR	Slice 1			1.89	2.24	2.40	1.61
	Slice 2			2.01	2.96	1.70	1.41
	Slice 3			2.00	1.59	1.57	1.86
48 HR	Slice 1				5.24	1.90	3.16
	Slice 2				2.70	1.48	3.05
	Slice 3				7.12	2.36	3.34
72 HR	Slice 1				3.03	2.46	1.96
	Slice 2				9.12	2.28	2.22
	Slice 3				4.26	2.30	2.22

Figure 5-9 Graph showing ATP content over time, expressed per mg of protein



5.3.3.2 Protein content

Mean protein content per slice at baseline ranged from 1.37mg to 3.26mg (Table 5-5), however the intra-patient variability was small suggesting that slices from patients were similar, with the variability reflecting physical differences between the hepatic tissue of patients.

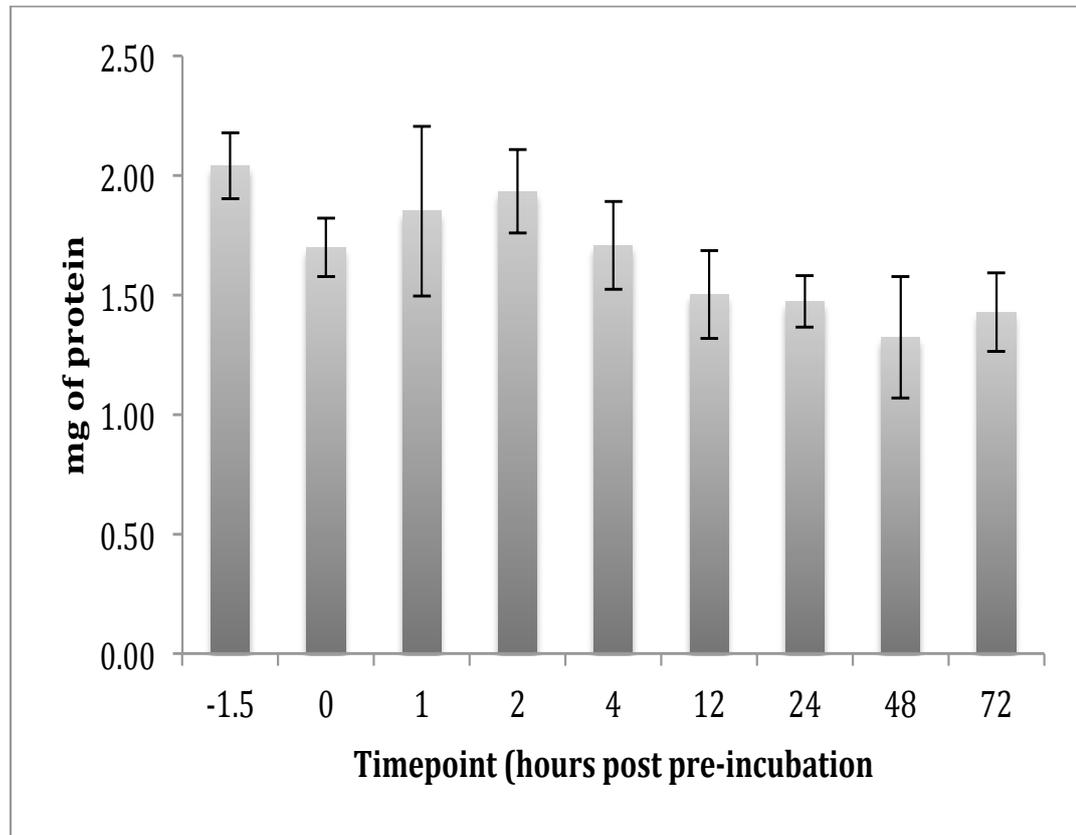
Table 5-5 Mean protein content of slices per patient, expressed in mg

Patient	Mean protein content mg (Standard deviation)					
	1	2	3	4	5	6
Initial	1.37 (0.07)	1.96 (0.06)	1.50 (0.19)	1.85 (0.31)	3.26 (0.11)	2.30 (0.09)
Post Pre-incubation	1.29 (0.03)	1.51 (0.39)	1.66 (0.04)	0.98 (0.06)	2.91 (0.09)	1.85 (0.13)
1 HR				1.38 (0.46)	2.65 (0.32)	1.52 (0.28)
2HR				1.30 (0.33)	2.48 (0.04)	2.03 (0.16)
4 HR	0.96 (0.27)	1.62 (0.04)	1.39 (0.18)	1.69 (0.18)	2.65 (0.25)	1.94 (0.19)
12HR				1.23 (0.16)	1.73 (0.21)	1.55 (0.18)
24 HR			1.18 (0.04)	1.34 (0.32)	1.85 (0.13)	1.52 (0.06)
48 HR				0.95 (0.57)	1.64 (0.13)	1.38 (0.06)
72 HR				0.89 (0.38)	1.63 (0.01)	1.77 (0.10)

Over time there was a drop in the protein content of slices. By 4 hours the reduction was between 8-30% of the initial weight, and by 72 hours the slices had lost between 23-52% of their initial protein content. There appeared to be an initial drop in protein content after pre-incubation followed by a recovery (Figure 5-10). This may be a reflection of the failure to take slices

from patients 1-3 at 1 and 2 hours, but could also represent the theoretical shedding of damaged cells on the cut surfaces during the pre-incubation period followed by a recovery of cellular protein.

Figure 5-10 Protein content change over time (mg)



5.3.4 Functional Assays

5.3.4.1 Mitochondrial Activity

Mitochondrial activity was measured for all patients with the exception of patient 3 where tissue was limited and it was elected to pursue other assays as a priority. Mitochondrial activity was available corrected for the protein content of the slice for patients 4-6, through to 72 hours. In patients 1 and 2 mitochondrial activity was not corrected for the protein content of the slices used for the study and protein content was estimated using the slices obtained for ATP content, thus allowing comparison of all 5 patients studied. Patients 1 and 2 only had mitochondrial activity measured through to 4 hours.

There was a consistent pattern in mitochondrial activity with a peak activity observed at 12 hours (Table 5-6 and Figure 5-11). Activity then levelled out at a level similar to that observed at 4 hours, and remained constant over the 72-hour incubation.

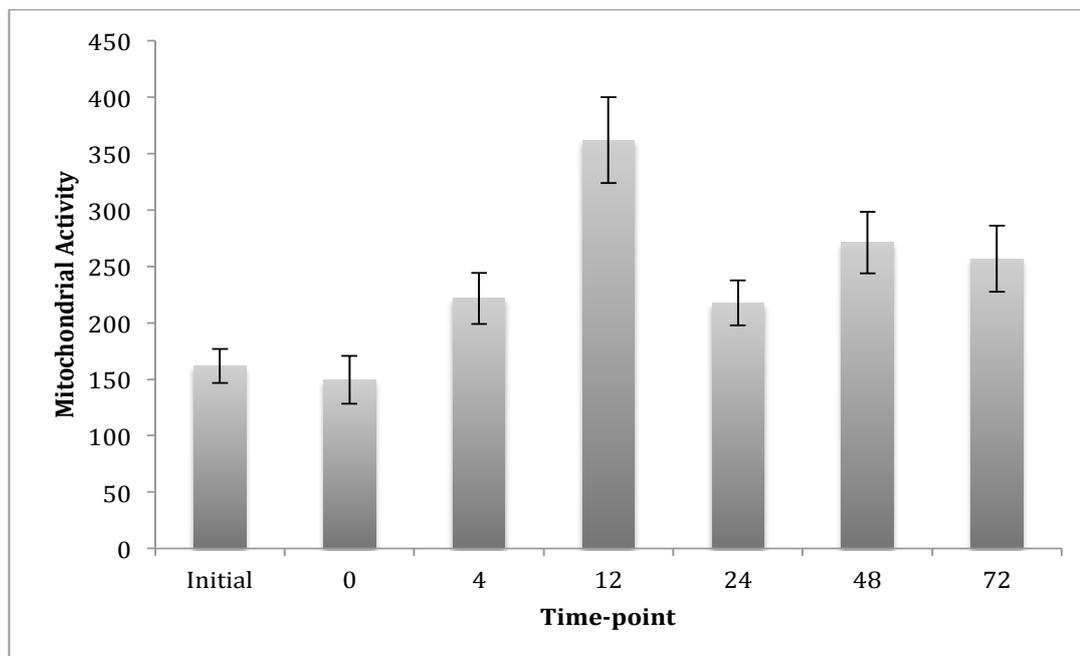
There was limited inter, and intra patient variability. The variations that were seen likely reflect variation in slice quality, incubation success and trauma sustained during collection and slicing.

Table 5-6 Mitochondrial Activity expressed relative to slice protein content (standard deviation)

	Time point						
	Initial	0	4	12	24	48	72
Patient 1	177* +/- (38)	155* +/- (15)	228* +/- (14)				
Patient 2	174* +/- (14)	163* +/- (43)	250* +/- (30)				
Patient 4	120+/- (4)	137+/- (12)	275+/- (37)	329+/- (21)	239+/- (18)	308+/- (45)	195+/- (35)
Patient 5	142 +/- (15)	151+/- (30)	183+/- (15)	423+/- (39)	170+/- (16)	184+/- (8)	246+/- (17)
Patient 6	195 +/- (5)	142+/- (6)	173+/- (17)	334+/- (54)	244+/- (26)	321+/- (29)	330+/- (36)
Average	162+/- (15)	150+/- (21)	222+/- (23)	362+/- (38)	218+/- (20)	271+/- (27)	257+/- (29)

*estimated protein content of slice based on alternative slices

Figure 5-11 Chart demonstrating average mitochondrial activity relative to protein content for all slices.



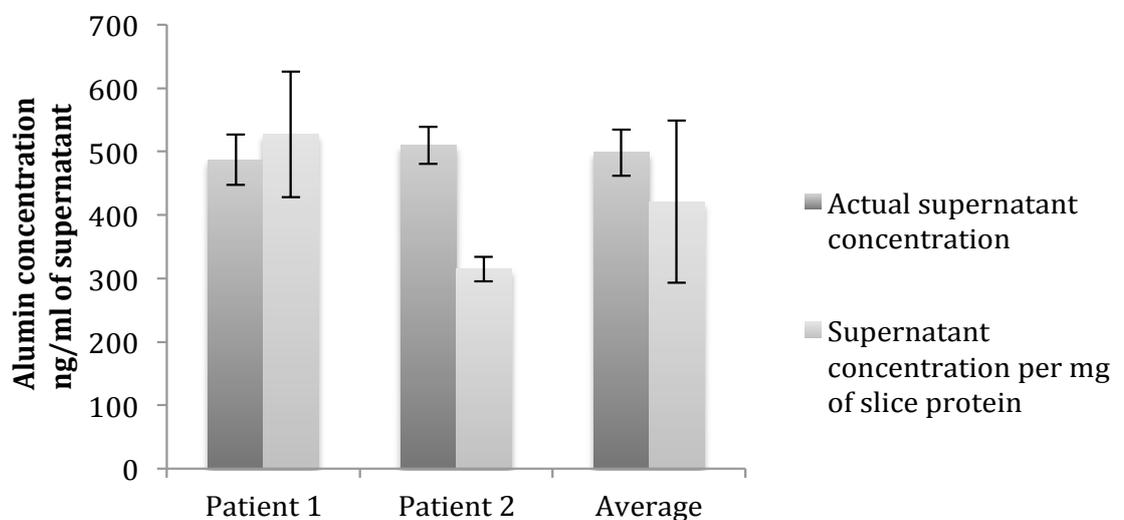
5.3.4.2 Albumin Production

Albumin production was measured in two patients (1 and 2). Albumin concentration in the supernatant after a 4-hour incubation is summarised in Table 5-7, and Figure 5-12. All slices demonstrated the ability to release albumin into the supernatant. There was a narrow range of albumin concentrations at 4 hours (498ng/ml +/- 37ng/ml), this is regardless of the slice protein content.

