Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Esophagus (PRE-HIIT)

A Randomized Controlled Trial

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Objective: This randomized controlled trial (RCT) compared the impact of high-intensity interval training (HIIT) versus standard care (SC) on preoperative cardiopulmonary fitness in patients before esophageal or lung cancer surgery.

Background: Exercise prehabilitation aims to optimise preoperative condition and attenuate postoperative risks. Although intuitive, defining the optimal training parameters to impact physiologically before surgery with attendant clinical benefit remains challenging.

Methods: Utilising a parallel, 2-armed RCT design, n = 79 participants [(mean age (SD): 64 (9.3) years, 67% males] scheduled for curative resection for lung (50.6%) or esophageal (49.6%) cancer with ≥ 2-weeks preoperative lead-in, were recruited and randomised to HIIT (n = 41) or SC (n = 38). HIIT was completed on an electronically braked cycle ergometer consisting of 30 minutes of 15-second intervals at 100% peak power output alternating with 15-second active recovery for 5 days/week. The SC arm was offered moderate-intensity exercises 2 to 3 days/week. The primary outcome was peak oxygen consumption (VO_2peak), measured by cardiopulmonary exercise testing. Secondary outcomes included lower limb strength and physical functioning.

Results: Baseline cardiopulmonary fitness was predominantly very poor [n = 75 (95%)]. Adjusting for baseline in a linear model, VO_2peak increased significantly ($P = 0.05$) in the HIIT group versus SC (6.6% between-group difference). HIIT increased VO_2peak from 18.7 (5.0) to 21.7 (5.7) ml/kg/min, whereas with SC it remained unchanged at 19.6 (5.4) to 20.1 (5.7) ml/kg/min from pre-intervention to post-intervention. Sit-to-stand scores were significantly ($P = 0.02$) improved with HIIT.

Conclusions: HIIT is effective for eliciting meaningful gains in preoperative fitness in a deconditioned cohort within short timeframes.

Key Words: cardiopulmonary fitness, esophageal cancer, lung cancer, prehabilitation

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Attenuating postoperative risk is a priority of patient-centered preoperative assessment and enhanced recovery after surgery protocols.[1] In lung and esophageal cancer, surgical resection is the preferred curative intervention;

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European Surgical Association: Pre-HIIT RCT.
Trial registration: The study was prospectively registered with clinicaltrials.gov on 7th June 2019 (NCT03978325).
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however, patient factors and the complexity of surgery underlie significant postoperative risks. For esophageal cancer, contemporary data from over 6000 patients from 39 high-volume centers report a 61% postoperative complication rate, and 4.5% 90-day mortality.[2] Comparably, high-volume centers report postoperative complications in up to 53.4% of patients after lung surgery,[3] with 9.2% experiencing more than 1 serious complication,[3] and a 90-day mortality of 3.1%.[4] Complications moreover have detrimental impacts on length of stay, readmission rates, health care costs, long-term morbidity, and recovery of health-related quality of life.[1]

Preoperative cardiopulmonary fitness is an established risk factor for postoperative complications.[5–7] In lung cancer, a peak oxygen consumption (VO_2peak) of < 10 ml/kg/min is associated with a 4 times greater risk of postoperative pulmonary complications compared with a VO_2peak > 17 ml/kg/min.[6] The prognostic value of VO_2peak in esophagectomy is unclear; however, several reports have described associations between higher preoperative fitness and better postoperative outcomes.[5,7] Although further validation of predictive cut-points is warranted, cardiopulmonary fitness is a key target, and there is significant interest in proactive interventions, in particular exercise, to enhance fitness preoperatively.[8]

Exercise prehabilitation aims to optimize a patient's preoperative condition, attenuate risk of postoperative complications, and accelerate postoperative recovery.[8] Although intuitive, defining the optimal training parameters to elicit meaningful physiological and clinical changes in patients undergoing complex cancer surgery remains challenging,[9–11] particularly in the context of short treatment timeframes.[12,13] Consequently, significant interest in more dose intense exercise prescriptions, such as high-intensity interval training (HIIT) has emerged. HIIT may elicit greater improvements in cardiopulmonary fitness within short timeframes in comparison to traditional moderate-intensity prescriptions.[14–16] To test this hypothesis, the preoperative high-Intensity Interval Training (PRE-HIIT) pilot randomized controlled trial (RCT) was designed to compare preoperative HIIT versus standard care (SC) on preoperative cardiopulmonary fitness in a relatively high-risk cohort of patients scheduled for esophageal or lung cancer surgery.

