

## Pooled Analysis of Four Prospective UK/Ireland Trials: Prehabilitation Reduces Major Complications and Preserves Cardiorespiratory Fitness in Oesophagogastric Cancer Surgery

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Received: 11 April 2025; Revised: 12 August 2025; Accepted: 15 August 2025

### ABSTRACT

The use of prehabilitation has grown among individuals undergoing multimodal management for oesophagogastric cancer (OGC). Most available research has consisted of limited, single-centre studies. This multi-institutional project was designed to evaluate how prehabilitation influences outcomes after surgery for OGC. Information was pooled from four prospective studies conducted in the UK and Ireland involving patients treated with multimodality therapy for OGC. These included three randomised trials and one observational comparison, each examining a prehabilitation protocol versus standard care. The intervention combined aerobic exercise, supervised by physiologists, and nutritional counselling was maintained across the treatment timeline. The main outcome was survival (both overall and disease-related mortality). Secondary endpoints assessed postoperative complications, cardiorespiratory performance (VO<sub>2</sub> peak and anaerobic threshold (AT)), completion of chemotherapy, hospital stay duration, body mass index change, tumour regression, and rates of pneumonia or anastomotic leak. Adjusted hazard ratios (HR) and odds ratios (OR) with 95% confidence intervals (CI) were generated using Cox and logistic regression. Out of 165 total participants, 88 underwent prehabilitation while 77 served as controls. Prehabilitation did not significantly improve overall or disease-specific mortality (HR 0.67, 95% CI 0.21-2.12 and HR 0.82, 95% CI 0.42-1.57, respectively). Major postoperative complications were less common among prehabilitation participants (20% vs. 36%,  $p = 0.034$ ; adjusted OR 0.54; 95% CI 0.26-1.13). Decline in VO<sub>2</sub> peak following neoadjuvant treatment was smaller in the prehabilitation arm ( $-1.07$  mL/kg/min vs.  $-2.74$  mL/kg/min;  $p = 0.035$ ), and chemotherapy completion was higher (90% vs. 73%;  $p = 0.016$ ). Hospitalisation length (10 vs. 12 days;  $p = 0.402$ ) and tumour response (Mandard 1-3: 41% vs. 35%;  $p = 0.494$ ) slightly favoured the prehabilitation group but lacked statistical significance. While methodological variation existed between studies, combined findings indicate several potential clinical advantages of prehabilitation before OGC surgery. Ongoing national standardisation projects and future trials are expected to further optimise these programmes and solidify their evidence base.

**Keywords:** Prehabilitation, Oesophagogastric cancer, Chemotherapy, Postoperative recovery, Aerobic fitness

**How to Cite This Article:** Georgiou C, Christou P, Ioannou E. Pooled Analysis of Four Prospective UK/Ireland Trials: Prehabilitation Reduces Major Complications and Preserves Cardiorespiratory Fitness in Oesophagogastric Cancer Surgery. Asian J Curr Res Clin Cancer. 2025;5(2):22-33. <https://doi.org/10.51847/HhrPTUUN1G>

### Introduction

Even with modern progress in surgical, anaesthetic, and intensive care practices, procedures for oesophagogastric cancer (OGC) continue to result in high postoperative morbidity [1]. Complication rates can reach 60%, leading to extended hospitalisation, delayed rehabilitation, greater costs, functional decline, and reduced survival [2]. The treatment of OGC, particularly in older patients with multiple health issues and low physiological reserve, remains complex [3, 4]. The combination of neoadjuvant therapy (NAT) and surgery is recognised as the preferred management for locally advanced disease, supported by randomised evidence showing improved survival [5-7]. However, chemotherapy can significantly diminish the physical capacity of these patients before surgery [8].

Prehabilitation—defined broadly as a proactive, multidisciplinary approach to enhance patient resilience before major treatment—aims to reduce the physical impact of surgery or chemotherapy. Various definitions have been proposed [9, 10]. It is now being increasingly incorporated into the OGC treatment pathway. Earlier investigations suggest that prehabilitation may lessen sarcopenia, maintain aerobic performance (VO<sub>2</sub> peak), and improve patient-reported outcomes during recovery [11]. Yet, most studies to date have been limited by small sample sizes and single-centre designs. Larger trials are still necessary to determine which specific parameters improve, how interventions should be structured, and the physiological reasons behind any benefit observed.

Supported by the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), this joint project integrated data from four prospective prehabilitation studies across the UK and Ireland to evaluate its effect on OGC surgery outcomes. The primary goal was to determine whether structured prehabilitation improved overall survival (OS) and disease-free survival (DFS) in patients undergoing NAT before surgery. Secondary aims were to assess complications, cardiorespiratory outcomes, chemotherapy completion, hospital stay, body composition change, tumour regression, and particular postoperative events.

## Materials and Methods

An initiative led by the Association of Upper Gastrointestinal Surgeons (AUGIS) in the United Kingdom aimed to create official recommendations for prehabilitation in patients with oesophagogastric cancer (OGC). Within this peri-operative quality improvement (POQI) framework, a modified Delphi consensus method was used. During this process, researchers compiled an updated synthesis of the evidence based on prehabilitation, and merged datasets from four forward-looking UK and Irish studies were supplied for expert review [12, 13].

