Randomized clinical trial

Randomized clinical trial of prehabilitation before planned liver resection

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Background: **Patients with low fitness as assessed by cardiopulmonary exercise testing (CPET) have higher mortality and morbidity after surgery. Preoperative exercise intervention, or prehabilitation, has been suggested as a method to improve CPET values and outcomes. This trial sought to assess the capacity of a 4-week supervised exercise programme to improve fitness before liver resection for colorectal liver metastasis.**

Methods: **This was a randomized clinical trial assessing the effect of a 4-week (12 sessions) high-intensity cycle, interval training programme in patients undergoing elective liver resection for colorectal liver metastases. The primary endpoint was oxygen uptake at the anaerobic threshold. Secondary endpoints included other CPET values and preoperative quality of life (QoL) assessed using the SF-36®.**

Results: **Thirty-eight patients were randomized (20 to prehabilitation, 18 to standard care), and 35 (25 men and 10 women) completed both preoperative assessments and were analysed. The median age was 62 (i.q.r. 54–69) years, and there were no differences in baseline characteristics between the two groups. Prehabilitation led to improvements in preoperative oxygen uptake at anaerobic threshold (+1·5 (95 per cent c.i. 0·2 to 2·9) ml per kg per min) and peak exercise (+2·0 (0·0 to 4·0) ml per kg per min). The oxygen pulse (oxygen uptake per heart beat) at the anaerobic threshold improved (+0·9 (0·0 to 1·8) ml/beat), and a higher peak work rate (+13 (4 to 22) W) was achieved. This was associated with improved preoperative QoL, with the overall SF-36® score increasing by 11 (95 per cent c.i. 1 to 21) ($P = 0·028$) and the overall SF-36® mental health score by 11 (1 to 22) ($P = 0·037$).**

Conclusion: **A 4-week prehabilitation programme can deliver improvements in CPET scores and QoL before liver resection. This may impact on perioperative outcome. Registration number: NCT01523353 (https://clinicaltrials.gov).**

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Introduction

Patients with lower oxygen uptake ($\dot{V}O_2$) at the anaerobic threshold (AT), as assessed by cardiopulmonary exercise testing (CPET), have higher mortality, higher morbidity and longer hospital stay when undergoing major surgery[1,2]. In patients with cancer, postoperative rehabilitative exercise therapy improves 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 while awaiting adjuvant treatments[3]. Postoperative rehabilitation also fails to add any of the benefits of exercise therapy to the immediate perioperative period[4]. 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[4,5]. The use of prehabilitation in addition to rehabilitation has been shown to increase preoperative walking capacity and to aid functional recovery following colorectal resection[6].

Currently no randomized study of prehabilitation has delivered improved fitness, as measured objectively with

CPET, in a cancer population. The largest randomized trial of prehabilitation to date failed to demonstrate an advantage of a home-based exercise programme over a control arm of walking and breathing exercises[5]. A number of non-randomized studies[7–9] have demonstrated that supervised exercise programmes, typically of 6 weeks or more, could deliver clinically relevant improvements in fitness. However, this delay is not always feasible when treating malignant disease. This randomized clinical trial sought to assess the feasibility of a 4-week supervised preoperative exercise programme in patients awaiting surgery for colorectal liver metastasis (CRLM), assessing the impact on preoperative fitness, QoL, perioperative outcomes and subsequent postoperative course.

Methods

This was a randomized clinical trial conducted with ethical approval from the UK Research Ethics Service (Integrated Research Application System ID: 65982), and registered on Clinicaltrials.gov (NCT01523353).

Participants

All patients with CRLM referred to the tertiary hepatobiliary service at Aintree University Hospital, Liverpool, UK, were screened for potential eligibility. Patients with resectable CRLM were eligible for recruitment if aged over 18 years, able to give informed consent, partake in cycle-based exercise, and complete the exercise programme before the proposed surgery date. Resectability was defined in the multidisciplinary meeting at the tertiary hepatobiliary centre as: metastases deemed surgically treatable with curative intent (either 1- or 2-stage resection). Patients were ineligible for recruitment if they had known pre-existing chronic liver disease.