METHODS

Trial Design and Setting

PRE-HIIT was a pilot, parallel, 2-armed RCT. Detailed descriptions of the trial protocol[17] and subsequent amendments in response to the COVID-19 pandemic are published.[18] The trial was completed at St James's Hospital, Dublin, incorporating the National Center for Esophageal and Gastric Cancer and a supra-regional designated surgical center for lung cancer. Ethical approval was granted by the institutional research ethics committee (Project ID: 0059) and the trial was registered with ClinicalTrials.Gov (NCT03978325). Procedures performed were in accordance with the Declaration of Helsinki (1964) and its later amendments. Study appointments were completed at the Wellcome-HRB Clinical Research Facility, St James's Hospital. This manuscript adheres to the Consolidating Standards of Reporting Clinical Trials (CONSORT) guidelines.[19]

Participants

Enrollment commenced in June 2021 and was completed in July 2024. Participant eligibility included planned curative resection for lung or esophageal cancer, ≥ 2-weeks preoperative lead-in, and successfully completed baseline maximal cardiopulmonary exercise test (CPET). Participants with any American Thoracic Society/American College of Chest Physicians absolute contraindications for exercise testing, including cardiovascular and respiratory insufficiency, were excluded.[20] Participants provided written informed consent.

Randomization, Allocation, Concealment, and Blinding

Participants were randomized in a 1:1 ratio to the intervention (HIIT) or control (SC) arm by computer-generated randomization managed independently. Study assessments were performed by an assessor blinded to treatment allocation (N.K.). Because of the nature of the intervention, neither the trial physiotherapists nor patients could be blinded to the randomization assignment.

Trial Interventions

HIIT Arm

Participants in the HIIT arm received an individualized, physiotherapist-supervised HIIT program. HIIT was completed 5 days/week for a minimum of 2 weeks preoperatively. After 2 weeks, the number of exercise sessions reduced to 3 days/week. All exercise sessions were completed on an electronically braked cycling ergometer (Cosmed Ergoline GmbH, Germany). Intensity was prescribed using the peak power output (PPO) reached during the baseline CPET. Sessions included a 5-minute warm-up at 50% of PPO, 30 minutes of 15-second intervals changing between 100% PPO and 0 watts, and a 3-minute cool-down at 30 watts. Vital signs and Borg Rating of Perceived Exertion scores were recorded every 2 minutes. If maximal perceived exertion and heart rate maximum during exercise sessions were not reached/achieved, resistance was increased to achieve a PPO to elicit maximal response.

Intervention classes were supervised either in-person at the Wellcome-HRB CRF at St James's Hospital or remotely. Participants completing the intervention remotely received an electronically braked ergometer to their home, at least one home visit from the trial physiotherapist and class supervision through videoconferencing.

SC Arm

SC comprised a physiotherapy-led exercise prehabilitation programme, which incorporated 20 minutes of moderate-intensity aerobic exercise and 3 to 5 resistance exercises, targeting the major muscle groups of the body. The programme was offered to all surgical patients, twice weekly in-person at the Physiotherapy Department at the hospital, and trice weekly online.

All participants received standard preoperative nutritional optimization and smoking cessation advice through the preoperative clinics.

Data Collection and Outcomes

Data were collected at baseline (T0) and immediately post-intervention/preoperatively (T1). Descriptive and clinical data were collected from medical records. Anthropometric measures including weight and height were measured using standard procedures. The primary outcome, peak oxygen consumption (VO_2peak), was measured by a symptom-limited cardiopulmonary exercise test (CPET). CPETs were performed on a cycle ergometer (Cosmed Ergoline GmbH, Germany). Tests followed a progressive incremental protocol (10-25 watts per minute). Step gradient was calculated for each participant individually.[21] CPETs were medically supervised with heart rate, heart rhythm (12-lead ECG), non-invasive blood pressure and oxygen saturation monitoring. VO_2peak was calculated using the validated Fitness and the Importance of Exercise: A National Data Base (FRIEND) prediction equation{[1.74*[Power Output (W)*6.12/body weight (kg)] + 3.5}.[22–24] PPO was recorded as the highest power achieved during the test.

Secondary outcomes included a battery of lower limb strength and physical functioning outcomes. The short physical performance battery (SPPB), a validated, reliable measure of physical functioning evaluating 3 lower extremities tests: gait speed, chair stand and balance test.[25] Muscle strength was measured using one repetition maximum (1RM), completed on the horizontal leg-press machine.[26] Postoperative variables including length of stay, postoperative complications (Claiven-Dindo Classification[27] and the Comprehensive Complication Index[28]), postoperative mobilization and in-hospital mortality were documented from the electronic patient record.