Among these four investigations, three were randomized controlled trials—carried out in Southampton, Guildford, and Dublin—and one non-randomized study originated from London. Recruitment was conducted from 2016 to 2020, specifically: London (2016-2020), Southampton (2016-2017), Guildford (2016-2018), and Dublin (2019-2020). Each trial compared a structured prehabilitation regimen with standard care for individuals receiving neoadjuvant chemotherapy or chemoradiotherapy for operable oesophageal or gastric adenocarcinoma.

Every participating institution obtained independent ethical clearance, and approval for handling de-identified multi-site data was held centrally (Research Ethics Committee references: 16/SC/0438, 15/SC/078, 16/LO/1702, Beaumont 18/58, ECM 4 (mm) 19/04/19, DCUREC/2018/255, C.A. 2160).

Across all centres, patient evaluation and treatment followed standardised staging and management routes, coordinated by multidisciplinary teams (MDTs). **Table 1** outlines how these studies aligned and where they differed.

**Table 1.** Summary of prehabilitation strategies and measured outcomes among four clinical investigations.

Centre	London	Southampton	Guildford	Dublin
<b>Trial design</b>	Non-randomised	Randomised	Randomised	Randomised
<b>Intervention period</b>	From diagnosis to start of adjuvant chemotherapy (26 weeks)	From diagnosis to postoperative phase (15 ± 2 weeks)	From diagnosis to postoperative phase (15 weeks)	From diagnosis to postoperative phase (18 ± 2.4 weeks)
<b>Aerobic exercise</b>	Yes *	Yes *	Yes *	Yes *
<b>Strength training</b>	Yes Full-body circuit with resistance bands (15-20 repetitions per exercise, 12 exercises, 3 circuits)	No	Yes 2 sets of 12 repetitions using free weights and bands, covering six major muscle groups	Yes 6-10 station circuit alternating upper- and lower-body movements
<b>Nutritional support</b>	Provided to both arms	Provided to both arms	Provided to both arms	Provided to both arms
<b>Psychological support</b>	Offered on an as-needed basis	Not provided	Provided only to intervention arm	Not provided
<b>Functional testing</b>	Cardiopulmonary exercise testing (CPET)	CPET	CPET	6-minute walk test (6 MWT)
<b>Delivery format</b>	Combination in-person and remote	In-person only	Combination in-person and remote	Combination in-person and remote

Exercise prescription	Individualised using FITT principles based on patient need	Individualised using FITT principles based on patient need	Individualised using FITT principles based on patient need	Individualised using FITT principles based on patient need
Supervisor	Exercise physiologist	Exercise physiologist	Exercise physiologist	Exercise physiologist
Endpoints	1. Cardiorespiratory fitness (CPET: anaerobic threshold, VO <sub>2</sub> peak, physical activity level) 2. Postoperative complications 3. Chemotherapy completion and toxicity 4. Skeletal muscle mass 5. Health-related quality of life 6. Hospital length of stay 7. Pathological tumour regression	1. Cardiorespiratory fitness (CPET: anaerobic threshold, VO <sub>2</sub> peak, physical activity level) 2. Postoperative complications 3. Chemotherapy completion and toxicity 4. Sarcopenia 5. Disability-adjusted survival (WHODAS) 6. Pathological tumour regression 7. Overall survival	1. Cardiorespiratory fitness (CPET: anaerobic threshold, VO <sub>2</sub> peak, weekly steps, hand-grip strength) 2. Postoperative complications 3. Chemotherapy completion and toxicity 4. Skeletal muscle mass 5. Insulin resistance 6. Health-related quality of life 7. Hospital length of stay 8. Pathological tumour regression	1. Functional capacity (6 MWT, sit-to-stand, handgrip, physical activity) 2. Complications, postoperative morbidity, pathology 3. Chemotherapy completion rates, toxicity, tolerability 4. Body mass index 5. Health-related quality of life (LOT-R, EQ-5D-5L, FACT-E)

Abbreviations: CPET - cardiopulmonary exercise test; 6MWT - six-minute walk test; AT - anaerobic threshold; HRQL - health-related quality of life; QOL - quality of life; WHODAS - WHO Disability Assessment Schedule; BMI - body mass index; LOT-R - Life Orientation Test-Revised; FACT - Functional Assessment of Cancer Therapy.

\*Detailed information on exercise design and dosage, organized according to the FITT (frequency, intensity, time, and type) model, is shown in **Table 2**.