Potentially eligible candidates were given details of the study at the first clinic attendance, but were invited to participate only once a decision to proceed to surgery had been made, and full informed consent obtained. Ethical approval stipulated that recruitment to the study must not result in delayed surgical care. Consequently patients were potentially eligible only when the provisional operative date allowed at least 4 weeks for prehabilitation.

Randomization

Candidates were randomized to either a prehabilitation exercise programme or standard care by means of a random number block randomization list created at the trial outset. An individual, independent of the study group, held this list and provided e-mail results of randomization following recruitment.

Interventions

Prehabilitation consisted of 12 interval exercise sessions over a 4-week period. The programme was developed within an exercise laboratory, and validated in a healthy population[10]. Two recovery exercise sessions were included at the end of the first and fourth weeks (sessions 3 and 12). The interval sessions included a warm-up and warm-down, and 30 min of interval training alternating between exercise of moderate (less than 60 per cent $V\text{O}_2$ at peak exercise) and vigorous (more than 90 per cent $V\text{O}_2$ at peak) intensity[11]. The sessions were delivered using a cycle ergometer (Optibike; Ergoline, Bitz, Germany). The exercise programme was personalized to candidates following a standardized equation based on the work rate at their anaerobic threshold on baseline CPET. No restrictions were placed on candidates in either arm of the study, and they were encouraged to follow clinical advice on exercise before surgery.

Cardiopulmonary exercise testing

The methodology for performing CPET has been described previously[12]. Clinical physiologists performed the tests. Patients were asked to continue their normal medication before the test. CPET was performed on an electromagnetically braked cycle ergometer (Ergoselect 200; Ergoline). The protocol consisted of 3 min of rest, followed by 3 min of freewheel pedalling, then a ramped, incremental protocol until volitional termination. This was followed by 5 min of recovery. Ventilation and gas exchange variables were measured using a metabolic cart (Geratherm Respiratory; Love Medical, Manchester, UK). Pulse rate, 12-lead ECG, non-invasive BP and pulse oximetry were monitored throughout. The exercise ramp gradient was set to 10–25 W per min, based on a calculation described by Wasserman *et al.*[13] using predicted $V\text{O}_2$ at unloaded pedalling, predicted $V\text{O}_2$ at peak exercise, height and patient age.

CPET-derived variables included $V\text{O}_2$ at AT (ml per kg per min), $V\text{O}_2$ at peak (ml per kg per min), $V_\text{E}/V\text{CO}_2$ (pulmonary ventilation during exercise/carbon dioxide output) at AT, absolute oxygen uptake at AT ($V\text{O}_2$ at AT (l/min)), absolute oxygen uptake at peak exercise ($V\text{O}_2$ at peak (l/min)), heart rate at AT (beats/min) and heart rate at peak (beats/min). These variables were defined as described by Wasserman and colleagues[13].

The AT was estimated using a conventional cluster of variables (breakpoint in the $V\text{CO}_2$–$V\text{O}_2$ relationship) with increases in the ventilatory equivalent of oxygen ($V_\text{E}/V\text{O}_2$) and end-tidal oxygen tension, but no increase in $V_\text{E}/V\text{CO}_2$ or fall in end-tidal carbon dioxide tension. $V\text{O}_2$ at peak was taken as the highest $V\text{O}_2$ attained over a 30-s average.