Intervention feasibility was measured using recruitment potential, attrition rates, adverse events and adherence. Adherence metrics included compliance to prescribed exercise dose and reasons for dose modification.[29] Compliance to prescribed exercise dose was presented as relative dose intensity, defined as the ratio of total completed cumulative dose to the total planned cumulative dose and is expressed as a percentage. The frequency and reason for attrition were recorded in both groups. Adverse events were graded according to the Common Terminology Criteria for Adverse Events.[30]

Data Analysis

Sample Size Calculation

To detect a mean between-group difference in VO_2peak of 1 ml/kg/min (SD: 1.4 ml/kg/min, 80% power, 5% significance), allowing for 20% drop-out, a sample target of 78 (n = 39 per arm) was required.

Statistical Analyses

Statistical analysis was performed using R version 4.4.2. Variables were examined for normality using a qqplot. Between-group baseline characteristics and postoperative variables were compared using independent t tests, Mann-Whitney U tests, the Fisher exact test, and the χ^2 test where applicable. A linear model including baseline measurement and a between-group treatment interaction was used to model the change in outcomes between the groups.

RESULTS

Between June 2021 and July 2024, 1352 patients were assessed for eligibility, of whom 1090 were ineligible. Seventy-nine of 262 eligible participants were enrolled (recruitment rate 31%) (Fig. 1). The main reasons for declining were travel burden (33.5%, n = 60) and lack of interest (21.2%, n = 38). After baseline assessment 41 participants were randomized to HIIT and 38 randomized to SC. Groups were comparable at baseline (Table 1). Baseline mean age was 63.59 (9.3) years, n = 53 (67.1%) male, n = 39 (49.4%) esophageal cancer and n = 40 (50.6%) lung cancer.

Cardiopulmonary Fitness and Physical Functioning

Baseline cardiopulmonary fitness classifications were predominantly very poor (n = 75 (95%)) or poor (n = 2 (3%)) for age-matched and gender-matched norms.[26] Adjusting for baseline, VO_2peak increased significantly in the HIIT group compared with the SC group with a magnitude of 6.6% between-group difference ($P = 0.05$) (Fig. 2). Within group, the HIIT arm increased from 18.7 (5.0) ml/kg/min to 21.7 (5.7) ml/kg/min [mean SD change 1.98 (2.2) ml/kg/min], whereas the SC remained unchanged [19.6 (5.4) ml/kg/min to 20.1 (5.7) ml/kg/min] [mean SD change 0.86 (2.8) kg/ml/min] from pre-intervention to post-intervention. In relation to lower limb function, sit-to-stand scores reduced by 2.9 (1.6) seconds in the HIIT group and by 1.0 (5.4) seconds in the control group representing a 14.9% pre-to-post-intervention difference in favor of the HIIT arm ($P = 0.02$). Other secondary endpoints including total SBBP scores, gait time and 1RM leg press did not change (Table 2). Postoperative outcomes were the same for both groups.

Feasibility Metrics

Mean HIIT class attendance was 9.8 (4.9) sessions [454 planned, 391 (86% attended), 349 (89%) fully compliant with prescribed exercise dose] and 2.16 (2.7) sessions in the SC arm. Compliance to the prescribed HIIT exercise dose (relative dose intensity) was 80.5 (27.1) %. Two (4.9%) participants required pre-treatment dose reduction during 13 sessions and 2 (4.8%) participants required dose modification during 3 sessions. Ten participants withdrew (attrition rate 12.7%) and 14 (17%) post-intervention assessments were missed due to logistical challenges associated with COVID-19. Five grade 1 (mild) and one grade 2 (moderate) adverse events were documented in the HIIT arm (transient musculoskeletal issues).

DISCUSSION

In testing the primary endpoint hypothesis whether high-intensity interval training could impact positively on VO_2peak compared with standard care, the Pre-HIIT RCT reports a positive outcome. In terms of secondary endpoint, this effect may be associated with observed favorable changes in SPPB sit-to-stand time. Importantly, short intensive exercise programs [mean 9.77 (4.9) HIIT sessions] led to greater gains in both preoperative fitness and function in comparison to less frequent moderate-intensity programme over the same period, and therefore may have clinical impact and feasibility in the context of short surgical timeframes. Although the absolute change in VO_2peak within the HIIT arm is relatively modest, at 1.98 (2.2) ml/kg/min, notwithstanding, in colorectal surgery, a 1.0 ml/kg/min increase in fitness reduces the odds of postoperative complications by > 20% [odds ratio: 0.77 (95% CI: 0.66–0.89] whereas an increase of 2.0 ml/kg/min leads to a 40% reduction [odds ratio 0.6 (95% CI: 0.45–0.80)].[31] The observed improvements in some metrics of lower limb functioning suggest that HIIT may target skeletal endpoints. This merits further testing in the context of sarcopenia and frailty which are also associated with poorer postoperative outcome.[32] Pre-HIIT, while demonstrating improved physiological and physical metrics, was not designed or powered to assess the impact on postoperative complications but