**Table 2.** Description of exercise intervention parameters applying the FITT framework.

Aspect	London	Southampton	Guildford	Dublin
Sessions per week	5 per week	3 per week (2 if receiving treatment)	2 supervised + 3 at home	3 per week (2-3 if receiving treatment)
Effort level	Moderate-high	Moderate-high	Moderate-high	Intervals (moderate-high); steady (moderate)
Duration per session	5 × 30 min	3 × 40 min or 2 × 30 min if on therapy	5 × 60 min	Pre-op: 30 min first, then 40 min Post-op: start 20 min, add 10 min weekly
Modality	Walking (steady or interval days)	Stationary bike at 60-65 rpm	5 min warm-up + 25 min cycling	Centre: cycle (upright/recumbent), treadmill, elliptical, rower Home: walk/jog/cycle
Weekly total	150 min × 26 weeks	60-120 min × 15 ± 2 weeks	300 min × 15 weeks	120 min or 80-120 min if on therapy × 18 ± 2.4 weeks

#### *Prehabilitation program (Exposure)*

In all included studies, prehabilitation began upon cancer diagnosis and was maintained throughout the neoadjuvant phase and up to the time of surgery. Each program was tailored to the participant's fitness level and followed standard FITT guidelines for defining exercise dose and prescription. Most interventions used a hybrid delivery model (a mix of in-person and virtual sessions across three centers) and incorporated aerobic training under the supervision of exercise physiologists, along with nutritional counseling by dietitians.

Resistance training was integrated into the regimen in three studies. Psychological support was offered to selected individuals in one trial and exclusively to the intervention arm in another. Three out of four studies employed CPET for physical fitness evaluation, while one utilized the 6-minute walk test. Baseline BMI, VO<sub>2</sub> peak, and AT (where available) were recorded prior to the program and reassessed after completion of neoadjuvant therapy.

The specific exercise dose and prescription using FITT principles [14, 15] are summarized below (**Table 2**).

#### *Combined study outcomes*

The primary endpoint was overall and disease-specific survival, comparing prehabilitation with control groups from the pooled data. Secondary endpoints included rates of major complications (classified by Clavien-Dindo), variations in cardiorespiratory fitness (changes in VO<sub>2</sub> peak and AT), chemotherapy completion rates, hospitalization duration, BMI/body composition, tumor regression grade (Mandard tumor regression grade

[MTRG]), and defined postoperative complications (such as anastomotic leakage and pneumonia) according to ECCG standards [16].

Overall survival was measured from the surgery date to either death or last follow-up (if alive). Disease-specific survival was measured from surgery to confirmed recurrence (radiologic or histologic) or last follow-up (if no recurrence occurred). Median follow-up time was 31 months (IQR: 20-43 months) after surgery.

Complications were categorized as none or minor (0-2) and major (3-4) per Clavien-Dindo grading [17]. A favorable BMI outcome meant either maintaining a healthy BMI or progressing toward one from baseline to post-NAT (e.g., obese → overweight, overweight → healthy, underweight → healthy). Tumor response was divided into responders (MTRG 1-3) and non-responders (MTRG 4-5).

### Statistical analysis

Descriptive analyses summarized baseline characteristics by center and for the combined dataset, dividing participants into prehabilitation and control groups. Categorical variables were examined via chi-squared tests.

Cox proportional hazards models were employed to determine relationships between prehabilitation and both time to death and time to recurrence. Both unadjusted and adjusted models were generated, controlling for age (continuous), sex (male/female), ASA score (1-2 vs. 3-4), tumor stage (cTNM T0-2/T3-4 or N0/N1-3), baseline BMI (healthy, overweight, obese), and type of neoadjuvant therapy (NAC vs. NACRT).

Directed acyclic graphs (DAGs) guided variable selection for adjustment. Each trial's dataset was first analyzed independently, followed by a random-effects meta-analysis to produce a pooled hazard ratio (HR) with 95% confidence intervals (CI).

For postoperative complications, Firth's logistic regression assessed associations between exercise intervention and Clavien-Dindo grade 3-4 complications. This technique accounted for small sample sizes and potential data separation. Models were adjusted for age, sex, ASA, and NAC/NACRT, and the resulting odds ratios (OR) with 95% CI were synthesized using random-effects meta-analysis.

Changes in VO<sub>2</sub> peak and AT before and after neoadjuvant therapy were compared between groups using Student's t-tests.

## Results and Discussion

### Patient characteristics

An overview of trial and patient characteristics is provided in **Table 3**. Across the four included studies, a total of 165 patients participated—88 underwent prehabilitation (intervention group) and 77 received standard care (control group).

**Table 3.** Overview of patient characteristics and key outcomes.

All Sites Combined					
	Prehabilitation Group (N = 88)		Control Group (N = 77)		p-Value
	n	%	n	%	
Age, years (mean (SD))	63.25 (9.34)		61.69 (8.50)		0.269 b
Sex					
Male	69	78.4	63	81.8	0.585 a
Female	19	21.6	14	18.2	
Baseline BMI, kg/m <sup>2</sup> (mean (SD))					
Underweight	0	0	0	0	0.756 a
Healthy	27	30.7	23	29.9	
Overweight	32	36.4	22	28.6	
Obese	24	27.3	22	28.6	
Missing	5	5.7	10	13	
Post-NAT BMI, kg/m <sup>2</sup> (mean (SD))					
Underweight	1	1.1	0	0	0.818 a
Healthy	27	30.7	22	28.6	
Overweight	31	35.2	28	36.4	
Obese	17	19.3	14	18.2	