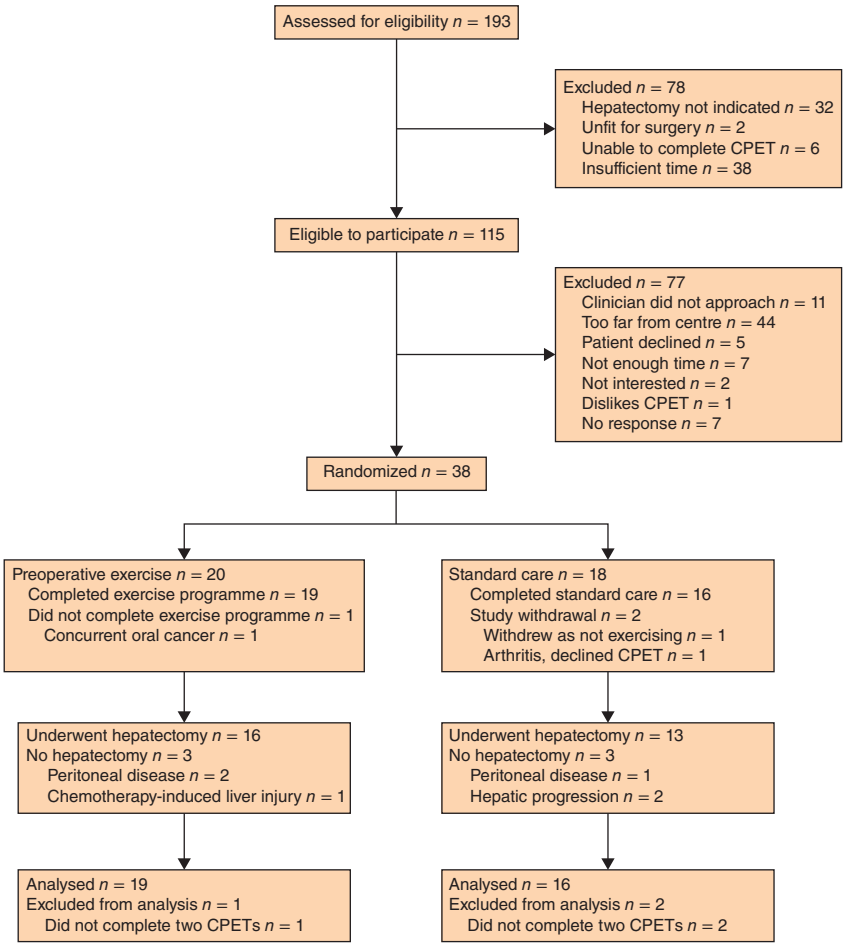

Fig. 1 CONSORT diagram for the study. CPET, cardiopulmonary exercise testing

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

Patients were considered high-risk if their baseline $V\mathrm{O}_2$ at AT was less than 11 ml per kg per min. High-risk patients were admitted routinely to critical care after surgery, and had increased intraoperative monitoring and support[14] .

Primary outcome measure

The primary aim of the study was to improve preoperative $V\mathrm{O}_2$ at the AT by 1·5 ml per kg per min. This was considered achievable and clinically relevant. If delivered across a patient population[14], it could reduce the proportion of patients considered high-risk ($V\mathrm{O}_2$ at AT of less than 11 ml per kg per min) by 30 per cent.

Secondary outcome measures

Secondary outcome measures included changes in the other preoperative CPET measures, and changes in the preoperative QoL score, assessed using the Short Form 36 (SF-36®; QualityMetric, Lincoln, Rhode Island, USA) questionnaire[15]. Data were also collected on operative intervention, perioperative outcomes and subsequent postoperative progress. The study was not statistically powered for formal assessment of differences in perioperative or long-term outcome, and these data are descriptive.

Blinding

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

Sample size

Preliminary data suggested that the target population had a mean(s.d.) $V\mathrm{O}_2$ of 12·0(2·0) ml per kg per min. To

Table 1 Characteristics of patients in the study cohort

	Study cohort ($n = 37$)	Prehabilitation ($n = 20$)	Standard care ($n = 17$)
Age (years)*	62 (54–69)	61 (56–66)	62 (53–72)
Sex ratio (M : F)	26 : 11	13 : 7	13 : 4
Body mass index (kg/m^2)†	29·5(4·1)	29·7(4·2)	29·3(4·2)
Smoking status			
Smoker	5	2	3
Ex-smoker	6	3	3
Non-smoker	26	15	11
Co-morbidity			
Cardiovascular	18	10	8
Respiratory	7	3	4
Diabetes	4	2	2
Renal disease	1	1	0
None	4	1	3
Primary tumour			
Node-positive	22	12	10
Adjuvant or neoadjuvant treatment	18	11	7
Metastatic presentation			
Synchronous presentation	18	8	10
Extrahepatic metastatic disease	7	3	4
> 3 hepatic metastases	12	5	7
Metastasis > 5 cm in diameter	13	7	6
Neoadjuvant chemotherapy	22	12	10

Values are *median (i.q.r.) and †mean(s.d.).