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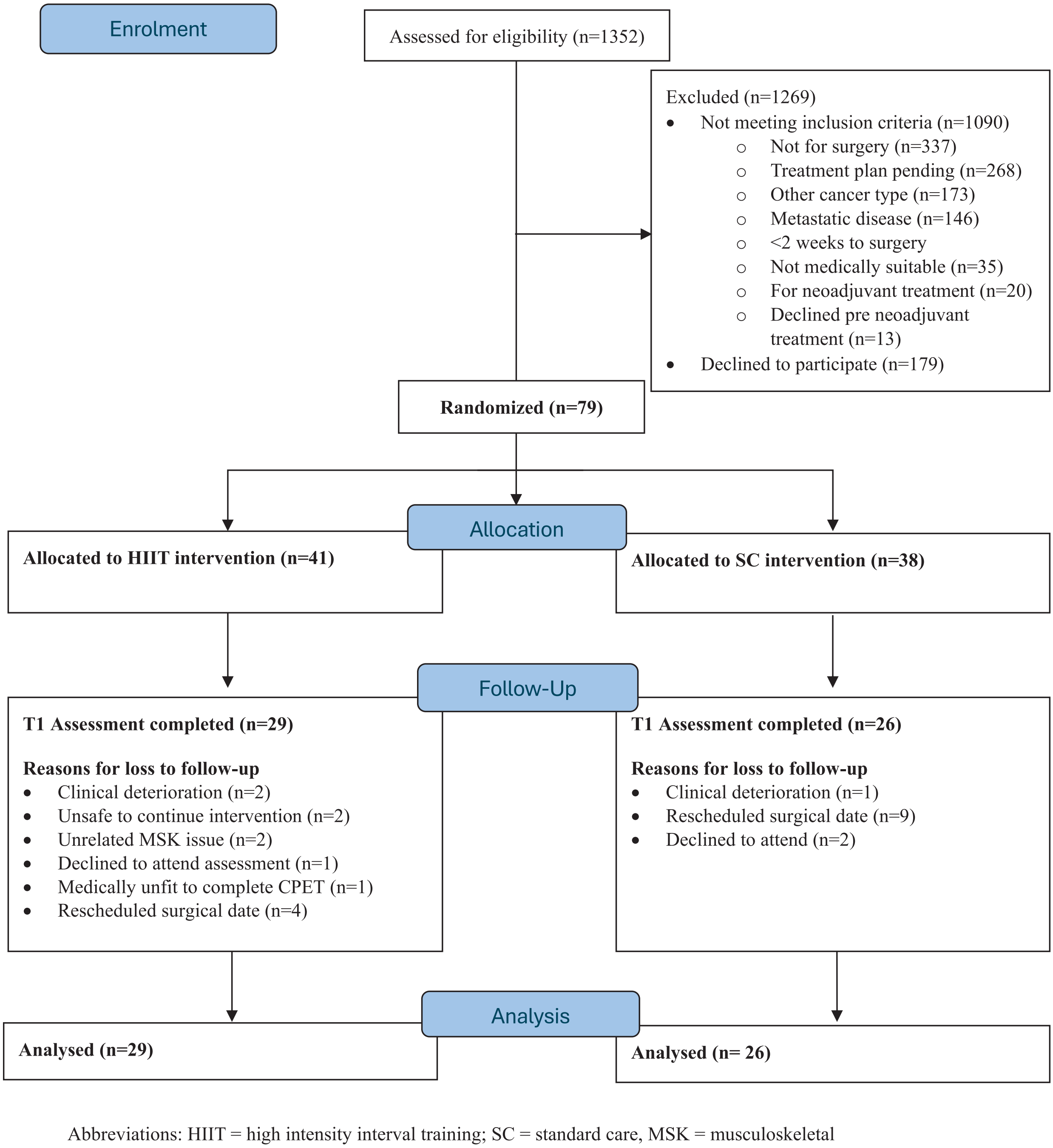

FIGURE 1. PRE-HIIT trial CONSORT flow diagram. MSK indicates musculoskeletal.

these data should stimulate the design of such studies in similar patient cohorts.