Table 5-7 Mean albumin concentration in supernatant after a four-hour incubation

	Albumin concentration ng/ml (Standard deviation)	Albumin concentration per mg of slice protein (ng/ml) (Standard deviation)
Patient 1	487 (+/- 40)	527.08 (+/- 99)
Patient 2	510 (+/- 29)	314.32 (+/- 19)
Mean	498 (+/- 37)	420.70 (+/- 128)

Figure 5-12 Graph depicting albumin concentration in the supernatant following a four-hour incubation



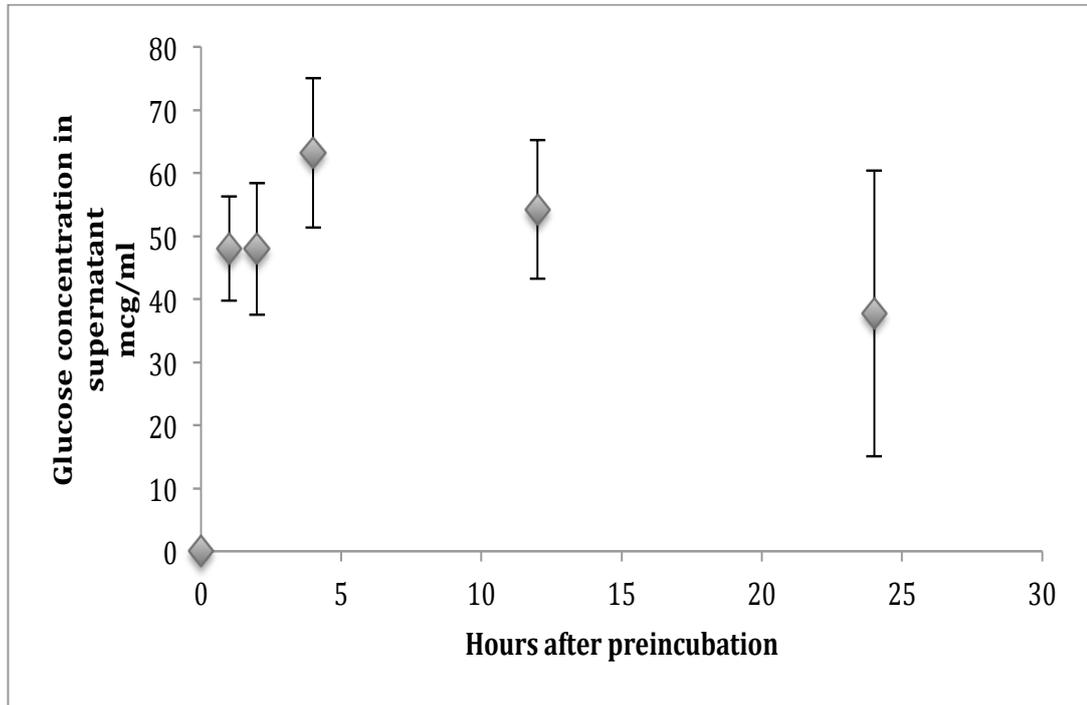
5.3.4.3 Glucose production

Glucose production into the supernatant was measured in 3 patients (4-6) (Table 5-8 and Figure 5-13). Patients 4 and 5 underwent culture to 72 hours, with patient 6 undergoing culture to 12 hours. The reduction in culture time was due to a rapid drop of glucose concentration in the media by 24 hours. The glucose concentration was not related to protein content of individual slices. Glucose concentration in the supernatant went from 0 mcg/ml at baseline to a maximum of 63 mcg/ml by 12 hours. The drop in glucose concentration by 24-72 hours was likely related to the culture media being inadequate for long cultures, and the absence of any prophylaxis to infection.

Table 5-8 Glucose concentration of supernatant

Time (Hours)	Mean Glucose concentration of supernatant (mcg/ml)			
	Patient 4	Patient 5	Patient 6	Average
0	0.00	0.00	0.00	0.00
1	38.85	50.08	54.97	47.97
2	36.24	51.18	56.34	47.92
4	49.92	72.74	67.02	63.23
12	48.71	66.92	47.01	54.21
24	53.74	21.70	N/A	37.72

Figure 5-13 Graph showing glucose concentration in supernatant



5.4 Conclusions

This chapter has demonstrated the success of our human liver slice model, with viable tissue at 72 hours post resection.

The results obtained in this study are difficult to compare to previously published work on PCLS²⁶⁴. Primarily this is due to the relative infrequency of using human tissue in such models. A comprehensive review of the characteristics and pharmaco-toxicology of PCLS identified only a handful of studies utilising human tissue²⁶⁴. None of the human studies used the ATP measure.

De Graaf et al suggested that an ATP of less than 2nmol mg^{-1} protein in a liver slice was non viable⁵⁸. We utilised slightly different methodology, and consequently our results are not directly comparable. However we achieved levels of ATP in keeping with their results, but our results suggests that an ATP of less than 2mmol mg^{-1} protein does not necessarily indicate non-viability.

It is reported that typically have a wet weight of 20-30mg, with a protein content of 1-2mg, which would be in keeping with our results (Table 5-5)²⁶⁴.

Owing to different methodological approaches, the albumin production, glucose production, and mitochondrial function assays are not directly comparable, but serve to underline the functional viability of our liver slice model²⁶⁴.

Working closely with the clinical teams meant that samples could be collected and placed in the collection fluid within the operating department. This will have minimised the warm ischaemia time of the tissues, and contributed to the preserved viability. Typically ATP levels are depressed and the period of pre-incubation serves to allow recover of the slices before utilising them in experimentation²⁶⁵. Within this model there was little depression and recovery of ATP levels suggesting that pre-incubation trauma (and consumption of ATP) had been minimised (Figure 5-10).

There was little variation in results from slices taken from the same patients, suggesting that the methodology for both incubation and reporting has been consistent, and that the variation arises from the patients themselves, and the operative trauma preceding collection. Access to patient level data may allow some explanation of the variation seen within the hepatic slices, although conclusions are limited by the small sample size.

When examining the ATP levels it is noted that patients 5 and 6 had the lowest levels of ATP. Both of these patients had limited aerobic capacity. This could suggest a correlation between hepatic ATP and aerobic capacity. However patient 4 also had depressed aerobic capacity but had high ATP levels. Patient 4 is however a relative anomaly within the series, given the underlying diagnosis of HCC. This HCC may reflect an underlying problem with hepatic tissue, as HCC in non-cirrhotic patients often evolves in part as a result of potentially harmful carcinogens²⁶⁶. Despite the very low numbers it

may be worth further investigating the correlation between aerobic capacity and hepatic ATP.

A number of alterations in the methodology as suggested by de Graff et al were adopted and may have affected our results accordingly⁵⁸. Primarily these adaptations were made owing to available resources. Firstly the liver tissue was not flushed or stored with University of Wisconsin preservation fluid, in part due to cost restrictions, but primarily due to the variability of the size of preserved tissue. Whilst our technique is used by others in similar circumstances it may have led to a reduction in viability²⁶⁷. The second major variation from their methodology was the absence of a circulating coolant in the Krumdiek liver slicer. Given the relatively few slices prepared over a short time in ice cold KHB it is unlikely to have impaired viability significantly.

The last major variation in the methodology is the variation in the incubation method. Slices were incubated in a standard incubation with a 5% CO₂/95% air environment in 12 well plates on an orbital shaker (Orbit LS, Labnet, Appleton Woods). Whilst the use of a 95%O₂/5%CO₂ atmosphere has been suggested to help preserve viability a number of studies have utilised the incubation environment used in this study with success²⁶⁴. Indeed some comparative studies have found little or no benefit of a high oxygen environment when culturing slices^{268,269}.

This component of my thesis demonstrates a viable model of hepatic function that has a number of potential advantages over currently established primary hepatocyte models^{206,255,270,271}.

As this model is utilised further, it should allow exploration of the hypothesis that patients with greater cardiopulmonary fitness have improved hepatic function. It should also allow exploration of the affect that neoadjuvant chemotherapy has on hepatic functional capacity. If this hypothesis were proven, it could allow cardiopulmonary exercise testing to be utilized to estimate the volume of hepatic tissue that can be safely resected, and the volumes at which a patient is at higher perioperative risk.

Chapter 6: Discussion

6.1 Introduction

This thesis focuses on the surgical management of colorectal liver metastases with particular emphasis on prehabilitation and the potential links between hepatic function and physical fitness.

The management of CRLM is constantly evolving. The number of treatments available has increased greatly over the last 20 years^{8,24,123,272}. Local, loco-regional and systemic therapies have been developed to improve efficacy and patient suitability^{24,123,273}, and consequently many patients are surviving longer and undergoing increasingly complex multi-modal treatment pathways.

Patients with CRLM are undergoing more treatments, and all of these treatments have associated morbidity. We can expect the cumulative effect of the associated morbidity to impair physical fitness. This poorer fitness is likely to cost patients in two ways, firstly in terms of a negative impact on their quality of life, and secondly the effect of poorer fitness on individual treatment outcome. Poorer physical fitness has been implicated to cause greater perioperative morbidity^{40,43,49,216,274}. Perioperative morbidity has also been linked with poorer long-term survival¹³⁵. Greater morbidity and poorer survival lead to greater treatment cost (cost of complications) for poorer overall gain (reduced survival).

Prehabilitation is likely to become more important in the future as colorectal cancer is increasingly prevalent with age, and global populations are aging⁵. Advancing age is associated with greater frailty and comorbidity, so a successful prehabilitation programme may help mitigate the effects of advancing age on patient outcomes^{5,116,117}.

6.2 Prehabilitation

This thesis has developed and demonstrated that a four-week prehabilitation programme can improve the mean VO_2 at the AT of patients²⁷⁵. A low VO_2 at AT is associated with increased complications, longer hospital length of stay, higher perioperative mortality, and poorer medium-term survival^{35,37,40,43,49,216,228,274,276,277}. Prehabilitation also led to improved quality of life preoperatively, as measured by the SF-36 questionnaire²⁷⁵.