Table 2 Changes in cardiopulmonary exercise testing values and quality-of-life indices following prehabilitation or standard care

	Prehabilitation				Standard care				Study arm comparison	
	Baseline*	Post*	Change†	P‡	Baseline*	Post*	Change†	P‡	Exercise *versus* standard†	P§
V_{O_2} at AT (ml per kg per min)	11·2(1·5)	12·2(2·4)	1·0 (–0·2, 2·1)	0·093	11·4(1·8)	11·0(2·1)	–0·5 (–1·2, 0·1)	0·088	1·5 (0·2, 2·9)	0·023
V_{O_2} at peak (ml per kg per min)	17·6(2·3)	19·6(3·8)	2·0 (0·4, 3·6)	0·019	18·6(3·9)	18·7(4·1)	0·0 (–1·3, 1·2)	0·958	2·0 (0·0, 4·0)	0·047
Oxygen pulse at AT (ml/beat)	8·8(2·5)	9·6(2·9)	0·8 (0·1, 0·5)	0·025	9·6(3·1)	9·6(3·3)	–0·1 (–0·7, 0·5)	0·766	0·9 (0·0, 1·8)	0·050
Oxygen pulse at peak (ml/beat)	10·7(3·0)	11·6(3·0)	0·8 (–0·1, 1·7)	0·078	11·8(3·8)	12·1(3·8)	0·2 (–0·6, 0·9)	0·643	0·7 (–0·5, 1·9)	0·263
Peak work rate (W)	125(26)	138(35)	13 (7, 19)	0·001	138(39)	140(39)	0 (–5, 6)	0·927	13 (4, 22)	0·005
Heart rate reserve (beats/min)	56(18)	62(20)	6 (1, 10)	0·031	57(18)	57(17)	0 (–4, 4)	0·869	1 (0, 12)	0·065
SF-36® scores										
Overall physical health	61(26)	72(20)	11 (4, 17)	0·003	65(21)	68(21)	3 (–4, 10)	0·360	8 (–1, 16)	0·102
Overall mental health	66(22)	77(19)	11 (5, 18)	0·003	72(19)	72(23)	0 (–9, 9)	0·989	11 (1, 22)	0·037
Overall QoL	65(23)	77(18)	12 (5, 19)	0·002	71(20)	71(22)	1 (–7, 9)	0·828	11 (1, 21)	0·028

Values are *mean(s.d.) and †mean (95 per cent c.i.). V_{O_2}, oxygen uptake; AT, anaerobic threshold; QoL, quality of life. ‡Paired t test; §independent t test.

demonstrate an increase of 1·5 ml per kg per min, with a power of 0·8 and a type I error probability of 0·05, 15 pairs of subjects were required. Assuming an attrition rate of 25 per cent[9], a total recruitment of 38 patients was required.

Statistical analysis

Continuous normally distributed data were analysed using a t test, and the Mann–Whitney U test was used for continuous data with a non-normal distribution. Categorical data were analysed with the χ^2 test or Fisher's exact test, as appropriate. All statistical tests were conducted using SPSS® version 20.0 (IBM, Armonk, New York, USA).