Systematic reviews and meta-analyses of preoperative HIIT report promising but inconclusive results, impacted by small sample sizes and concerns regarding protocol fidelity.[33,34] A meta-analysis of 6 RCTs found that HIIT did not significantly impact preoperative VO_{2peak} in comparison to usual care or moderate-intensity exercise (MD: 0.83, 95% CI: −0.51 to 2.17 kg/ml/min, $P=0.12$)[33] whereas a subsequent analysis of 8 interventions (7 RCTs, and 1 quasi-experimental trial) reported significant gains in preoperative VO_{2max} (MD: 2.76, 95% CI: 1.65, 3.86).[35] In abdominal surgery, HIIT increases VO_{2peak} by $>4.9\%$ in comparison to moderate-intensity training; however, trial methodology issues limit generalizability.[36] PRE-HIIT among RCTs is unique in several respects. First, it includes personalized pre-enrollment risk assessment incorporating medically supervised CPET. Second, there is full reporting of training adherence incorporating dose intensity and dose adjustment metrics, and, finally, objective monitoring of training completed in the HIIT arm providing for the first time high-fidelity data to guide personalized exercise prescription.

TABLE 1. PRE-HIIT Trial Participant Baseline Demographic, Clinicopathologic, and Physical Performance Characteristics

Demographic characteristics	Total cohort (n = 79)	HIIT (n = 42)	Standard care (n = 37)
Age (yrs)	63.59 (9.3)	62.07 (10.2)	65.24 (8.2)
Height (cm)	170.55 (9.1)	170.79 (9.5)	170.28 (8.7)
Weight (kg)	80.94 (16.3)	82.3 (16.9)	79.44 (15.7)
Female	26 (32.9)	14 (34.1)	12 (31.6)
Male	53 (67.1)	27 (65.9)	26 (68.4)
Clinicopathologic characteristics			
Esophageal cancer	39 (49.4)	21 (50.0)	18 (48.7)
Adenocarcinoma	31 (79.5)	20 (95.2)	11 (61.1)
SCC	7 (17.9)	1 (4.8)	6 (33.3)
Other	1 (2.5)	NA	1 (5.6)
Lung cancer	40 (50.6)	20 (47.6)	20 (55.1)
Adenocarcinoma	26 (32.9)	12 (60)	14 (70)
SCC	9 (11.4)	5 (25)	4 (20)
Other	5 (6.3)	3 (15)	2 (10)
Esophageal cancer neoadjuvant treatment	31 (79.5)	17 (41.5)	14 (77.8)
Neoadjuvant FLOT	16 (41.0)	11 (52.4)	5 (27.8)
Neoadjuvant CROSS	14 (35.9)	5 (23.8)	9 (50)
Physical performance measures			
Cardiopulmonary fitness			
$V0_{2peak}$(ml/kg/min)	19.12 (5.2)	18.7 (5.0)	19.6 (5.4)
Peak power output (Watts)	117.34 (43.7)	117.1 (45.1)	117.6 (42.8)
Short performance battery test (SPBT)			
Balance (point score)	4 (0)	4 (0)	4 (0)
Gait speed (point score)	4 (0)	4 (0)	4 (0)
Sit to stand (point score)	4 (1)	4 (1)	4 (1)
Total SPBT score (point score)	11.3 (1.2)	11.3 (1.2)	11.2 (1.1)
Gait time (s)	2.9 (0.7)	2.9 (0.7)	2.9 (0.7)
Sit to stand time (s)	10.34 (4.4)	10.3 (3.6)	11.3 (6.0)

Continuous data are presented as mean (SD) or median (interquartile range). Categorical data are presented as frequency (percentage).
FLOT indicates fluorouracil, leucovorin, oxaliplatin, and docetaxel; NA indicates not applicable; SCC, squamous cell carcinoma

The PRE-HIIT intervention was designed and delivered for the immediate preoperative period where the timeline to surgery is short, and the protocol aimed to elicit optimal gains in cardiopulmonary fitness without causing delays to surgery. This is particularly relevant in lung cancer where surgery is the primary treatment for stage I and II cancers and where preoperative exercise may have considerable clinical impact.[37] A systematic review of RCTs and quasi-RCTs of preoperative exercise interventions reported a 50% reduction in major postoperative complications (RR: 0.47; 95% CI: 0.27–0.80) and 2.5 day reduction in length of stay (MD: 2.52; 95% CI: 1.18–3.87) in lung cancer, albeit from low quality evidence.[38,39] In contrast to lung cancer, most patients requiring surgery for esophageal