Prior to this research no programme of just 4 weeks has demonstrated improvements in preoperative fitness and none in a population with metastatic cancer. The improved preoperative quality of life has not previously been demonstrated in a randomised study, though small cohort studies have found similar results²⁰⁷. The high adherence seen in this programme suggests that it is acceptable to the patient population.

At the commencement of this study no randomised trial had demonstrated the capacity of prehabilitation to significantly improve the mean VO_2 at AT of cancer patients²⁷⁷. Even now as the research completes only 4 randomized

studies have been performed involving cancer patients^{162,171,173,278}. The largest of these failed to deliver significant improvements in VO_2 at AT over their control arm¹⁶².

The prehabilitation programme achieved its primary objective to deliver a $1.5 \text{ ml.kg}^{-1}.\text{min}^{-1}$ improvement in the VO_2 at AT, when compared to standard care. This is an important achievement given the failures of previous randomized studies of prehabilitation^{162,171}. Within the prehabilitation arm it can be seen that a variety of measures of preoperative fitness seen as potentially relevant to predicting outcome have also improved, or have trends towards improvement, such as the VO_2 at Peak ($\text{ml.kg}^{-1}.\text{min}^{-1}$), and the o_2 pulse^{29,30}. Both of these have been identified as factors closely tied to perioperative outcomes including morbidity, mortality and hospital length of stay^{40,43}.

The prior randomized studies in abdominal cancer surgery have had inconsistent results^{162,278-280}. The shortest programme, a supervised 2-4 week programme (mean 5 sessions), demonstrated the feasibility of prehabilitation in a cancer population²⁷⁹. The authors suggested improved respiratory muscle endurance following prehabilitation, when compared to exercise advice. There was, however, no improvement in physical exercise capacity or quality of life. The largest trial randomized 133 patients prior to colorectal resection to a home based exercise programme, or a sham control of walking and breathing exercises¹⁶². The programme had a longer prehabilitation time (mean 43 days) but failed to demonstrate an

improvement in peak Vo_2 , or distance achieved in the 6-minute walk test. This was thought to relate to poor compliance in the home-based exercise programme. Recently a study randomized 77 patients to either rehabilitation or prehabilitation (plus rehabilitation) before colorectal resection¹⁷³. The prehabilitation took place at home and was similar timescale to the current study (mean 24.5 days). The authors demonstrated that prehabilitation led to improved functional walking capacity, and a quicker return to baseline levels post-surgery. There were no differences in complications, or hospital length of stay.

The non-randomized studies have consistently demonstrated that prehabilitation leads to improvements in Vo_2 uptake at AT and Peak^{169,170,172}. Some studies have also demonstrated improvements in the 6 minute walk capacity both pre and postoperatively, and an improved SF-36 mental health composite score¹⁷⁰.

The general trend towards improved CPET variables when comparing prehabilitation with standard care supports the view that prehabilitation led to a global improvement in physical functioning. Prehabilitation led to improved work rate at both peak exercise and the anaerobic threshold, and an increase in the heart rate reserve. The heart rate at the anaerobic threshold and the heart rate reserve were identified as a variables of potential relevance to predicting postoperative outcome in the patients in this study and by Hightower et al^{34,281}. The mechanism underpinning this relationship remains

unclear, but may relate to improvements in cardiac functioning. This should be examined in future studies.

The development and validation of a new exercise program has contributed to the success of the main study²³². This development was not planned at the outset of the research, however it became evident that no suitable programme existed. The challenge was to design a program of short enough duration, and low enough frequency that it would fit around preoperative cancer pathways. This programme needed to deliver clinically relevant improvements in preoperative fitness. Even defining the concept of “clinically relevant” improvements in fitness had to be conceptualized. An improvement on $1.5 \text{ ml.kg}^{-1}.\text{min}^{-1}$, was felt to be clinically relevant, as if deliverable across our patient cohort would shift up to 30% of our patients out of the category “high risk” who were automatically admitted to critical care¹¹². Our institutional policy was based on the work by Older et al who identified “high risk” patients and managed them accordingly^{35,36}.

These “high-risk” patients were a group who had arguable the greatest benefit from prehabilitation. With an average improvement in the AT being greater than for the cohort as a whole²⁷⁵. These patients who are at higher risk of complications also consume greater healthcare spending. Focusing prehabilitation on these patients is likely to yield greatest benefit⁵³. A recently published randomised study in patients deemed high risk for surgery has shown that prehabilitation reduces complications by 50%, shortens

hospital and critical care stay²⁷⁸. This study classified high risk as patients over the age of 70 or patients assessed as ASA 3 or 4. The prehabilitation utilised in this study employed an exercise programme almost identical in nature to the programme utilised in this study, in addition nutritional and psychological interventions were employed²⁷⁸. This trial adds weight to the suggestion that prehabilitation should be adopted into clinical practice, at least for those deemed high risk.

Further studies should examine the cost efficacy of prehabilitation. Work conducted in our centre has shown no association between Vo_2 uptake at the AT and perioperative mortality, or morbidity³⁴. This was thought to reflect how the CPET was being used to delimitate perioperative care. This tailored care means that patients with poorer Vo_2 uptake at the AT cost more to treat in the perioperative period even if they suffer no complications⁵³. Therefore even if prehabilitation failed to improve perioperative outcomes it may dramatically reduce the cost of care.

Adherence to the exercise programme in the RCT component of the study was similar to that seen in the pilot study. This is despite the population in the RCT having metastatic cancer and significant comorbidities^{232,275}. The adherence was high in comparison to other studies, and this will have contributed to the success of the programme^{162,168,171,207}. This high adherence also suggests that the programme is appropriate to the target population.

The underlying reasons for this high adherence are likely to be multi-factorial. All patients volunteered to take part, knowing it could involve participation in an exercise programme. Consequently they are likely to be a highly motivated group. In addition interval-based training programmes have been shown to have higher ratings of perceived enjoyment than constant load programmes²²¹. The underlying mechanism for this is difficult to distinguish but is likely to relate to a combination of the varied exercise profile with the direct effects of high intensity exercise.

Calculating the programme based on a baseline symptom limited CPET has significant advantages. It allows patients to be screened for major risks when undertaking exercise, thus reducing any risks of the exercise programme itself. Prehabilitation programmes utilising submaximal testing have seen significant adverse events during the exercise sessions¹⁶⁸. The ability to calculate the entire programme based on a baseline test minimises on-going management of the exercise programme, and should minimise cost if CPET is utilised when expanding to a service level provision. The VO_2 at AT, detected during cardiopulmonary exercise testing, was used to design the programme as it has been shown to correlate well with endurance capacity, and is detectable in most patients^{30,45}.

An unexpected finding within this study was the marked deterioration in those patients randomized to standard care. This finding has not been previously demonstrated though this may stem from an absence of true control arms in

the majority of studies. West et al, utilised CPET in a non-randomised study and suggested a possible underlying trend, towards deteriorating VO_2 uptake at the AT in the control patients following chemo radiotherapy for primary rectal cancer¹⁷². In West et al this deterioration could relate to progressive changes following the neoadjuvant treatment, rather than the disease process. However Gillis et al found that 36% of patients not partaking in prehabilitation (rehabilitation only arm) had a significant drop in the distance achieved in the 6-minute walk test¹⁷³. This would further support the view that without intervention patients are deteriorating prior to surgery.

It had been established that there was heterogeneity in gains of the VO_2^{\max} to endurance training ranging from 0-100%, and that some people lacked capacity to improve the aerobic capacity²⁸²⁻²⁸⁴. The work by Timmons et al established a series of gene biomarkers that could account for 50% of the variation in VO_2^{\max} response, though the exact mechanisms underpinning the role these gene markers play remains largely unclear²³⁷. Their work also identified that around 20% of patients lack the capacity to increase the VO_2^{\max} response, which is not dissimilar to the 30% (6 of 19) patients on the prehabilitation arm who had either unchanged or deteriorating VO_2^{peak} . This is slightly higher than may have been expected in a general population, though low numbers and metastatic cancer represent potential explanations.

We could expect greater benefit of prehabilitation in responders, however an absence of a VO_2 response, may not represent a failure. Prehabilitation may

have prevented the deterioration in VO_2 uptake seen in the control arm. Exercise is known to have other benefits which may have been accrued in the non - VO_2 responders.

Exercise is a known treatment for sarcopenia²⁸⁵⁻²⁸⁷. Sarcopenia has been identified in around 20% of patient with CRLM and is associated with higher complications, poorer survival and higher treatment cost^{127,235,236}. Whilst it could be argued that sarcopenia is a marker of adverse disease biology, and that this is the reason for these findings there is evidence that sarcopenia is a significant predictor of adverse outcome in a variety of other settings. It has been identified as a predictor of poor outcome following trauma, and also in the elderly hospitalised and non-hospitalised patient²⁸⁸⁻²⁹⁰. Given this established role in the non-cancer setting, it may be postulated that the sarcopenia may not relate to the disease but the physical conditioning of the patients. The improvements in the workloads achieved at both the AT and peak exercise suggests improvements in skeletal muscle mass. Prehabilitation may affected sarcopenia, and thus could impact on survival. This warrants further investigation.

Insulin resistance develops as part of a series of homeostatic alterations leading to the development of a catabolic state as a normal response to any trauma, including surgery²⁹¹. This insulin resistance develops in a dose dependant manner correlating with the magnitude of surgery²⁹². It is predominantly related to extrahepatic modifications, but there is also a

significant increase in hepatic glucose production following surgery²⁹³. The degree of insulin resistance has been shown to correlate with postoperative length of stay, and reducing insulin resistance has been a focus of research^{292,294}. Reduction of insulin resistance is thought to be a key mechanism of the success of ERAS programmes²³⁹.

Exercise is known to be an effective strategy for diminishing insulin resistance²⁹⁵. The mechanisms underlying the exercise-induced improvement in whole body glucose tolerance are not fully understood. Established contributors are improved glucose disposal and enhanced insulin mediated cellular transport in skeletal muscle²⁹⁶. The hyperglycaemia resultant from increased insulin resistance is known to be associated with poorer outcome in variety of setting including in critical care patients²⁹⁷. Interestingly aggressively treating the hyperglycaemia with insulin does not appear to be associated with improved outcomes²⁹⁸. This would suggest that the hyperglycaemia is not the cause of the worse outcome but a symptom of the underlying mechanisms. Whilst not investigated in this study prehabilitation may have affected these underlying mechanisms. If prehabilitation could deliver reduced perioperative insulin resistance it may lead to improved perioperative outcomes regardless of the changes in aerobic capacity, and this should form a focus for further work.

Interestingly Timmons et al identified that 30% of patients failed to improve insulin sensitivity in response to exercise, it would be useful to examine the

relationship between these patients, the patients who could not increase aerobic capacity and the incidence of sarcopenia^{127,237}. It would appear that the mechanisms of action of a variety of these pathways overlap, and it may be that a cohort of patients who will not benefit from exercise therapy exists. If these could be identified triage for patients who are unlikely to benefit from prehabilitation could be performed.