Results

The first candidate was recruited in August 2011, and the trial closed in February 2013, when planned recruitment was achieved. Of 193 consecutive patients assessed for eligibility, 115 were deemed potentially eligible. Some 104 patients were approached, of whom 38 agreed to participate and were randomized. One of the commonest reasons for ineligibility (38 patients) or failure to recruit (7)

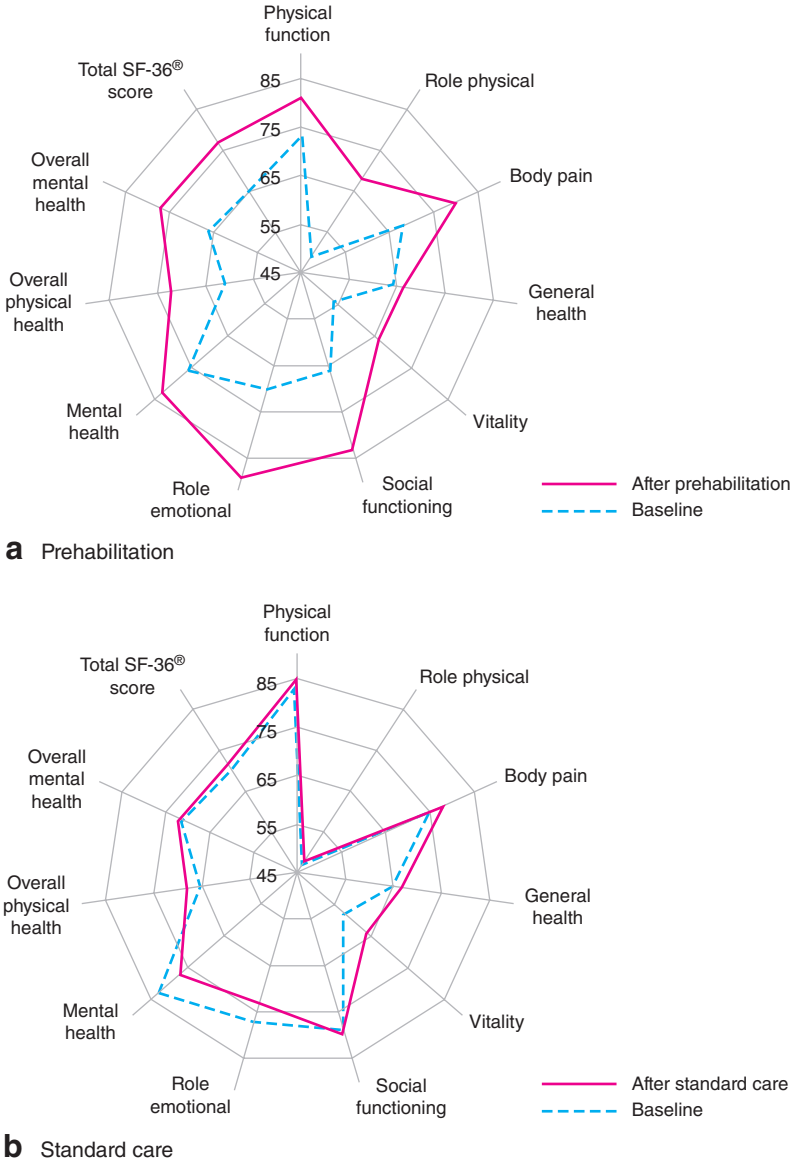

Fig. 2 Radar graphs demonstrating changes in quality-of-life scores for patients undergoing **a** the prehabilitation exercise programme and **b** standard care

was insufficient time to complete the prehabilitation programme before the surgery date. Forty-four patients declined to participate owing to the distance from the tertiary centre. One patient withdrew before completing the baseline assessment, before being informed of the results of randomization, and was excluded from the analysis (*Fig. 1*).

Study cohort demographics

There were no significant differences in baseline demographic characteristics (*Table 1*), cardiopulmonary exercise test variables or QoL scores between the prehabilitation and standard care arms. Based on the $V\text{O}_2$ at AT, nine patients were defined as high-risk in the prehabilitation arm, and eight in the standard care arm. One of the high-risk patients on standard care discontinued the study following baseline assessment, leaving seven in that arm for subgroup analysis.