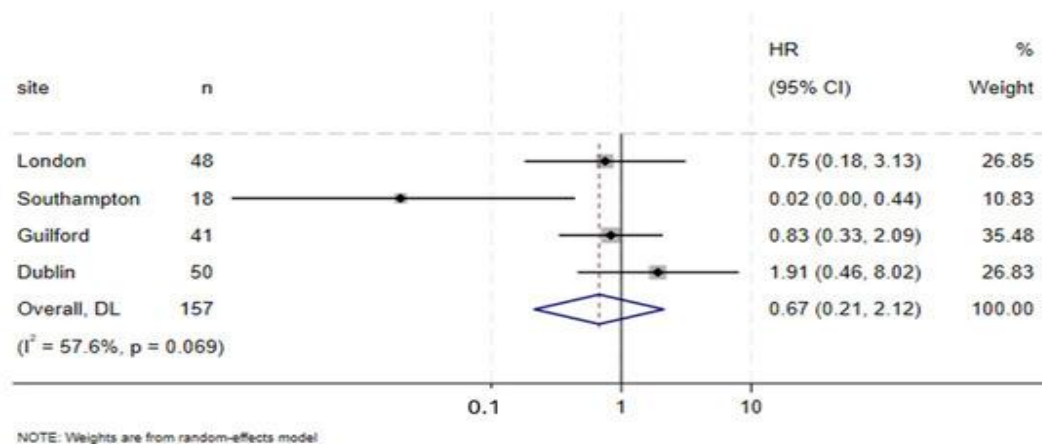
Missing	12	13.6	13	16.9	
<b>VO<sub>2</sub> peak, mean (SD), mL/kg/min</b>					
At baseline	22.19 (5.54)		22.18 (3.89)		
Post-neoadjuvant treatment	20.92 (3.99)		19.23 (3.25)		
Delta/change in VO <sub>2</sub> peak	-1.07 (4.47)		-2.74 (2.91)		0.035 b
<b>AT, mean (SD), mL/kg/min</b>					
At baseline	14.04 (3.69)		14.48 (3.24)		
Post-neoadjuvant treatment	12.81 (2.62)		11.81 (2.68)		
Delta/change in anaerobic threshold	-0.96 (4.00)		-1.78 (5.72)		0.385 b
<b>ASA</b>					
2	58	65.9	51	66.2	0.965 a
3	30	34.1	26	33.8	
<b>Treatment characteristics</b>					
Neoadjuvant chemotherapy (NAC)	55	62.5	58	75.3	0.077 a
Neoadjuvant chemoradiotherapy (NACRT)	33	37.5	19	24.7	
<b>Chemotherapy type</b>					
ECF/EOX/ECX	32	36.4	33	42.9	0.357 a
FLOT	24	27.3	24	31.2	
Others-CROSS/CF/Ciscape	32	36.4	20	26	
<b>Chemotherapy completion</b>					
No	9	10.2	18	23.4	0.016 a
Yes	79	89.8	56	72.7	
Missing	0	0	3	3.9	
<b>Clavien-Dindo (CD) excluding CD 5 d</b>					
CD 0-2	68	80	49	64	
CD 3-4	17	20	27	36	0.034 c
<b>Tumour regression grade (TRG)</b>					
<b>All patients</b>					
Responder Mandard 1-3	49	56	35	45	
Non-responder Mandard 4-5	38	43.2	42	55	0.211 c
Missing	1	1.14			
<b>Neoadjuvant chemotherapy</b>					
Responder Mandard 1-3	22	41	20	35	
Non-responder Mandard 4-5	32	59	38	65	0.494 a
<b>Neoadjuvant chemoradiotherapy</b>					
Responder Mandard 1-3	27	82	15	79	
Non-responder Mandard 4-5	6	18	4	21	0.800 a
<b>Anastomotic Leak</b>					
No	83	94.3	71	92.2	0.588 a
Yes	5	5.7	6	7.8	
<b>Pneumonia</b>					
No	74	84.1	62	80.5	0.548 a
Yes	14	15.9	15	19.5	
<b>Post-operative mortality</b>					
Yes	35	39.8	31	40.3	0.878 a
No	51	58	43	55.8	
Missing	2	2.3	3	3.9	
<b>Recurrence</b>					
No	64	72	58	75	
Yes	24	28	18	23	
Missing			1	2	

ASA: classification system of the American Society of Anesthesiologists; BMI: body mass index; SD: standard deviation; ECF: epirubicin, cisplatin, and fluorouracil; EOX: epirubicin, oxaliplatin, and capecitabine; ECX: epirubicin, cisplatin, and capecitabine; FLOT: a regimen of docetaxel, fluorouracil, folinic acid, and oxaliplatin; CROSS: carboplatin with paclitaxel administered alongside radiotherapy; CF: a combination of 5-fluorouracil and cisplatin; Ciscape: cisplatin plus capecitabine.