Quality of life has been a major focus for this research. In metastatic colorectal cancer survival has dramatically improved over the last 2 decades, meaning that quality is ever more important than just quantity. In patients with resectable CRLM survival to 5 years is in the order of 50%^{24,78}. Even in patients with incurable metastatic disease undergoing palliative chemotherapy median survival has more than doubled to greater than 2 years²⁷². Given this increasing survival, quality of life has become an increasingly important clinical outcome²⁹⁹.

Prehabilitation led to improved quality of life preoperatively, as measured by the SF-36 questionnaire. In contrast standard care did little to alter the quality of life. Interestingly when the quality of life was assessed with the EORTC questionnaire there was no statistically significant difference between the study arms. However this may relate to an under powering for analysis using the EORTC questionnaire, particularly given the general shift in values in favour of prehabilitation.

No other randomized prehabilitation study in abdominal surgery has demonstrated significant improvements in quality of life^{162,278-280}. It was assessed in three of the four studies^{162,278,279}. One utilised the EORTC questionnaire and found similar results to this study, this may relate to under powering with only 87 patients randomised²⁷⁹. The largest study, Carli et al, was largely affected by the apparent success of the “sham” control arm of breathing/walking¹⁶². They found improvements in the hospital anxiety and depression scores³⁰⁰ in both study arms. This would suggest that it is not necessarily the exercise that makes the difference, but perhaps the empowering the patients to feel like they can make a difference to their outcomes. The recent study where high-risk patients underwent a prehabilitation programme utilized the SF-36 assessment. It found no significant differences in pre-surgical quality of life, no explanation for this variation was postulated, though it may reflect the variation in disease processes within the treatment population.

In other prehabilitation studies utilising SF-36^{170,173} Gillis et al found a non-significant trend towards improved mental health ($p=0.085$) in the prehabilitation arm, similar to our study¹⁷³. Li et al found prehabilitation improved a variety of SF-36 domains including Role Physical, Vitality, and mental health. This study was, however, limited by a non-randomized historical control arm, and an absence of baseline SF-36 scores in this

cohort. These results are not surprising given the findings in lung resectional surgery suggesting that prehabilitation leads to improved quality of life²⁰⁷.

The majority of SF-36 improvement was delivered by improvements in mental health, in particular emotional and social functioning. This finding of improved emotional and social functioning is in keeping with other studies of exercise in cancer sufferers^{242,243}. It is however interesting that a four week programme of just 12 sessions can achieve similar improvements to programmes typically of much longer duration¹⁵⁰. In particular this trial suggests improved preoperative psychological status, a factor known to be associated with improved long-term survival in colorectal cancer¹⁵⁹.

Prehabilitation would appear to represent the natural progression for ERAS programmes that are now established in many surgical disciplines^{112,140,144,301,302}. These ERAS programmes have revolutionised surgical practice in the last decade leading to reduced morbidity, and healthcare cost^{139,140}. The suggested mechanisms of action underpinning prehabilitation are similar to those thought to underpin the benefits delivered by ERAS. These include improved insulin sensitivity, better physical conditioning and an opportunity to improve the preoperative education a key pillar of ERAS¹³⁹.

Despite the success of the programme, there was no demonstrable difference in activity levels between the cohorts when assessed utilizing the Dukes activity questionnaire. This is similar to previous studies utilising

activity questionnaires²⁷⁹. The activity questionnaire may not be sensitive enough to detect this. Further research into this area may be aided by the widespread adoption of smart devices, and should be considered in future studies.

6.2.1 Limitations

The findings of this study offer interesting avenues for future development, but there are limitations that must be considered when interpreting the results. Importantly whilst this study demonstrates that it is possible to deliver significant improvements in CPET values, and it would appear logical to assume this will deliver the benefits associated with better fitness²¹⁷, this requires confirmation in a larger trial. Future studies should be powered to detect differences in postoperative morbidity, alongside survival and quality of life benefits.

There is a potential recruitment bias that may limit generalizability to a wider population overall. The cohort is younger than the typical patient group, suggesting an preoperative exercise intervention is more appealing to the younger patient population¹¹². Younger patients have been reported to have more aggressive disease, meaning the study population may have been more likely to have aggressive disease than the overall patient population²⁵³. These study patients also had a greater preponderance to an advanced primary than seen in other studies¹⁶⁰. The relatively high rate of failure to progress to hepatectomy is much higher than expected from the unit's own

published data, and would support the assumption that the cohort had more aggressive tumour biology²³⁴.

A final concern within the study is the difficulty presented within blinding. All clinicians were blinded to the 2nd cardiopulmonary exercise test results, and the randomization of patients. Despite this patients were prone to reveal their attendance at preoperative exercise programme. The patients attending prehabilitation were immensely proud of their achievements. Many had not partaken in exercise for a number of years before starting prehabilitation. In addition a number of patients within the prehabilitation arm had gone beyond the prehabilitation programme. One of those achieving the greatest response had taken to cycling to and from the prehabilitation sessions, which was nearly a 20 mile round trip. Whilst it could be argued that it was not the prehabilitation programme that achieved the improvement, there were no incidences of patients taking up exercise within the standard care arm.

6.2.2 Future work

This thesis has demonstrated that a short prehabilitation programme can deliver significant improvements in aerobic fitness, but has also identified a number of potential areas for future research. Replicating the work by Barberan-Garcia et al in a hepatectomy cohort would be useful to confirm the positive effects of prehabilitation on perioperative outcome²⁷⁸.

Selecting the appropriate endpoint to study in such a study is challenging. Numbers would be exceptionally high for assessing the effect on postoperative mortality given a published mortality of 0.3%¹¹². Other perioperative outcome measures that could be considered are postoperative morbidity, hospital length of stay, or treatment cost.

The effect of prehabilitation on rates of postoperative complications is possibly not appropriate. Some complications are a result of technical failure, and prehabilitation is unlikely to influence a surgical team's performance. Consequently it may be more appropriate to investigate the effect of prehabilitation on cardiorespiratory complications, as other studies have explored^{303,304}. However in liver surgery there is a significant interplay between surgical complications and cardiorespiratory complications, owing to the proximity of the liver to the diaphragm³⁴.

Hospital length of stay may be a more appropriate choice of outcome; given the relationship of CPET values to length of stay in blinded studies^{40,43}. However following CRLM surgery length of stay is typically 5-6 days regardless of extent of hepatectomy, meaning such a trial may require very high numbers to show differences¹¹².

Treatment cost could be considered though it would require un-blinding the clinical team to the intervention, and 2nd cardiopulmonary exercise test. As without this it would not be able to affect the triage of care that goes on for

those patients deemed higher risk. Any trial would therefore be subject to significant bias.

Overall survival could be considered but there are a number of well-documented problems with this endpoint³⁰⁵. In particular the developments in colorectal cancer make powering any study challenging, and identifying the contribution a short prehabilitation programme had to survival is likely to be challenging.

Quality of life is another potential endpoint to consider. Unfortunately, the postoperative results suggested QoL was largely similar at 12 weeks (data not included in thesis). Though this could in part relate to the aforementioned confounds, but it makes powering a future study difficult. A future quality of life study should combine prehabilitation with rehabilitation.

Given these difficulties and the findings in high-risk patients undergoing hepatectomy, these probably represent the group in which to focus a larger study. The primary endpoint should probably be either quality of life or perioperative complications, as this has meaningful implications on cost, and disease recurrence^{53,135,306}. It should combine prehabilitation with rehabilitation.

The other challenging questions that future work should try and answer include:

1. What is the most effective form of prehabilitation?
2. Are there patients who gain no benefit from prehabilitation?

6.2.2.1 What is the most effective form of prehabilitation?

This study utilised a supervised interval exercise programme, alternating between severe and moderate intensities²³². This has likely contributed to the success of the programme given the limited success of previous unsupervised or constant load studies^{162,171,279}. Interval training is also the most effective way to achieve maximal aerobic capacity gain, and aerobic capacity has been identified as correlating with postoperative outcome^{40,43,48,49}. However there are other aspects of prehabilitation programmes to consider.

Sarcopenia has been identified as correlating with post operative and long-term outcomes, following a variety of surgical interventions^{127,235,236,290}. Several studies have combined aerobic prehabilitation with resistance or strength training^{170,279,307,308}. Unfortunately these studies fail to address sarcopenia directly though this may stem from the difficulties this provides as an endpoint³⁰⁹. Sarcopenia has a variety of definitions, and methods of assessment, which can be both costly and time consuming to measure. Given this there has been an increasing interest in utilising simple tests such

as hand grip tests²⁷⁹, and gait speed^{170,308}. The studies utilising some form of measurement of strength have suggested that prehabilitation could improve muscle strength, and the 6-minute walk capacity^{170,308}. However Dronkers et al²⁷⁹ found no difference in the timed “up and go test”³¹⁰, which has been correlated with sarcopenia³⁰⁹. Future prehabilitation work should address sarcopenia utilising a measurement of muscle bulk, in combination with sarcopenia measurement on routine scans in the prehabilitation and follow-up period.

Prehabilitation works on more than just the physical needs of a patient as seen by the reduced anxiety levels seen in this study. This may in part be due to a feeling of an improved fitness level reducing the worry prior to surgical intervention. However it is likely that other factors contribute. The act of prehabilitation empowers the patient to do something about their disease, giving them more control over a situation they have previously felt powerless within³¹¹. Prehabilitation also allows time for patients ask questions about their upcoming intervention. This improved understanding is likely to reduce anxiety³¹¹. Preoperative education is a key component of ERAS¹³⁹, and prehabilitation offers an ideal setting to maximise preoperative education. Future prehabilitation programmes should make use of structured education programmes to enhance this aspect of care.

A final area of interest is the combination of prehabilitation with rehabilitation. This has been done in patients with cirrhosis prior to hepatectomy for

HCC¹⁵⁹. In this study they found that at 6 months post-operatively patients who had undergone prehabilitation combined with rehabilitation had lower BMI, and body fat. Little data was provided about other parameters, though comment was made that those who performed exercise more frequently had greater benefit. Given the established benefits of rehabilitative exercise, combining it with prehabilitation in future studies would seem logical, though it would make deciphering the benefit of prehabilitation from rehabilitation more difficult¹⁵⁰.

Given the evidence it is likely that a future prehabilitation programme would be multimodal, involving aerobic training, with strength work and preoperative education. This should be combined with an active rehabilitation programme.

6.2.2.2 Are there patients who gain no benefit from prehabilitation?

The benefits of any prehabilitation programme are likely to be highly variable and work should be devoted to detecting from the outset those patients in whom no benefit is to be accrued so they can proceed directly to other therapy.

Timmons et al identified that a cohort of people lack the genetic ability to improve aerobic capacity or reduce insulin resistance²³⁷. When approaching the subject of identifying those who are not going to get benefit, both the patients genetics and the biologically of the underlying disease should be considered.