Study progress

Of the 37 patients who completed the baseline assessment and were randomized, there were two withdrawals

Table 3 Changes in cardiopulmonary exercise testing values and quality-of-life indices following prehabilitation or standard care for patients considered high-risk at baseline testing (oxygen uptake at anaerobic threshold less than 11 ml per kg per min)

	Prehabilitation				Standard care				Study arm comparison	
	Baseline*	Post*	Change†	*P*‡	Baseline*	Post*	Change†	*P*‡	Exercise *versus* standard†	*P*§
V_{O_2} at AT (ml per kg per min)	10·0(0·9)	11·9(2·2)	1·9 (0·1, 3·6)	0·037	9·8(1·1)	9·4(1·1)	−0·4 (−1·4, 0·6)	0·379	2·3 (0·3, 4·2)	0·029
V_{O_2} at peak (ml per kg per min)	16·1(2·2)	18·9(4·7)	2·8 (−0·4, 5·9)	0·075	15·7(2·2)	16·0(3·5)	0·3 (−2·0, 2·6)	0·760	2·5 (−1·3, 6·2)	0·157
Oxygen pulse at AT (ml/beat)	8·1(1·9)	9·3(2·2)	1·2 (0·1, 2·3)	0·035	7·3(1·7)	7·3(1·7)	0·0 (−0·5, 0·6)	0·907	1·2 (−0·1, 2·4)	0·062
Oxygen pulse at peak (ml/beat)	9·9(1·9)	11·3(2·2)	1·3 (−0·1, 2·9)	0·068	8·9(2·1)	9·5(2·0)	0·5 (−0·2, 1·3)	0·132	0·8 (−0·9, 2·6)	0·308
Peak work rate (W)	117(20)	130(34)	13 (0, 27)	0·052	118(27)	117(28)	−1 (−9, 7)	0·738	14 (−1, 30)	0·066
Heart rate reserve (beats/min)	54(18)	58(23)	4 (−4, 13)	0·278	59(21)	55(22)	−3 (−7, 1)	0·113	7 (−2, 17)	0·074
SF-36® scores										
Overall physical health	53(27)	66(27)	13 (2, 24)	0·027	53(21)	56(15)	1 (−8, 14)	0·536	10 (−5, 24)	0·151
Overall mental health	63(25)	75(24)	12 (1, 23)	0·038	61(20)	61(25)	0 (−21, 22)	0·963	11 (−9, 31)	0·247
Overall QoL	59(25)	73(23)	14 (1, 27)	0·039	59(21)	59(21)	0 (−14, 15)	0·945	13 (−5, 30)	0·140

Values are *mean(s.d.) and †mean (95 per cent c.i.). V_{O_2}, oxygen uptake; AT, anaerobic threshold; QoL, quality of life. ‡Paired *t* test; §independent *t* test.

before the second assessment. One patient in the prehabilitation arm developed an unrelated malignancy and underwent emergency surgery. One patient withdrew from the standard care arm upon hearing the results of randomization, as this patient wished to participate only if randomized to the exercise programme. Of patients within the exercise arm, 18 of 19 completed 100 per cent of the exercise sessions, with one patient missing two sessions whilst having emergency colonic stenting for an obstructing primary tumour. Of the 35 patients (25 men and 10 women) who completed both CPET assessments, 34 underwent surgical intervention. One patient was found to have advanced extrahepatic disease during investigation for abdominal pain, and did not proceed to surgery. This patient was included in analysis of the prehabilitation effect but excluded from the operative intervention analysis. Of 34 patients who had surgery, five underwent laparotomy without liver resection because of the intraoperative identification of unresectable disease. This comprised three patients with peritoneal metastases, one patient with multiple additional hepatic metastases, and one with chemotherapy-induced liver injury that precluded extended resection. There were no reported adverse outcomes of the exercise intervention.

Cardiopulmonary exercise test variables

Prehabilitation led to an improvement in V_{O_2} at AT of 1·5 ml per kg per min ($P = 0·023$), as well as an improvement in V_{O_2} at peak (2·0 ml per kg per min) ($P = 0·047$), oxygen pulse at AT (0·9 ml/beat) ($P = 0·050$) and a higher peak work rate (13 W) ($P = 0·005$) compared with values in the standard care arm (*Table 2*).