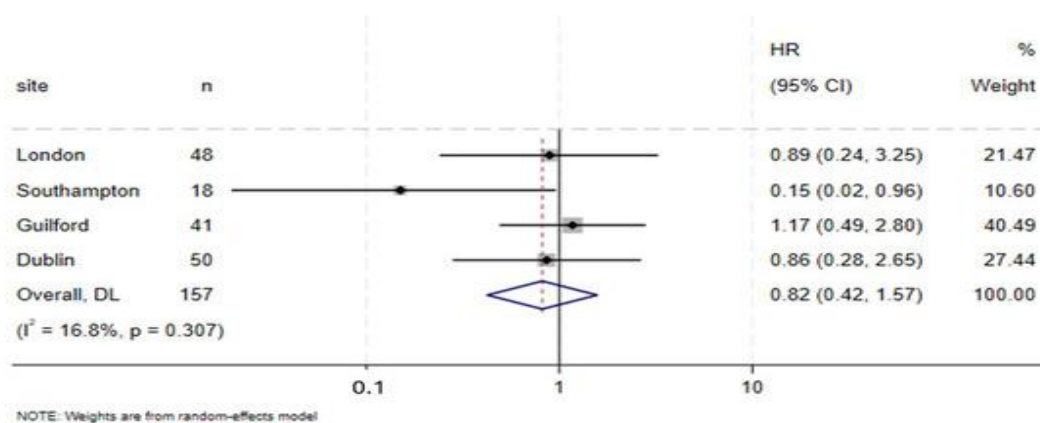
a = chi-square test; b = t-test; c = Fisher's exact test; d = M1 cases excluded.

### Survival

When results from all trials were combined, no statistically clear gap appeared between the prehabilitation and control cohorts regarding either total or disease-related mortality. Nonetheless, hazard ratios tended to support the intervention (OS: HR = 0.67, 95% CI 0.21-2.12; DFS: HR = 0.82, 95% CI 0.42-1.57) (**Figures 1a and 1b**).



a)



b)

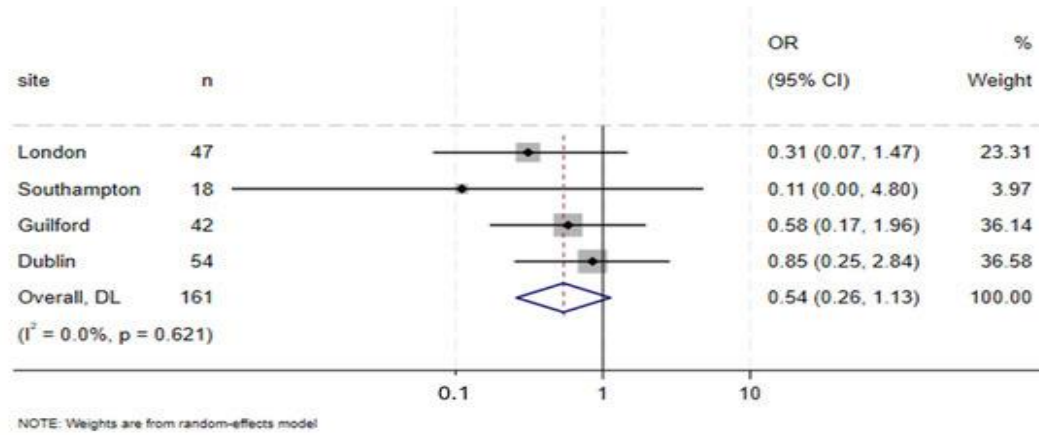
**Figure 1.** (a) Pooled forest plot illustrating overall survival following neoadjuvant therapy and subsequent surgery. (b) Forest plot for disease-free survival after neoadjuvant treatment. All values are corrected for age, sex, ASA score, initial BMI, T/N stage, and neoadjuvant regimen (NAC/NACRT).

### Complications

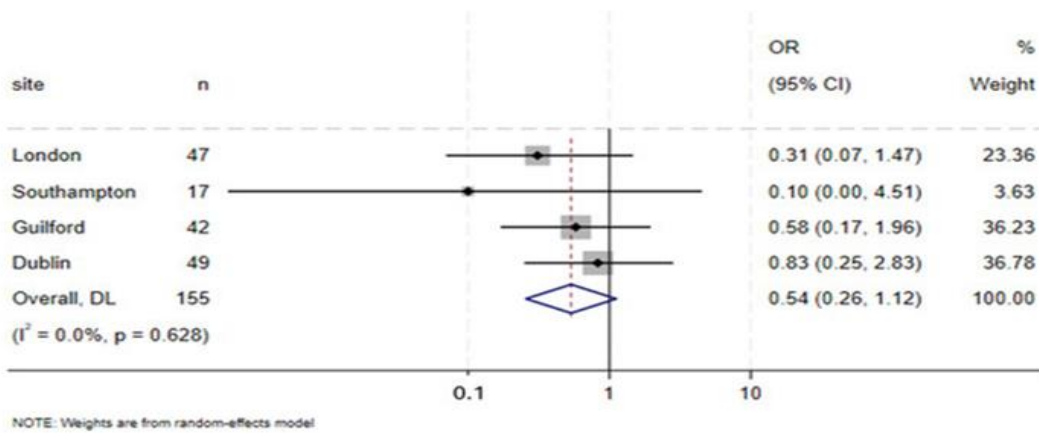
Patients who completed prehabilitation showed fewer severe postoperative complications, both in the complete cohort and when distal gastrectomy cases were removed. Major events (Clavien-Dindo 3-4) occurred in 20% of the prehabilitation group versus 36% of controls ( $p = 0.034$ ); the subgroup comparison showed 21% versus 37% ( $p = 0.032$ ).