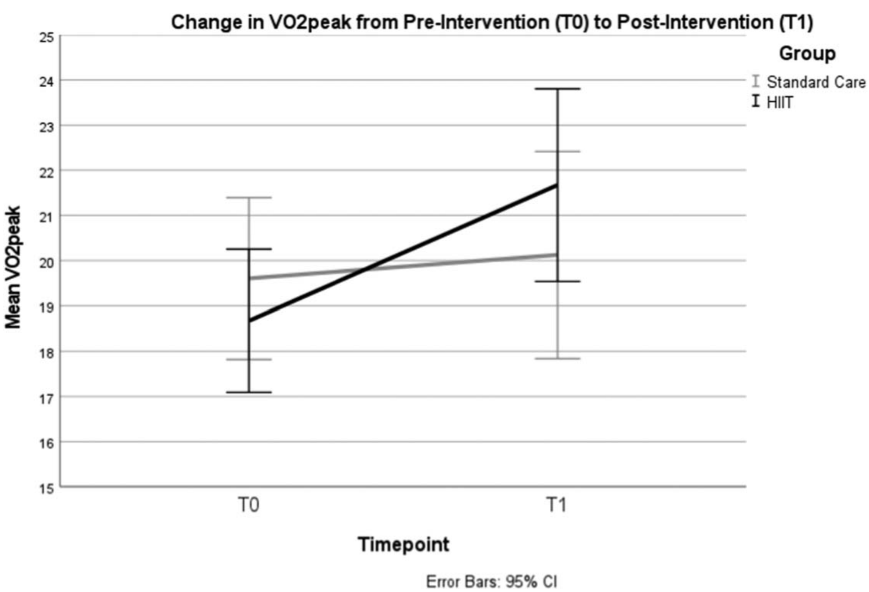

FIGURE 2. Changes in cardiopulmonary fitness [VO_2peak (ml/kg/min)] from T0 to T1. Correcting for baseline covariates, VO_2peak increased significantly in the HIIT group compared with the SC group with a magnitude of 6.6% between-group difference ($P = 0.05$).

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TABLE 2. PRE-HIIT Trial Results of Cardiopulmonary Fitness and Physical Functioning Outcomes

Measures	**Group**	**T0 mean (SD)**	**T1 mean (SD)**	**Mean change (SD)**	***P***
Cardiopulmonary Fitness					
$V0_{2peak}$(ml/kg/min)	HIIT	18.7 (5.0)	21.7 (5.7)	1.98 (2.2)	0.05
	SC	19.6 (5.4)	20.1 (5.7)	0.86 (2.8)	
Peak power output (watts)	HIIT	117.1 (45.1)	141.4 (48.7)	15.7 (18.9)	0.24
	SC	117.6 (42.8)	122.1 (48.2)	8.4 (18.1)	
Physical functioning					
Total SPPB score (point score)	HIIT	11.3 (1.2)	11.5 (1.1)	0.0 (0.9)	0.39
	SC	11.2 (1.1)	11.5 (1.1)	0.3 (0.5)	
Gait time (s)	HIIT	2.9 (0.7)	2.8 (0.8)	−0.1 (0.5)	0.92
	SC	2.9 (0.7)	2.8 (0.6)	−0.1 (0.5)	
Sit to stand time (s)	HIIT	10.3 (3.6)	8.3 (2.9)	−2.9 (1.6)	0.02
	SC	11.3 (6.0)	8.2 (3.7)	−1.0 (5.4)	
Leg strength [1RM leg-press (lbs)]	HIIT	201.8 (59.5)	227.7 (58.0)	17.3 (33.9)	0.55
	SC	187.3 (63.8)	207.6 (63.1)	22.9 (23.9)	

Postoperative Data*	Group	Postoperative Outcome		*P* for Between-Group Difference
First postoperative mobilization	HIIT	POD 0/1	24	0.94
		POD 2+	10	
	SC	POD 0/1	25	
		POD 2+	10	
		Missing	1	
In-hospital mortality	HIIT	Yes	1	0.30
		No	33	
	SC	Yes	0	
		No	36	
Postoperative complications (Clavien-Dindo classification)	HIIT	0	6	0.21
		II/II	19	
		III+	9	
	SC	0	12	
		II/II	19	
		III+	5	
Postoperative complications (Comprehensive Complications Index)	HIIT	22.6 (34.6)		0.39
	SC	20.9 (32.83)		
Critical care length of stay (d)	HIIT	4.0 (8.75)		0.16
	SC	2.5 (4.0)		
Hospital length of stay (d)	HIIT	11.0 (11.0)		0.46
	SC	9.0 (6.8)		

Continuous data are presented as mean (SD) or median (interquartile range). Categorical data are presented as frequency.