Future work should involve assessment at baseline of both the patient genetics and the tumour to facilitate identifying those in whom resource could be better directed, and help facilitate personalized prehabilitation programmes to deliver maximal benefit to individual patients.

6.3 Hepatic slicing

The assessment of hepatic function is an on-going challenge for the research community¹⁹⁷. It is possible to measure levels of hepatic functioning in humans using a variety of tests^{65,312-314}. These tests, however, do not measure total capacity; rather they measure function at a point in time. Models of human hepatic function are all associated with limitations¹⁹⁷. The initial aim of investigating links between cardiopulmonary fitness and hepatic function was not feasible without a viable model of hepatic functioning. Establishing such a model of hepatic functioning has implications beyond this research including drug toxicity studies, physiological studies and also work on hepatic regeneration.

Whilst few firm conclusions were drawn from the work on hepatic slicing (Chapter 5, page 154) it has established a viable model of hepatic functioning that has offered a variety of potential avenues for future research.

6.3.1 Optimizing slicing methodology and incubation.

The quality of hepatic tissue has been identified as the major factor in in vitro studies²⁵⁶. In resection specimens it would be useful to establish how much of the damage to hepatic tissue is created during the operative trauma. This could easily be facilitated by slices taken from cores of tissue being taken from the intended resection specimen, immediately upon opening the abdomen, being compared slices generated from cores taken from the resected specimen. This would require intraoperative coring of the liver tissue by the operating surgeon.

The collection buffer utilised in this study was ice cold KHB, in keeping with similar methodology underway at Maastricht University²⁶⁷. However, a variety of groups propose perfusion of a specimen with UW solution prior to creating cores of tissue^{58,315}. It would be useful to investigate whether this has adversely affected the viability of our tissue, though reportedly in humans UW makes little difference as long as hypothermic incubation time is under 18 hours²⁰⁶.

In terms of optimising the methodology, of real interest would be incubation within a dynamic 3-D culture system¹⁹⁷. A variety of technologies are already available. Primarily these were designed to incubate primary hepatocytes within a 3–D culture system but it would be interesting to see the effect these have upon the preservation of viability in hepatic slices.

6.3.2 Hepatic function and exercise

At the outset of this research there was a suggestion that the liver may play a role in fitness, or vice versa. This was thought to be the case as the liver is intrinsically involved in metabolism and gluconeogenesis, and previous work has demonstrated an effect of exercise on this function, with significant inter-patient variation²⁷. It has also been shown that during exercise, despite reduced blood delivery, the liver has an increased uptake of lactate and increased glucose output²⁸. Once the human liver slice collection and incubation methodology has been standardised correlations could be drawn with patients CPET results. If there is a correlation between fitness and hepatic functioning this should become identifiable.

6.3.3 Preoperative carbohydrate loading and preservation of hepatic function

Poor hepatic function is an established predictor of poor outcome following surgery¹⁹³. Liver resection associated hepatic insufficiency, where the residual liver is insufficient to meet the systemic needs, is a major cause of morbidity and the leading cause of mortality^{10,54,55}. Furthermore a degree of hepatic insufficiency is almost universally observed following major hepatectomy³¹⁶. Defining hepatic function has remained one of the challenges of liver surgery, and currently there is no universally accepted method to define liver function preoperatively^{59,62}.

Preoperative carbohydrate loading (PCL) has been purported to improve peri-operative outcome, as part of the ERAS^{139,142}. However, evidence of individual benefit is limited, and very little is understood about the mechanism. One suggested mechanism for PCL is via preservation of hepatic glycogen content, which has been demonstrated in patients given PCL before gallbladder removal³¹⁷. Preservation of glycogen content is thought to prevent inhibition of both liver and systemic metabolism, allowing the body to respond to increased energy demands following surgery³¹⁸⁻³²⁰. Currently, however, evidence to support the preservation of liver function is limited, and has not been explored in humans.

The liver slice model of hepatic functioning would serve as a useful model to investigate this further, and to that end a study protocol has been devised and we are currently exploring avenues for funding.

6.3.4 Development of liver extracellular matrix

Regenerative medicine has identified that tissue engineering requires a scaffold for optimal effectiveness. Appropriate scaffolds facilitate cells with a surface for adhesion and also space for growth³²¹. Utilization of extracellular matrices promotes cell adhesion, and expression of organ-specific functions and cell differentiation³²²⁻³²⁴. Interestingly primary hepatocytes, cultured on organ-specific matrices sustain expression of organ-specific functions^{325,326}. This had led to an interest in development of improved organ scaffolds.

There is currently an interest in developing a de-cellularized extracellular matrix from PCLS. Such a model has a number of advantages over formal hepatic specimens. Primarily they are more easily obtainable, and multiple slices of a similar size are easily produced. These slices could be made to an appropriate thickness, which could be thicker than the optimal 240µm utilized in culture.

These extracellular matrices could then be utilized in the development of both 3-D culture systems and bio-artificial livers, concepts that are currently a key goal of regenerative hepatic science¹⁹⁶.

6.3.5 Co-culture

The concept of a cancer micro-environment is long established, and the interplay between normal cells and cancer cells is a key to both their progression and response to chemotherapy³²⁷. Work from the University of Liverpool identified that the function of normal hepatic tissue was key to predicting response to irinotecan³²⁸. Culturing precision cut liver slices is a form of co-culture, given that all cell types are represented. There is on-going interest in the culture of cancer slices with PCLS hepatic tissue. This should facilitate a greater understanding of the interplay of drug efficacy on differing cell types. Ultimately it may offer an alternative method for ex vivo investigation of response to chemotherapy, particularly for drugs where hepatic metabolism is relevant³²⁹.

6.4 Conclusions

The affects of a globally aging population mean that colorectal cancer is likely to become more prevalent, with older more comorbid patients presenting with the disease. Advances in the chemotherapeutic and surgical armamentarium mean that patients with CRLM are undergoing more treatment in increasingly complex treatment pathways. These pathways are associated with significant morbidity and hepatic injury.

ERAS and better preoperative assessment of patients using CPET may help mitigate some the challenge of treating a more elderly co-morbid population. Significant challenges remain and methods to improve perioperative care are needed.

This thesis has demonstrated that prehabilitation is feasible, deliverable within cancer pathways, and associated with improved preoperative aerobic fitness and quality of life ²⁷⁵. The response to the prehabilitation programme was variable in keeping with prior work into the genetic response to aerobic exercise training. Future prehabilitation work should examine if there is a cohort of patients in whom prehabilitation offers no benefit.

The development of a PCLS model should allow investigation of the links between cardiopulmonary fitness and hepatic function. It should also allow investigation into other areas of hepatic functioning including research into

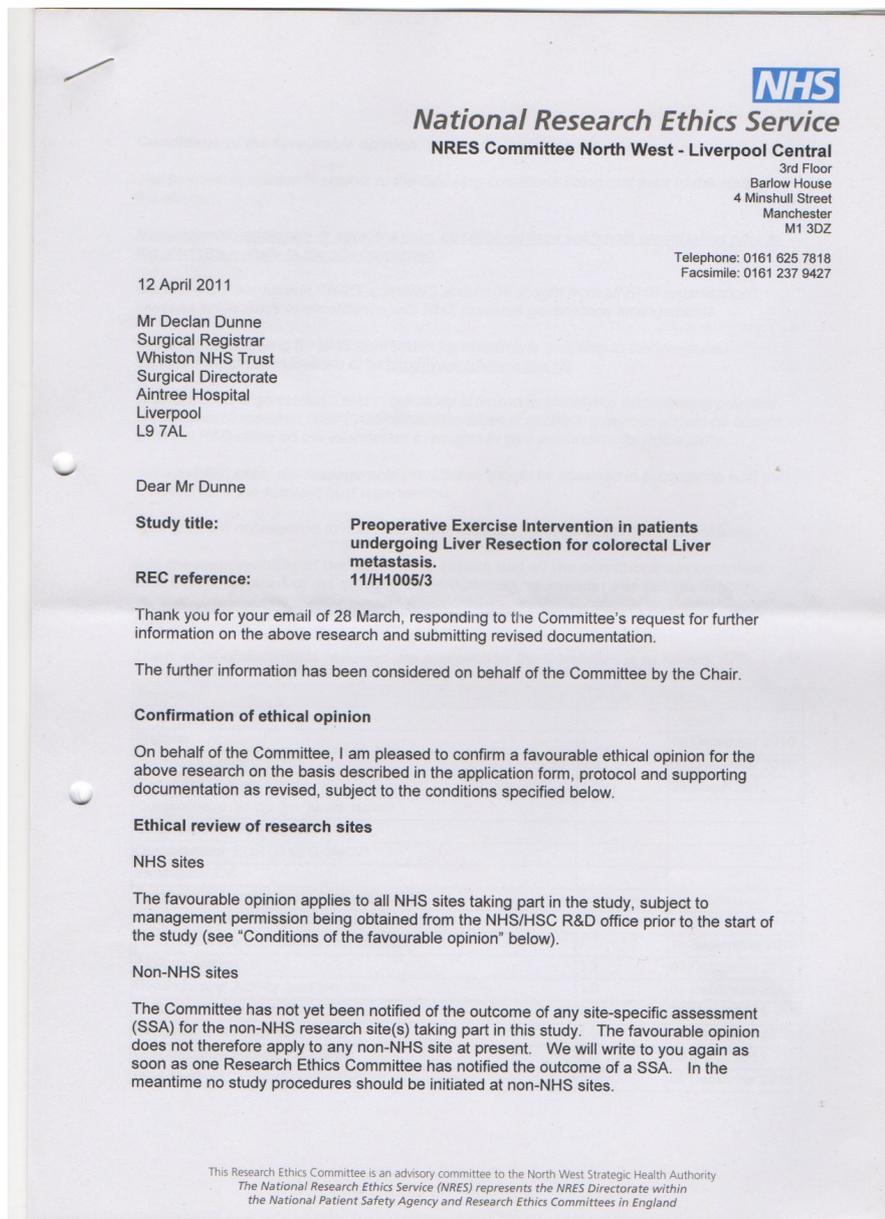
hepatic regeneration and chemotherapy toxicity. That may allow further improvements in our treatment of CRLM.

Developing on the work contained within this thesis should involve a large trial focusing on clinical outcome as a primary endpoint, possibly quality of life. Research into the mechanisms underpinning prehabilitation including sarcopenia, and insulin resistance should be a priority.

Prehabilitation represents the natural progression from enhanced recovery, which is now recommended as standard of care for patients undergoing hepatectomy for CRLM ¹⁴⁸. I would expect a form of prehabilitation to become a standard of care for all patients undergoing hepatectomy for CRLM in the future.

Appendix 1: Prehabilitation programme development

1.1 Ethical Approval



1.2 Patient information leaflet

Patient Information Sheet

Preoperative Exercise Intervention in Liver Surgery

Introduction

You are currently undergoing investigations to see whether you are suitable for surgery to remove bowel cancer that has spread to your Liver.