Multivariable analyses yielded odds ratios that pointed toward benefit without reaching significance (overall OR = 0.54; 95% CI 0.26-1.13; subgroup OR = 0.54; 95% CI 0.26-1.12) (**Figures 2a and 2b**).





a)



b)

**Figure 2.** (a) Forest plot comparing minor (0-2) versus major (3-4) complications in both groups. (b) Same analysis excluding distal gastrectomy procedures.

### Fitness

Data from three contributing studies indicated that the reduction in  $VO_2$  peak during neoadjuvant therapy was smaller among prehabilitation participants ( $-1.07$ ) compared with controls ( $-2.74$ ;  $p = 0.035$ ) (**Table 4**). For the anaerobic threshold, the trend was similar though statistically nonsignificant ( $-0.96$  vs.  $-1.78$ ;  $p = 0.385$ ) (**Table 5**).

**Table 4.** Mean difference in  $VO_2$  peak between prehabilitation and control groups, incorporating all surgical categories and M1 cases.

Parameter	Prehabilitation (N = 88)	Control (N = 77)	p-value (t-test)
Baseline $VO_2$ peak, mL/kg/min (mean $\pm$ SD)	22.19 $\pm$ 5.54	22.18 $\pm$ 3.89	—
Post-neoadjuvant $VO_2$ peak, mL/kg/min (mean $\pm$ SD)	20.92 $\pm$ 3.99	19.23 $\pm$ 3.25	—
$\Delta$ $VO_2$ peak, mL/kg/min (mean $\pm$ SD)	-1.07 $\pm$ 4.47	-2.74 $\pm$ 2.91	0.035

**Table 5.** Change in anaerobic threshold ( $\Delta$ AT) comparing both groups, inclusive of all operation types and M1 cases.

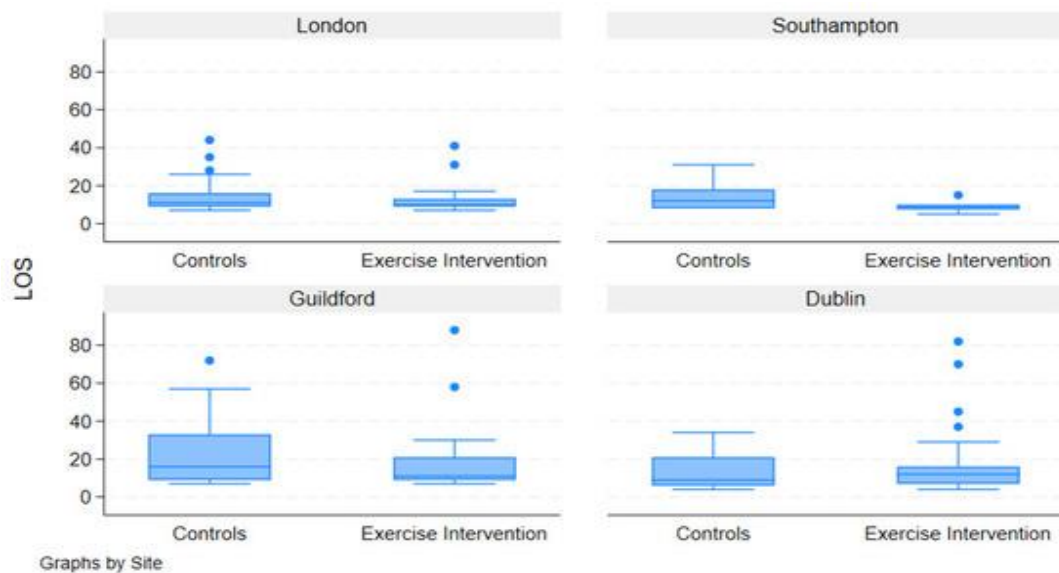
Parameter	Prehabilitation (N = 88)	Control (N = 77)	p-value (t-test)
Baseline AT, mL/kg/min (mean $\pm$ SD)	14.04 $\pm$ 3.69	14.48 $\pm$ 3.24	—
Post-neoadjuvant AT, mL/kg/min (mean $\pm$ SD)	12.81 $\pm$ 2.62	11.81 $\pm$ 2.68	—
$\Delta$ AT, mL/kg/min (mean $\pm$ SD)	-0.96 $\pm$ 4.00	-1.78 $\pm$ 5.72	0.385