*Postoperative data are available for n = 69 participants (n = 7 did not proceed to surgery; n = 2 had surgery completed in a different hospital due to COVID-19 emergency measures).

POD indicates postoperative day

cancer undergo tri-modality treatment pathways incorporating perioperative chemo(radio)therapy, or perioperative chemotherapy, and this extends the prehabilitation timeframe. Hence, this represents an excellent model to study exercise prescriptions to target mitigation of the potential deleterious impact of these treatments on cardiopulmonary fitness and muscle strength,[1] and to optimize treatment tolerance and preoperative condition[40] and influence postoperative outcome.[41]

Cancer prehabilitation trials are challenging to deliver due to the complex treatment pathways often in elderly or comorbid cohorts.[42] In this study, the logistical challenge was amplified during the COVID-19 pandemic when clinical trials faced profound implementation and integrity difficulties.[43] Accordingly, PRE-HIIT implemented protocol amendments, including provision of hybrid programme delivery, telephone consultations and reducing the outcome battery to minimize assessment duration.[18,44] Intervention fidelity-assurance measures included delivering cycle ergometers to participants' homes, and online exercise supervision. Despite protocol adaptations, new barriers emerged, primarily disruption to admissions and late rescheduling of surgeries impacting opportunity for post-intervention assessment and subsequent attrition in PRE-HIIT. Statistical analysis accounts for trial attrition; however, future trials should consider how to maximize post-intervention data collection in pragmatic exercise prehabilitation trials.

Notwithstanding the challenges, PRE-HIIT reports that this approach is both feasible and safe in these patient cohorts and may lead to meaningful physiological and functional benefit. There was high attendance at planned sessions and comparable levels of attrition with SC moderate-intensity exercise, and no serious adverse events, consistent with other reports of preoperative exercise prescriptions.[45–47] Furthermore, through high-quality intervention monitoring,[29] PRE-HIIT reports high adherence to HIIT exercise dose [relative dose intensity 80.5 (27.1)%] and minimal alterations to dose prescription. There is considerable potential for high-intensity interventions such as

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HIIT to be delivered safely, accurately and effectively within time-sensitive surgical pathways for deconditioned cancer cohorts.

We acknowledge some limitations. First, this trial received ethical approval to open in March 2020, and the pandemic had a major impact.[18] Participation was optimized through hybrid programme delivery; however, travel burden, particularly for in-hospital assessments, was the most highly cited reason for non-participation. This is reflected in our recruitment rate of 31%, which albeit consistent with the published literature,[48,49] is lower than our previous experience.[50] Notwithstanding, we achieved 100% accrual. Furthermore, the major challenge for PRE-HIIT was the impact of the pandemic on surgical planning and move towards the day of surgery admission at our Center, which limited the opportunity for patients living significant distances from the hospital (up to 285 km) to attend for T1 assessments. Second, the global shift towards telehealth post-pandemic has profoundly changed patients' expectations for interventions such as prehabilitation and future trials should consider incorporating an assessment battery suitable for remote completion. Third, we could not use breath-by-breath analysis as planned due to equipment failure. Finally, PRE-HIIT was always powered for preoperative change in fitness. The impact on postoperative outcomes should be examined in larger, adequately powered future studies.

In conclusion, preoperative HIIT resulted in significantly greater gains in preoperative cardiopulmonary fitness in comparison to clinical SC. Notwithstanding the logistical challenges, HIIT was feasible for patients to complete, with minimal adverse events and high programme fidelity. We trust, however, that these data will encourage validation of this approach with large trials in these patient cohorts encompassing physiological, functional, and preoperative and postoperative study endpoints.

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DISCUSSANTS

Jari Rasanen (Helsinki, Finland)

Thank you to the association for the opportunity to discuss this paper. I also thank the authors for providing the manuscript well in advance and for presenting it so clearly. Cardiopulmonary fitness is widely accepted as an excellent predictor of a patient's ability to recover from major surgical procedures. In this randomized controlled trial, the authors compared intensive high-intensity interval training (HIIT; 5 sessions/week) with a moderate-activity control group (2–3 sessions/week) over a short preoperative period. The results showed: (a) VO2 peak improved in patients randomized to HIIT; (b) the HIIT group also demonstrated superior gains in sit-to-stand time, and (c) HIIT proved to be safe and well tolerated. I find this study very enlightening in the field of prehabilitation for these patients. Your work has many strengths. It is well-structured, well-written, and the research question is clear. Although conducting the study during the COVID-19 pandemic posed challenges, you handled these admirably.