Once these investigations are complete, you may require surgery, in which case we will invite you to take part in our research project.

Before you decide whether to take part in this research, we would like you to understand why the research is being done and what would be involved.

One of our team will go through the information sheet with you and answer any questions you have.

Please talk to others about the study if you wish.
Ask a member of the team if there is anything that is not clear.

Part 1: Explains the purpose of this study and what will happen to you if you take part.
Part 2: Explains more detailed information about the conduct of the study.

Part 1

What is the purpose of the study?

As part of the normal assessment to decide whether an operation on your Liver is the right treatment for you, we perform an exercise test. This gives us measures of your fitness.

Studies have shown that patients who are physically fitter have fewer complications and a shorter hospital stay after surgery.

The Liver plays a crucial role in exercise as it recycles some products of exercise and helps produce energy. Very little research has been done looking at the effect of exercise training on Liver function.

We want to see if a short period of exercise training in the weeks before surgery can make people fitter, and whether this will reduce the number of complications patients suffer after surgery. We also want to study the effect of exercise on the function of the Liver.

Why have I been invited?

Patients who have bowel cancer that has spread to the liver, who may benefit from an operation to remove part of the Liver, are being asked to take part in the study. The study will involve around 40 patients.

Do I have to take part?

It is entirely up to you whether you join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent 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?

This is all summarised in the diagram on the page 4.

Preoperative Assessment

As part of your assessment for surgery you will undergo an exercise test, blood tests, and possibly other tests which your consultant feels are necessary. Once these have been completed and you have decided to undergo surgery, then we will give you the option to be involved in this research project.

Recruitment

If you decide to take part in the research we will first talk you through the project, describing what is involved and ask you to sign a consent form. We will then ask you to fill in three short questionnaires, asking you about your general fitness and how you feel. This should take around 10-15 minutes. We would then take a blood sample. This should take about 5 minutes.

We are unsure of the benefits that a short exercise program before surgery may bring. To find out, we need to compare different groups. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). This is done by computer putting you into one of two groups, a 50% chance of being in either group.

Both groups will be asked to use an activity monitor for the next 3-5 days. This is a band which sits round your upper arm and gathers information on your level of activity. We would ask you to continue as normal when using this. We would arrange for its return.

Group 1

In this group you would be completing an exercise program. This would involve 3 visits to hospital each week for 4 weeks. The exercise would be on an exercise bike and involve short bursts of quite hard effort with periods of recovery after. It will probably make you feel a little out of breath at some points, but through the majority of the exercise you should be able to talk comfortably. It will not make you as out of breath as your initial exercise test and should not be as hard.

Group 2

In this group we would ask you to continue as normal, following our standard advice before surgery.

Assessment: The week before Surgery

In this week we would bring you back to the hospital. We would go through the same 3 questionnaires that you filled in at the start. Before surgery you will need further blood tests as part of the normal assessment for surgery. While these are being taken we would take one further 3ml blood bottle for our study.

We would also repeat the exercise test you had in the assessment for surgery, and afterwards give you an exercise monitor to take home again. We would collect the activity monitor from you when you come for surgery.

Your Operation

Your operation will be carried out in exactly the same way, except that 2 samples of tissue and one blood bottle will be taken.

The blood bottle would be taken whilst you are asleep from the drip lines that are put in as part of normal surgery, and would not bring any increased risk.

When your consultant is making a cut in the abdomen he will cut through some of your abdominal muscles. At this time a small sample of muscle will be taken for study, this carries no increased risk.

The second tissue sample is from your Liver. Normally this will be taken from an area of normal Liver tissue that needs to be cut away during the operation, and would include a portion of the cancer. This tissue would normally be discarded. This brings no increased risk to you.

Occasionally the amount of liver tissue being taken away is very small, if this were the case we would take a small biopsy from the liver that is staying behind so that we could still measure the liver function. This would pose no significant increase in risk.

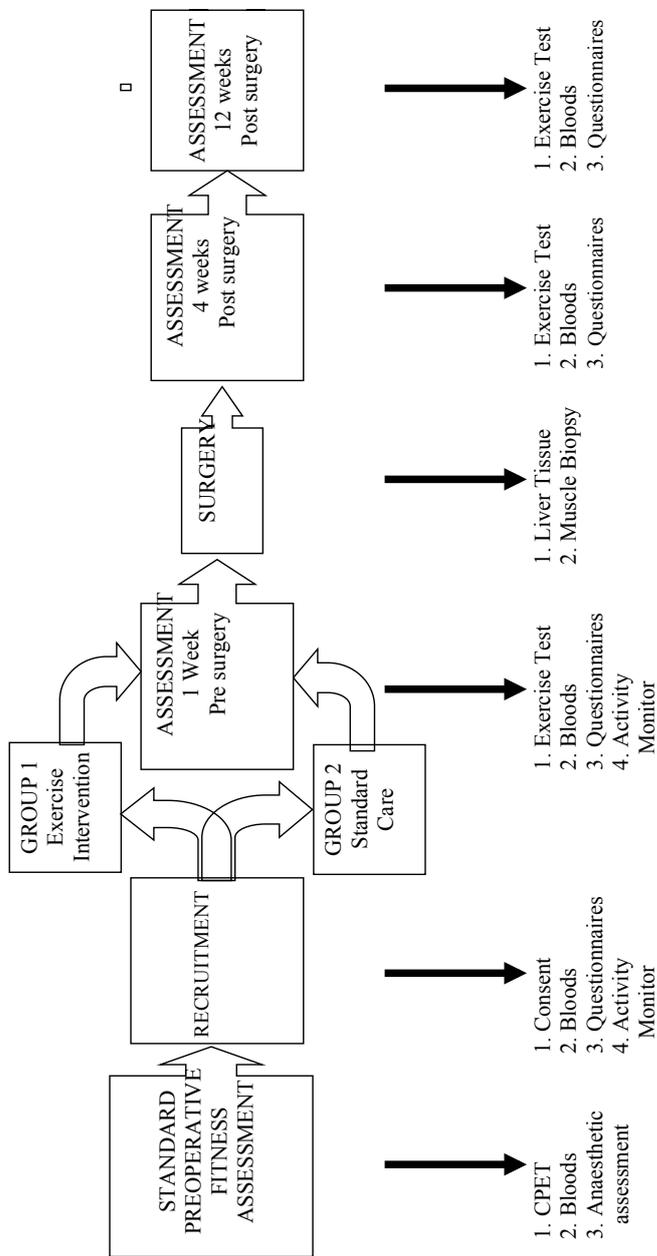
Follow-up after surgery

After you are discharged from hospital you will be seen in the clinic around 1 month later, and then again at around 3 months later. When you come for these clinic visits we would ask you to complete the same questionnaires done before surgery, and do an exercise test (the same as before surgery). Normally at these visits your doctor would request blood tests, when these are taken we would take a further blood sample.

Ongoing Follow-up

After this your formal involvement in the study will finish. As part of your normal care you will be followed up for a period of 10 years. During this time we will keep our research data, so that we may analyse it again at intervals to see if the study has had an effect on your long term outcome.

Flow Diagram Summarising Study



Expenses and payments

Unfortunately there is no money available to help with travel expenses incurred by the study, however all parking at Aintree Hospital in relation to the study would be free (In the multi-storey car park). We are seeking additional funding to support travel costs and if this becomes available we will inform you.

What will I have to do?

We would expect you to attend all clinic appointments, and both exercise tests before surgery. After surgery we would like to repeat the exercise tests, however this would only be if you felt you had recovered enough.

If you are unable to attend some of the exercise sessions it would not exclude you from the study, however we think it is likely that the more sessions you attend the more likely we are to see improvements in your fitness.

Other than the involvement in the sessions, we would expect you to continue as normal following the standard advice given to you by your surgeon in the run up to surgery.

What are the alternatives for diagnosis or treatment?

Currently there are no standardised exercise programs in use before surgery at Aintree.

What are the possible disadvantages and risks of taking part?

The risks associated with taking part are minimal.

Risks of the Exercise test

This is the test you would normally undergo. There is a very small risk of problems with breathing or your heart associated with this. We will repeat the test as part of the study a further 3 times. We would not expect any problems in the repeat tests, we would expect if you were going to have a problem it would be on the first test (the one you normally have as part of the workup for surgery).

Risks of the exercise program

As you would have had a full fitness assessment we would not expect any problems during the exercise test. During the exercise program we would not exercise you as hard as in the original test.

Disadvantages of taking part

The project will require extra visits to the hospital, particularly for those who are allocated to the exercise group. This will involve time and the costs of transport to the hospital. Parking will be free.

What are the side effects of taking part?

If you do not normally exercise regularly then it is likely that your legs will ache a little following the initial exercise; these side effects should disappear over the course of the training program.

If you do not ride a bike regularly before taking part in the study, you may get some mild discomfort on the bottom from sitting on the cycle seat towards the end of the exercise. This could be reduced through using padded cycling shorts. This should also improve over the course of the training program.

We would not expect any other side effects. If you have other concerns you can always contact the lead researcher or their deputy.

CONTACT NUMBERS AT END OF INFORMATION LEAFLET

What are the possible benefits of taking part?

In both groups you will be able to undergo fitness tests 3 further times in comparison to our normal practice. This will give you extra information on your fitness.

Within the exercise group, you will be given advice and training on how to improve your fitness. This may increase your fitness before surgery, though this has not been proven. If we can improve your fitness this means you are at a lower risk for complications during surgery, and it may help you recover after surgery, and shorten your hospital stay.

Exercise programs have also shown improvements in the feeling of general wellbeing, so it may be that you also feel better.

What happens when the research study stops?

Once the research stops we will continue to follow you up as we would in our normal practice. Currently this is ongoing for 10 years. We will continue to collect follow up data and will look for long term benefits from the study.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

Part 2

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue.

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

If you don't wish to continue in the study you may withdraw at any time, and your treatment will not be affected. We would be grateful if you would let the lead researcher know, through the contacts available at the end of this information leaflet, or through your specialist nurse or consultant, so that your ongoing care can be arranged.

If you decide not to continue in the project and you wish your samples and any data collected to be destroyed, then please contact the lead researcher so that this can be arranged.

What if I have a complaint about the study?

If you are not happy with the general care and treatment you receive during the study, please speak first to your study doctor who will try to resolve the problem. They can tell you about the hospital's standard complaints procedure in case you wish to take the matter further.

Complaints can also be directed to:

Mr Stephen Fenwick
Hepatobiliary Unit
Aintree Hospital
Lower Lane
Fazakerly
Liverpool
L9 7AL

0151 529 2740 / 0151 529 8578

When you call or write about a concern, please give as much information as you can. Include the name of the study leader and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Will my taking part in this study be kept confidential?

Your data and samples will be stored on secure NHS and university computers with your name and date of birth removed. The lead researcher and the clinical team will be able to access a secure list which would allow your data to be retrieved should the need arise. It will be used only for this study and other studies that subsequently may be ethically approved by the local ethics committee.