Within the prehabilitation arm there were significant improvements in a number of CPET variables, including V_{O_2} at peak, heart rate reserve and oxygen pulse at AT (*Table 2*). By comparison, there were no significant improvements within the standard care arm. No patient in the standard care arm had a significant improvement in V_{O_2} at AT, and four had a deterioration in excess of 1·5 ml per kg per min. Overall, there was a non-significant trend towards worse V_{O_2} at AT ($P = 0·088$).

Quality-of-life changes

Changes in the preoperative QoL measures are summarized in *Table 2* and *Fig. 2*. Within the prehabilitation arm there were significant improvements in the SF-36® scores, but not in the standard care arm.

When the study arms were compared, prehabilitation was associated with improvements in overall SF-36® QoL (+11, 95 per cent c.i. 1 to 21; $P = 0·028$) and SF-36® mental health (+11, 1 to 22; $P = 0·037$) scores. There was also a trend toward greater SF-36® physical health (+8, −1 to 16; $P = 0·102$).

Subgroup analysis of high-risk patients

A subgroup analysis of patients deemed high-risk on baseline CPET demonstrated similar results to those for the overall cohort (*Table 3*). Mean V_{O_2} at AT in the prehabilitation arm improved by 2·3 (95 per cent c.i. 0·3 to 4·2) ml per kg per min ($P = 0·029$), so that the mean V_{O_2} at AT was above the 11·0 ml per kg per min threshold considered to indicate high risk. Of the nine patients defined as high-risk at baseline, five were no longer considered to be so.

Trends towards improvement that approached statistical significance were seen for several other measures following

Table 4 Summary of operative intervention and perioperative outcome

	Overall ($n = 34$)	Prehabilitation ($n = 19$)	Standard care ($n = 15$)
Extent of liver resection			
Major	10	6	4
Minor	19	10	9
None	5	3	2
Additional procedure			
Yes	5	3	2
No	29	16	13
Additional procedures			
Bile duct reconstruction	1	1	0
Right hemicolectomy	1	1	0
Incisional hernia repair	1	0	1
Excision of wound metastasis	2	1	1
Portal vein ligation	1	0	1
Hepatic segments treated*	3 (1–4·3)	3 (1–4·5)	3 (1–4)
Hepatic metastases treated*	2 (2–4)	2 (1–4)	2 (1–4·3)
Elective critical care admission*	12	8	4
Duration of stay in critical care (days)*	1 (1–2)	1 (1–2)	1·5 (1–2)
No. with complications			
All grades	15	8	7
Grades III and IV	4	3	1
Duration of hospital stay (days)*	5 (4–6·5)	5 (4–6)	5 (4·5–7)
Readmission	4	4	0

*Values are median (i.q.r.).

prehabilitation (*Table 3*). Little change, or even deterioration, was seen in patients managed on standard care.

Perioperative intervention and outcomes

Surgical interventions and perioperative outcomes are summarized in *Table 4*; there was no statistically significant difference in any postoperative outcomes between the two arms. Complications are summarized in *Table S1* (supporting information). Again, there were no significant differences in complication types between study arms.

Discussion

This randomized study demonstrates that a short preoperative prehabilitation programme can deliver considerable improvements in preoperative CPET scores. Better CPET-derived variables are associated with lower morbidity, mortality and hospital stay after major abdominal surgery[2]. Although the impact of improved CPET scores on operative morbidity and mortality has yet to be demonstrated, this study suggests that patients deemed high-risk[14] for major abdominal surgery may be able to modulate their risk by means of prehabilitation.

The prehabilitation programme achieved its primary objective of a 1·5-ml per kg per min improvement in $V\text{O}_2$ at AT, in comparison with standard care. This is an important achievement given the failures of previous attempts to deliver this result within a similar time interval[5]. Patients of poorer fitness, deemed high-risk on baseline assessment, had considerable gains in $V\text{O}_2$ at AT. This suggests that these patients may have more to benefit from prehabilitation, certainly if the operative risk can be brought into line with the patients of higher baseline $V\text{O}_2$ at AT. Within the prehabilitation arm, a number of measures of preoperative fitness seen as potentially relevant to predicting outcome[16] also improved.