I just have one question:

Screening involved 1352 patients, of whom 1090 did not meet the inclusion criteria. Participation acceptance was relatively low, with 179 patients declining to participate and only 79 patients enrolled. What lessons can we draw from your experience to optimize prehabilitation for patients with esophageal and lung cancer in everyday clinical practice?

Response From Emer Guinan (Dublin, Ireland)

Regarding the clinical impact, the first thing to say is that these patients were highly deconditioned at baseline. There is a major need to improve cardiopulmonary fitness in this group. We see evidence from other areas where improvement in cardiopulmonary fitness can have an impact on postoperative outcomes. Some of that varies by surgery type or patient cohort. However, ultimately, the big question is whether this improvement in fitness translates to better postoperative outcomes. I suppose that is something we need to investigate further in other trials in this group. That said, it would certainly seem that, as an exercise training modality, it may lead to greater gains in cardiopulmonary fitness over a shorter timeframe.

Christiane Bruns (Cologne, Germany)

Thank you for this great initiative. My first question regards the inclusion criteria. You talked about major surgery for lung cancer or esophageal cancer. Could you say something about the technology that was used for

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lobectomies or esophagectomies? Has this been done using minimally invasive, open, or hybrid techniques?

Second, did you exclude patients with particularly low respiratory function at baseline? From what I understood, there was a 2-week training program, after which improvement was mandatory. Were there limitations regarding the initial respiratory function? Did you exclude patients with particularly low respiratory function?

Response From Emer Guinan (Dublin, Ireland)

Thank you for your questions. In terms of the surgery, the majority of lung resections were minimally invasive (n = 26). All esophageal resections were open during the study period. We screened everyone for contraindications to exercise testing, but we did not exclude anyone based on preoperative lung function. Patients who have lower function are more deconditioned at baseline and have greater potential for gain from these types of interventions. Unless they fell under the absolute contraindications for exercise testing, we did not exclude them, and within our cohort, only 6% were excluded due to comorbidities. So, the study was highly inclusive in terms of that preoperative decondition.

Mickaël Lesurtel (Clichy, France)

We are talking about prehabilitation. However, prehabilitation involves exercise, nutrition, and psychology. Don't you think that, perhaps, the lack of clinical impact can be due to the fact that you only focus on exercise?

Response From Emer Guinan (Dublin, Ireland)

That's a very good question. All of these patients were evaluated in the preoperative surgical clinic, and a dietetic review was incorporated as part of that. Our main question was around whether this mode of exercise prescription can prove fitness as a primary outcome. So, in terms of our study design, looking at the exercise prescribed is highly important. However, we have completed other trials where we have embedded dietetic support for the esophageal cohort, and it has proven to be very beneficial in supporting patients to exercise at their maximum. It is certainly something that can be considered for future trials. We're also learning more about the need to embed psychological support, and evidence is emerging in that space.

Richard van Hillegersberg (Utrecht, The Netherlands)

I think that this is a great initiative. We all think that patient preparation is important, but it's difficult to prove its effect, which is also the conclusion of this study. Most trials show a maximum benefit from 3 weeks, but you included 2 weeks. Do you think that there would be a benefit in training the patient for a longer period of time?

Response From Emer Guinan (Dublin, Ireland)

Absolutely. We see this in exercise trials all the time. There's this dose response: the more exercise you do, the greater the gains in cardiopulmonary fitness you're likely to see, or if it's a strength training exercise, the greater the gain in muscle mass. We stipulated at least 2 weeks because we were working with surgical timelines, particularly with the lung cancers that we were dealing with. The idea was that we didn't want to delay the day of surgery but deliver a highly impactful exercise program. The majority of our patients were in that 2-week window, which was clinically appropriate within that pathway.

Giovanni De Manzoni (Verona, Italy)

We have a similar program. As they are cancer patients, we need to focus on nutrition, psychological support, and exercise. However, we start this before the neoadjuvant treatment. In my opinion, this is the meaning of prehabilitation. Please comment.

Response From Emer Guinan (Dublin, Ireland)

Yes, guiding patients from the time of diagnosis through neoadjuvant treatment and into preoperative optimization is an excellent model—one that is well-supported by numerous studies. I suppose it's slightly different when you're exercising someone through neoadjuvant treatment because, of course, you don't expect them to achieve enormous gains in fitness during that time due to the negative impact of the treatment; however, you might expect to blunt the impact of the treatment on physiological parameters. So, that could be very helpful. Certainly, we are starting to move patients towards exercising while they're on treatment. It's a different set of complications for these types of complex behavioral change interventions, but there's also a huge opportunity, particularly in multimodal pathways to do that.