### Chemotherapy completion

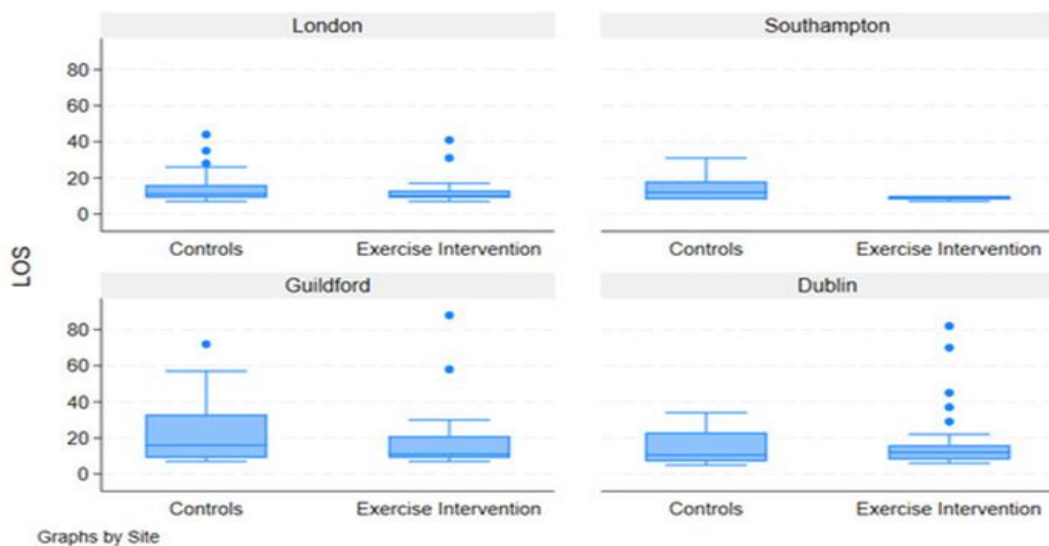
Adherence to the full neoadjuvant chemotherapy schedule was markedly higher with prehabilitation (79 of 88 = 90%) than among controls (56 of 74 = 73%), achieving statistical significance ( $p = 0.016$ ).

### Hospital stay

Hospitalization tended to be shorter in those receiving prehabilitation, with a median of 10 days versus 11 days overall ( $p = 0.377$ ) and 10 days versus 12 days when distal gastrectomy patients were excluded ( $p = 0.402$ ). These differences were not statistically meaningful. Overall t-test  $p = 0.377$  (**Figures 3a and 3b**).



a)



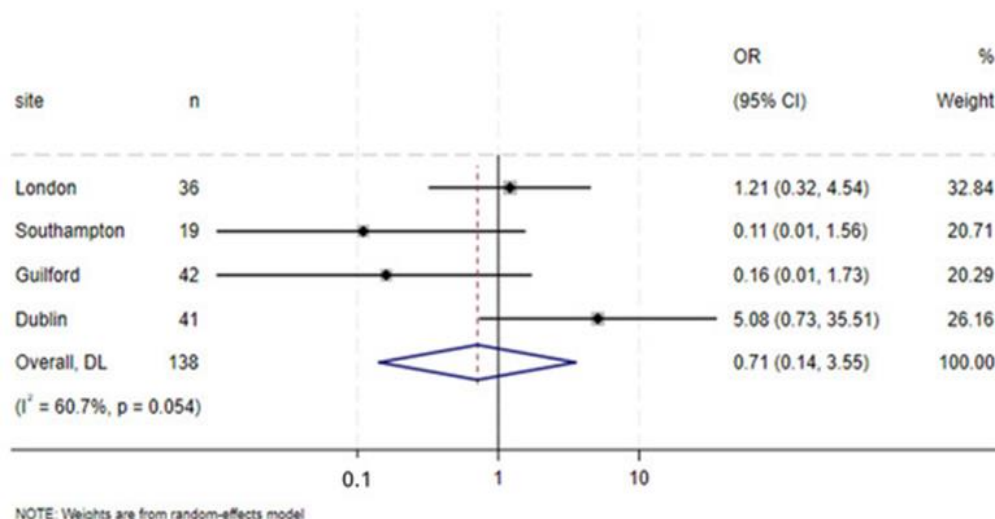
b)

**Figure 3.** (a) Box plot of total hospital stay duration across all operations. (b) Box plot excluding distal gastrectomy procedures.

### Body mass index

Changes toward a healthier BMI during neoadjuvant therapy did not differ significantly between groups (OR = 0.71; 95% CI 0.14-3.55;  $I^2 = 60.7\%$ ;  $p = 0.054$ ) (**Figure 4**).





**Figure 4.** Forest plot showing improvement in BMI adjusted for age, sex, baseline BMI, and cT/cN staging.

#### *Tumor regression*

The proportion of patients showing histological tumor regression (Mandard 1-3) was greater in the prehabilitation cohort (56%) than in controls (45%), though this was nonsignificant ( $p = 0.2105$ ). Because prehabilitation participants more often underwent NACRT and less frequently FLOT, analyses were also separated by treatment type.

Among NAC patients, 41% in the prehabilitation arm and 35% in the control arm were responders ( $p = 0.494$ ), despite a higher rate of FLOT use in controls.

For NACRT, responder frequencies were almost identical (82% vs. 79%;  $p = 0.800$ ).