An unexpected finding was the marked deterioration in some patients randomized to standard care. Crucially, this raises the question about timing of any preoperative CPET. Many studies of CPET fail to report on the timing of the test in relation to surgery[1,2] . CPET 4 weeks before surgery that suggests a patient is low-risk may in fact be inaccurate by the time of operation, representing a major confound to the literature.

The variation in response to the standard exercise programme is interesting and in keeping with the theory of 'responder/non-responder' based on genetic markers[17]. This variation in response to a prehabilitation programme means that it is difficult to justify delaying surgical intervention. Future work should focus on identifying individuals in whom benefit is likely to be greatest, so that more resources can be dedicated to their prehabilitation.

The greatest benefit would be expected in $V\text{O}_2$ responders, although absence of a $V\text{O}_2$ response may not represent a failure of delivering benefit. In the prehabilitation arm, nearly 40 per cent of patients

responded to the exercise programme in terms of increasing V_{O_2} at AT; however, it may be that the programme prevented the 'non-responders' from deteriorating as seen in the standard care group. The prehabilitation programme may have delivered other established exercise benefits, including improved muscle bulk, insulin resistance and preoperative psychological status, which could all contribute to an improved outcome[18–20].

Most of the improvement in QoL was the result of improvements in mental health, particularly emotional and social functioning, in concordance with other studies of exercise in patients with cancer[21]. It is, however, interesting that a 4-week programme of just 12 sessions was able to achieve similar improvements to programmes typically of much longer duration[22]. The improvements in QoL are probably related to participation in the exercise programme, rather than improved physical function. In the control arm, in comparison to the deterioration in CPET values, QoL values were largely unchanged, suggesting that QoL was independent of physical fitness. This suggests that improvements in physical fitness do not necessarily correlate with improved QoL, although participation in the exercise programme itself seemed to be key. This is similar to previous findings, although the mechanism for this improvement is not clear[23].

Study completion and attendance was high in comparison to that in other studies[5,9]. The high adherence suggests that the exercise intervention is acceptable, and that patients in the study cohort were highly motivated. This is likely multifactorial, including the supervised nature of the exercise and the interval-based nature of the training programme, with interval training shown to be more enjoyable than constant load programmes[24].

The results of this study offer an interesting avenue for future development, but some limitations must be considered. Importantly, although the study demonstrates that it is possible to deliver major improvements in CPET values, and it would appear logical to assume this will deliver the benefits associated with improved fitness[1,2], confirmation is required in a larger trial. A potential recruitment bias may limit generalizability to the wider population. The study cohort was younger than a typical patient group, suggesting that a preoperative exercise intervention may be more appealing to the younger patient population[14]. However, younger patients often have more aggressive disease[25], which may explain the rate of failure to progress to liver resection.

This study focused on improving the aerobic capacity of patients. However, a number of other patient factors, including nutritional status, conditioning and physiological status, can also affect outcome[26–28]. Some studies[6,29] have examined a multimodal prehabilitation programme. Utilizing the 6-min walk test (6MWT), these have consistently demonstrated an advantage over control arms in improving functional capacity. More recently, a pilot study[30] showed that the addition of whey supplementation to a nutritionally controlled diet can lead to improved 6MWT capacity. The optimal components of prehabilitation and rehabilitation programmes are yet to be established.

Prehabilitation offers an opportunity to improve preoperative education that is a key pillar of enhanced recovery after surgery (ERAS)[26]. The additional time spent with patients during the exercise programme provides an opportunity for education, which can reduce preoperative anxiety, improving postoperative gut motility and wound healing[26–28]. The benefits of improved fitness, alongside the potential benefits of increased preoperative education, are consistent with the goals and mechanisms underpinning ERAS programmes, and warrant evaluation in a larger randomized study.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Complications (Word document)