Will my GP be involved?

We would inform your GP that you were taking part in the research project, but there will not be direct involvement from your GP. We will not be sending copies of the research data to your GP.

What will happen to my samples?

Your samples will be given to the University of Liverpool, where researchers will perform studies trying to assess Liver function. If there is any tissue or samples left at the end of this study they will be stored. Any further tests on the samples will only be done with full ethical approval.

How will my sample be anonymised?

When your sample is transferred from Aintree Hospital to the University of Liverpool it will be labelled with a unique code. The only person who knows this code will be the lead researcher in this study. Scientists using your cells will not be able to find out who they are from, and any medical information linked to your sample will be anonymised. The link between your sample and your code will be kept on a password protected database in Aintree Hospital. It will only be accessible by the lead researcher. This link means that your specimen can be identified, but only indirectly.

What will happen to the results of the research study?

The result of the study as a whole will be published in medical literature. If there are results relevant to the general public then we will endeavour to disseminate these results through the local and national media. Any published results will not include any identifiable data. If there are any results that the researchers feel pertinent to yourself these will be given to you during your follow-up appointments at the Aintree Hepatobiliary unit.

Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Liverpool Central Research Ethics Committee.

Who is organising and funding the research?

The study has been organised by the Aintree Hepatobiliary unit in conjunction with the University of Liverpool and the Liverpool School of surgery.

Who can I contact for more information or to discuss the study?

There are a number of people you can contact for more information or to ask questions. The Lead researcher (contact details below) is probably the best first point of call, though you could also contact your Liver specialist nurse or your surgeon.

Lead Researcher:	Mr Declan Dunne
Contact via Aintree	Hepatobiliary Unit Aintree Hospital Lower Lane Fazakerly Liverpool L9 7AL
Mobile Phone Number :	07970501231
Telephone	0151 529 2740 / 0151 529 8578

1.3 Consent Form

Patient Identifier:

Consent Form Page 1

Preoperative Exercise Intervention in Liver Surgery

Name of Researcher:

Please initial each box

1. I confirm that I have read and understand the information sheet dated February 2012 version 2.2, and have had the opportunity to consider the information, ask questions and have these answered satisfactorily.

I understand my participation is entirely voluntary and that I am free to withdraw my permission at any time without giving reason. This will not affect my treatment. I will not receive any compensation for my participation.

If I wish to withdraw from the study, I will contact my surgeon or a member of the research team. They will contact the Lead researcher (or subsequent nominated guardian) who will destroy my samples and delete my records. They will contact other researchers who are using my sample to arrange their destruction.

I give permission for samples to be taken. I understand I will not be told any results generated from my samples. I understand all data generated from my samples will be anonymous, and it will not be directly linked to me.

I understand that relevant information from my medical notes will be linked to my samples. I understand that these notes will be anonymised, and only the lead researcher will be able to identify me from this information.

I understand that my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the nhs trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to this information.

I understand that my liver tissue sample will be stored under secure conditions in the University of Liverpool for as long as 10 years.

I understand that decisions on who can use my samples and what research they can perform, will be only subject to future ethical approval

I agree to my GP being informed of my participation in the study.

Patient Identifier:

Aintree University Hospitals 

NHS Foundation Trust

Consent Form Page 2

Preoperative Exercise Intervention in Liver Surgery

I agree to the collection of data, and its use for research purposes, for the duration of my follow-up at Aintree hospital.

I agree to take part in the aforementioned study

Name of Participant _____ Date _____

Signature _____

Name of Researcher _____ Date _____

Signature _____

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

1.4 Study cohort candidate characteristics

Table 6-1 Individual candidate characteristics candidates 1-13

Candidate	Sex	Age at		Presenting symptoms	Site	TNM at Diagnosis	PMH	Primary Surgery	Liver Surgery
		Primary detection	Metastasis detection						
1	M	49	49	Obstruction	Ascending	T3N1M1	Nil	Right Hemicolectomy	Open and Close
2	M	65	69	anaemia	Descending	T3N0M0	NIDDM, Hypertension	Left hemicolectomy	Metastectomy
3	M	52	53	PR bleed	Rectal	T4N1M0	Hypertension	APR	Right Hemi + Multiple metastectomy
4	F	37	41	COBH	Rectal	T2N0M0	Nil	Lap. Anterior Resection	Left Hemi
5	M	65	65	PR Bleed	Descending	T3N2M1	BPH, Gastric Cancer	Left hemicolectomy	Metastectomy
6	M	60	61	Diverticulitis	Rectal	T2N0M0	Lung metastectomy	Anterior Resection +Loop ileostomy	Multiple Metastectomy + Ablation
7	M	70	72	Obstruction	Sigmoid	T3N2M1	Liver resection	Hartmans	Metastectomy
8	M	63	66	Screening	Sigmoid	T3N2M0	PE	Lap Sigmoid colectomy	Open and Close
9	F	64	64	BCSP	Sigmoid	T4N0M1	Tonsilar Carcinoma diagnosed	Open Sigmoidcolectomy + oophorectomy	Open and Close
10	F	43	43	Anaemia	Caecal	T3N1M1	Cardiac Failure	Lap right hemicolectomy	Open and Close
11	M	59	61	Screening	Rectal	T3N2M0	Hypertension	Low Hartmans	Extended Right + caudate
12	M	67	67	Rectal Bleeding	Rectum	T3N1M0	Liver resection, Hypertension, NIDDM, AF	Anterior Resection	Multiple Metastectomy
13	M	51	54	Rectal Bleeding	Rectum	T3N0M0	PE, Alcohol abuse, incisional hernia, hypertension	Anterior resection +loop ileostomy	Right Hemi

Table 6-2 Individual candidate characteristics candidates 14-24

Candidate	Sex	Age at		Presenting symptoms	Site	TNM at Diagnosis	PMH	Primary Surgery	Liver Surgery
		Primary detection	Metastasis detection						
14	M	53	53	Anaemia	Caecum	T3N0M1	Epilepsy	Right hemicolectomy	Left hemi + Multiple metastectomy
15	M	53	55	Obstruction	Rectum	T3N2M0	Electrocution, Prior Colorectal Ca(separate primary)	Anterior resection + loop ileostomy	Right Hemi
16	M	71	71	Rectal Bleeding	Rectum	T3N1M0*	Melanoma, PE, AF, Prostate Ca	Anterior Resection	Multiple metastectomy
17	M	69	74	COBH	Rectum	T2N1M0	2005 - Pacemaker (Complete heart Block) Hiatus Hernia, BPH	Anterior Resection	Left Hemi
18	M	72	72	COBH (missed by GP 3 years)	Rectal	T3N1M1	Hypertension, Arthritis, PE	Anterior Resection	Left Lateral
19	M	61	60		Rectal	T2N0M1	Gout, AF, Hypertension, Cardioversion	Anterior Resection +loop ileostomy	Multiple metastectomy
20	M	71	71	BCSP	Rectal	T3N1M1*	Nil	Never came to surgery	Right Hemi
21	M	69	69	Anaemia	Ascending	T2N0M1	NIDDM	X(had right hemicolectomy)	Open and Close
22	F	59	61		Rectal	T4N2M0	PE, Bladder Ca, GORD, Asthma	Anterior Resection + loop ileostomy	Open and Close
23	M	72	74	COBH	Rectal	T3N1M0	DVT, Arthritis, Knee replacement	Anterior Resection + loop ileostomy	Metastectomy
24	F	60	64	PR bleed	Descending	T3N1M0	Nil	Left hemicolectomy	Multiple metastectomy

Table 6-3 Individual candidate characteristics candidates 25-31

Candidate	Sex	Age at		Presenting symptoms	Site	TNM at Diagnosis	PMH	Primary Surgery	Liver Surgery
		Primary detection	Metastasis detection						
25	F	60	60	COBH	Transverse	T4N2M0	Carotid endarterectomy x2, Hysterectomy, IDDM, Hypertension, TIA, Hyperlipidaemia	Right Hemicolectomy	Metastectomy
26	M	58	58	PR Bleed	Upper Rectal	T4N1M1	Guianne Barry syndrome, Meningitis, Pneumonia (prolonged ITU admission)	Laparoscopic Anterior resection	Metastectomy
27	M	56	56	COBH	Upper Rectal	T4N2M1	Tonsillectomy, Glaucoma, Hypertension	High Anterior Resection	Multiple metastectomy
28	F	54	54	COBH	Sigmoid	T3N1M1	Hysterectomy, Hypothyroid	Sigmoid Colectomy	Multiple metastectomy
29	M	62	62	BCSP	Right	T3N2M0	Cheekbone fracture, Hypertension	Laparoscopic converted to open Right hemicolectomy	Multiple Metastectomy
30	M	69	72	PR Bleed	Rectum	T2N0M0	CABG, Emphysema, Fibrosing alveolitis, Hypertension, IHD	Panproctocolectomy	Multiple Metastectomy + Ablation
31	F	46	47	COBH	Sigmoid	T3N2M0	Asthma	Sigmoid Colectomy	Metastectomy

Table 6-4 Individual candidate characteristics candidates 32-37

Candidate	Sex	Age at		Presenting symptoms	Site	TNM at Diagnosis	PMH	Primary Surgery	Liver Surgery
		Primary detection	Metastasis detection						
32	M	58	59	COBH	Upper Rectal	T4N2M0	Hyperlipidaemia, Prostate Ca	Laparoscopic anterior resection + Small bowel resection	Metastectomy
33	F	41	41	Obstruction	Descending	T4N1M0	Nil	Left hemi with stoma and mucus fistula	Open and Close
34	M	73	74	PR bleed	Upper Rectal	T3N0M0	Hyperlipidaemia, Hypertension, NIDDM, Prostate Ca, Arthritis, AF	Anterior resection + ileostomy	Multiple Metastectomy
35	F	47	46	lethargy, anaemia	Upper Rectal	T3N2M1	Chronic Fatigue Syndrome, Depression	Planned	Extended Right Hemi Hepatectomy
36	M	71	71	COBH,PR bleed			NIDDM, Hypertension, tonsilectomy	Withdrawn	Withdrawn
37	F	59	60	COBH	Upper Rectal	T3N1M1	Osteoporosis, Ventral Septal Defect recently closed	Sigmoid colectomy and reversal of defunctioning ileostomy	Right Hemihepatectomy +multiple ablation

1.5 Questionnaire based assessments

1.5.1 SF-36

SF-36(tm) Health Survey

Instructions for completing the questionnaire: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

Patient Name: _____

SSN#: _____ Date: _____

Person helping to complete this form: _____

1. In general, would you say your health is:

- Excellent
- Very good
- Good
- Fair
- Poor

2. Compared to one year ago, how would you rate your health in general now?

- Much better now than a year ago
- Somewhat better now than a year ago
- About the same as one year ago
- Somewhat worse now than one year ago
- Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

- a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
 - Yes, limited a lot.
 - Yes, limited a little.
 - No, not limited at all.
- b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?
 - Yes, limited a lot.
 - Yes, limited a little.
 - No, not limited at all.
- c. Lifting or carrying groceries.
 - Yes, limited a lot.
 - Yes, limited a little.
 - No, not limited at all.
- d. Climbing several flights of stairs.
 - Yes, limited a lot.
 - Yes, limited a little.
 - No, not limited at all.
- e. Climbing one flight of stairs.
 - Yes, limited a lot.
 - Yes, limited a little.
 - No, not limited at all.
- f. Bending, kneeling or stooping.
 - Yes, limited a lot.
 - Yes, limited a little.
 - No, not limited at all.