#### *Specific complications*

No measurable differences were found in rates of anastomotic leakage between groups — overall (6% vs. 8%;  $p = 0.757$ ) and after excluding distal gastrectomy (6% vs. 8%;  $p = 0.429$ ).

Likewise, pneumonia incidence was comparable in the full sample (16% vs. 20%;  $p = 0.682$ ) and in the subgroup without distal gastrectomy (18% vs. 20%;  $p = 0.379$ ).

Drawing on pooled results from four prospective UK-based trials on prehabilitation in patients with oesophagogastric cancer (OGC), this investigation demonstrated measurable advantages associated with prehabilitation interventions [11, 18, 19]. Although differences in primary outcomes—overall and disease-free survival—did not achieve statistical significance, the point estimates consistently leaned in favor of prehabilitation compared to conventional perioperative care. Participants who underwent prehabilitation exhibited lower rates of severe postoperative complications, a smaller reduction in cardiopulmonary capacity during neoadjuvant therapy, and greater completion rates of chemotherapy.

Several methodological aspects merit consideration. This study was developed to contribute real-world data for a national perioperative quality initiative supported by professional societies, aiming to establish recommendations for prehabilitation in OGC management [13]. Within that initiative, a systematic literature review was carried out, and aggregate data from four UK clinical trials were analyzed and presented to stakeholders [12]. Key advantages of combining these datasets include the multicenter design, which enhances generalizability and external validity, and the expanded sample size, which allows for more robust statistical modeling and greater control for potential confounders. Nevertheless, the total cohort size remained relatively modest, limiting the power of subgroup analyses. Another challenge stemmed from heterogeneity: three of the four included trials were randomized controlled designs, while one was non-randomized, introducing a possible element of selection bias. Accordingly, statistical adjustments were applied for confounding variables. Each participating center's dataset was first analyzed separately, followed by an integrated pooled assessment. Sensitivity analyses, in which one site was excluded sequentially, confirmed the consistency of results, including when the non-randomized study was omitted. Variations in prehabilitation program content likely introduced some interstudy variability, and differences were also present in the neoadjuvant regimens used (NAC vs. NACRT), reflecting contemporary

practice. Additionally, exercise capacity assessments varied, as three trials used cardiopulmonary exercise testing (CPET), whereas one employed the six-minute walk test, thereby reducing the overall statistical power after stratification.

Extensive prior research has explored prehabilitation across multiple tumor types [20-24]. While improvements in overall survival have not been consistently demonstrated, a large-scale U.S. population study reported a 25% reduction in all-cause mortality among fitter patients receiving oncologic therapy [25]. In the UK, one study showed poorer outcomes among OGC patients who declined or discontinued prehabilitation, underscoring the need to engage high-risk individuals in such programs [26]. The OptiTrain study tested a 16-week high-intensity interval training (HIIT) protocol combined with aerobic (AT-HIIT) or resistance (RT-HIIT) exercises against standard care during chemotherapy for breast cancer, revealing significantly better overall survival in the intervention groups [27]. Similarly, a systematic review reported fewer postoperative complications—particularly Clavien-Dindo grade  $\geq 2$ —and reduced pneumonia incidence among OGC patients receiving prehabilitation [28]. In the BEAUTY study, participants in the exercise arm achieved gains in  $\text{VO}_2$  peak and approximately a one-minute improvement in submaximal treadmill time after 24 weeks [29]. The PREPARE trial, focused specifically on OGC, found a decline in postoperative pneumonia from 66% to 26% and a reduction in median hospital stay from 13 to 10 days [30]. Furthermore, meta-analytic findings suggest prehabilitation shortens hospital stay by nearly two days compared with standard treatment across diverse surgical populations [31]. Several investigations have linked prehabilitation with better histopathologic responses to neoadjuvant therapy [18]; for example, breast cancer patients who exercised showed higher rates of complete tumor regression than controls [32], while a rectal cancer study reported significantly enhanced pathological response following NACRT and surgery among prehabilitation participants [33].

Until the outcomes of ongoing large-scale randomized trials are available [34, 35], uncertainties persist regarding which components of prehabilitation yield the greatest clinical benefit. A nationwide survey assessing prehabilitation practices in the UK identified major obstacles to implementation, most prominently limited funding and workforce shortages. Additional variability was seen in where and by whom exercise interventions were delivered, alongside inconsistent access to complementary components such as psychological support [36]. Despite these gaps, updated societal recommendations have recognized the accumulating evidence and now endorse prehabilitation as part of the standard care pathway for patients undergoing treatment for OGC [13].

## Conclusion

In summary, despite some heterogeneity among study methodologies and intervention designs, this pooled analysis highlights multiple favorable effects of prehabilitation for patients receiving neoadjuvant therapy and surgery for oesophagogastric cancer. Although survival outcomes did not differ significantly between groups, prehabilitation was associated with reduced complication severity, preserved cardiopulmonary function, and improved chemotherapy completion.

**Acknowledgments:** None

**Conflict of Interest:** None

**Financial Support:** None

**Ethics Statement:** None

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