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- g. Walking more than one mile.
- Yes, limited a lot.
 - Yes, limited a little.
 - No, not limited at all.
- h. Walking several blocks.
- Yes, limited a lot.
 - Yes, limited a little.
 - No, not limited at all.
- i. Walking one block.
- Yes, limited a lot.
 - Yes, limited a little.
 - No, not limited at all.
- j. Bathing or dressing yourself.
- Yes, limited a lot.
 - Yes, limited a little.
 - No, not limited at all.
4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
- a. Cut down the amount of time you spent on work or other activities?
- Yes No
- b. Accomplished less than you would like?
- Yes No
- c. Were limited in the kind of work or other activities
- Yes No
- d. Had difficulty performing the work or other activities (for example, it took extra time)
- Yes No
5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
- a. Cut down the amount of time you spent on work or other activities?
- Yes No
- b. Accomplished less than you would like
- Yes No
- c. Didn't do work or other activities as carefully as usual
- Yes No
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
- Not at all
 - Slightly
 - Moderately
 - Quite a bit
 - Extremely
7. How much bodily pain have you had during the past 4 weeks?
- Not at all
 - Slightly
 - Moderately
 - Quite a bit
 - Extremely

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8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

a. did you feel full of pep?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

b. have you been a very nervous person?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

c. have you felt so down in the dumps nothing could cheer you up?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

d. have you felt calm and peaceful?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

e. did you have a lot of energy?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

f. have you felt downhearted and blue?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

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- g. did you feel worn out?
- All of the time
 - Most of the time
 - A good bit of the time
 - Some of the time
 - A little of the time
 - None of the time
- h. have you been a happy person?
- All of the time
 - Most of the time
 - A good bit of the time
 - Some of the time
 - A little of the time
 - None of the time
- i. did you feel tired?
- All of the time
 - Most of the time
 - A good bit of the time
 - Some of the time
 - A little of the time
 - None of the time

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

11. How TRUE or FALSE is each of the following statements for you?

- a. I seem to get sick a little easier than other people
- Definitely true
 - Mostly true
 - Don't know
 - Mostly false
 - Definitely false
- b. I am as healthy as anybody I know
- Definitely true
 - Mostly true
 - Don't know
 - Mostly false
 - Definitely false
- c. I expect my health to get worse
- Definitely true
 - Mostly true
 - Don't know
 - Mostly false
 - Definitely false
- d. My health is excellent
- Definitely true
 - Mostly true
 - Don't know
 - Mostly false
 - Definitely false

1.5.2 EORTC

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

1.5.3 EORTC LMC



EORTC QLQ – LMC21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :	Not at All	A Little	Quite a Bit	Very Much
31. Have you had trouble with eating?	1	2	3	4
32. Have you felt full up too quickly after beginning to eat?	1	2	3	4
33. Have you worried about losing weight?	1	2	3	4
34. Have you had problems with your sense of taste?	1	2	3	4
35. Have you had a dry mouth?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you been less active than you would like to be?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had pain in your stomach area?	1	2	3	4
40. Have you had discomfort in your stomach area?	1	2	3	4
41. Have your skin or eyes been yellow (jaundiced)?	1	2	3	4
42. Have you had pain in your back?	1	2	3	4
43. Have you felt slowed down?	1	2	3	4
44. Have you felt lacking in energy?	1	2	3	4
45. Have you had trouble having social contact with friends?	1	2	3	4
46. Have you had trouble talking about your feelings to your family or friends?	1	2	3	4
47. Have you felt stressed?	1	2	3	4
48. Have you felt less able to enjoy yourself?	1	2	3	4
49. Have you worried about your health in the future?	1	2	3	4
50. Were you worried about your family in the future?	1	2	3	4
During the past four weeks:				
51. Has the disease or treatment affected your sex life (for the worse)?	1	2	3	4

1.5.4 Dukes Activity Questionnaire

Activity Questionnaire

Please read the below questions and answer them as fully as possible.

Are you Physically capable of doing the following:

1. Take care of yourself, that is, eat dress, bathe or use the toilet?
2. Walk indoors, such as around your house?
3. Walk 200 yards on level ground?
4. Climb a flight of stairs or walk up a hill?
5. Run a short distance?
6. Do light work around the house like dusting or washing dishes?
7. Do moderate work around the house like vacuuming sweeping floors or carrying groceries?
8. Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?
9. Do yard work like raking leaves, weeding or pushing a power mower?
10. Have sexual relations?
11. Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a ball?
12. Participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?

Publications

1.6 Published Manuscripts

Prehabilitation before hepatectomy: A randomized controlled trial.

Dunne DFJ, Jack S, Jones RP, Lythgoe DT, Malik HZ, Poston GJ, Palmer DH, Fenwick SW. Published April 22 2016 BJS

Routine staging laparoscopy has no place in the management of colorectal liver metastases. Dunne DFJ, Gaughran J, Jones RP, McWhirter D, Sutton PA, Malik HZ, Poston GJ, Fenwick SW. Published April 22 2013 in the European Journal of Surgical Oncology.

Enhanced recovery in the resection of colorectal liver metastases.

Dunne DFJ, Yip V, Jones RP, Mchesney EA, Lythgo DT, Psarelli EE, Lacasia C, Malik HZ, Poston GJ, Fenwick SW. Published in 2014 in the Journal of Surgical Oncology (110:2,197-202)

Cardiopulmonary Exercise Testing before liver surgery. Dunne DFJ,

Jones RP, Lythgoe, DT, Pilkington FJ, Palmer DH, Malik HZ, Poston GJ, Lacasia C, Jack S, Fenwick SW. Published in 2014 in the Journal of Surgical Oncology (110:4, 439-444)

Improving the perioperative management of resectable colorectal liver metastases

Conversion of Unresectable Metastatic Colorectal Cancer. Dunne DFJ, Jones RP, Malik HZ, Fenwick SW, Poston GJ. Published in the Journal of Oncopathology. 2013 Dec 1 (4): 91-98

Current management of colorectal liver metastases. GJ Sunderland, **DFJ Dunne**, HZ Malik, GK Poston, SW Fenwick. Colorectal Cancer 2014 April 2 (2): 163-181

Optimal preoperative imaging in colorectal liver metastasis. YIP V, Collins B, **Dunne DFJ**, Koay MY, Tang JM, Wiesmann H, Fenwick SW, Poston GJ, Malik HZ. Published European Journal of Cancer 2014 50 (5): 937-943

Controversies in the Oncosurgical management of liver limited stage IV colorectal cancer. Jones RP, Stattner S, Sutton P, McWhirter D, Fenwick SW, Malik HZ, Poston GJ. Published Surgical Oncology 2014 23: 53-60

1.7 Book Chapters

Colorectal Liver Metastasis. Dunne DFJ, Jones RP, Adam R, Poston GJ. Chapter in Hepatobiliary and Pancreatic Surgery: Companion to Specialist Surgical Practice. Companion to Specialist Surgical Practice. 5, illustrated. Elsevier Health Sciences; 2013.

Colorectal Liver metastasis. Jones RP, Dunne DFJ, Poston GJ. Chapter in Recent advances in Surgery. Recent advances in surgery: 35. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2013.

Appendix 2: Presentations and abstracts.

2.1 Oral Presentations at Conferences

Prehabilitation before liver surgery. Dunne DFJ, Jones RP, Lythgoe DT, Malik HZ, Poston GJ, Palmer DH, Jack S, Fenwick SW.

ASGBI 2014, Harrogate

Age should not be used to determine fitness for hepatectomy. Dunne DFJ, Parry G, Miller S, Jones RP, McWhirter, D, Sutton P, Poston GJ, Malik HZ, Fenwick SW.

BASO 2013, London

The impact of fitness of the cost of hepatectomy. Dunne DFJ, Misra N, Estebanez G, Poston GJ, Malik HZ, Fenwick SW.

Presented BASO 2013, London

A prehabilitation program for liver surgery. Dunne DFJ, Jones RP, Malik H, Poston GJ, Palmer DH, Jack S, Fenwick S.

IHPBA 2012, Paris

Predicting complications in liver surgery. Dunne DFJ, Jones RP, Pilkington F, Misra N, Malik H, Jack S, Fenwick SW.

ASGBI 2012, Liverpool

Cardiopulmonary exercise testing increases hepatectomy rate in the elderly. Dunne DFJ, Malik H, Palmer DH, Poston GJ, Jack S, Fenwick SW.

Improving the perioperative management of resectable colorectal liver metastases

Digestive Disease Federation 2012, Liverpool

Improved patient selection combined with enhanced recovery can reduce length of stay in elderly patients undergoing resection of colorectal liver metastasis. Dunne DFJ, Jones R, Grunhagen D, Mchwirter D, Smith R, Lacasia C, Malik H, Poston G.

BASO 2011, London

2.2 Invited speaker presentations

Risk Assessment before Liver Surgery

Invited speaker, NCRI Future of Surgery Workshop. Royal College of Surgeons. November 2016

Prehabilitation before Liver Surgery

Invited speaker, AUGIS 2016, Leeds

Hepatectomy and the elderly: Cardiopulmonary exercise testing and prehabilitation.

Invited speaker, Dutch national surgical conference 2015, Eindhoven

Cardiopulmonary exercise testing in liver surgery: from research to practice.

Invited speaker Austrian National Surgical Conference 2014, Salzburg

Enhanced recovery in Liver surgery.

Invited speaker, Salzburg University hospital. February 2013, Salzburg

2.3 Poster Presentations

Age should not be used to determine fitness for hepatectomy. AUGIS

2013, Newcastle

The impact of fitness on hepatectomy. AUGIS 2013, Newcastle

Enhanced recovery following colorectal liver metastasis resection.

BASO 2012, London

Routine Staging Laparoscopy should not be used in Colorectal liver

metastasis. ESSO 2012, Valencia

Cardiopulmonary exercise testing (CPET) as a predictor of outcome in a

mixed hepatobiliary surgical cohort. ECCO 2011, Stockholm

Liver Resection in the Elderly: combined anaesthetic assessment and

enhanced recovery improves outcome. ECCO 2011, Stockholm

Enhanced Recovery in colorectal liver metastasis resection: Shorter

Hospital Stay and improved management of complications. AUGIS

2011, Belfast

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Morris EJ, Middleton R, Steward J, Richards MA, and ICBP Module 1 Working Group. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet*. England; 2011Jan1;377(9760):127-38.

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