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Randomized Clinical Trial

Supervised exercise after oesophageal cancer surgery: the PERFECT multicentre randomized clinical trial

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Information from this trial was presented at ASCO, 29–31 May 2020, poster presentation (abstract #577927) 'Randomized clinical trial on the effect of a supervised exercise program on quality of life, fatigue and fitness following oesophageal cancer treatment (PERFECT study)'.

Abstract

Background: This study investigated whether a supervised exercise programme improves quality of life (QoL), fatigue and cardiorespiratory fitness in patients in the first year after oesophagectomy.

Methods: The multicentre PERFECT trial randomly assigned patients to an exercise intervention (EX) or usual care (UC) group. EX patients participated in a 12-week moderate- to high-intensity aerobic and resistance exercise programme supervised by a physiotherapist. Primary (global QoL, QoL summary score) and secondary (QoL subscales, fatigue and cardiorespiratory fitness) outcomes were assessed at baseline, 12 and 24 weeks and analysed as between-group differences using either linear mixed effects models or ANCOVA.

Results: A total of 120 patients (mean(s.d.) age 64(8) years) were included and randomized to EX (61 patients) or UC (59 patients). Patients in the EX group participated in 96 per cent (i.q.r. 92–100 per cent) of the exercise sessions and the relative exercise dose intensity was high (92 per cent). At 12 weeks, beneficial EX effects were found for QoL summary score (3.5, 95 per cent c.i. 0.2 to 6.8) and QoL role functioning (9.4, 95 per cent c.i. 1.3 to 17.5). Global QoL was not statistically significant different between groups (3.0, 95 per cent c.i. –2.2 to 8.2). Physical fatigue was lower in the EX group (–1.2, 95 per cent c.i. –2.6 to 0.1), albeit not significantly. There was statistically significant improvement in cardiorespiratory fitness following EX compared with UC (peak oxygen uptake (1.8 ml/min/kg, 95 per cent c.i. 0.6 to 3.0)). After 24 weeks, all EX effects were attenuated.

Conclusions: A supervised exercise programme improved cardiorespiratory fitness and aspects of QoL.

Trial registration: Dutch Trial Register NTR 5045 (www.trialregister.nl/trial/4942).

Introduction

Patients with potentially curable oesophageal cancer often undergo multimodal treatment. The introduction of neoadjuvant chemoradiotherapy[1] and recent developments in (minimally invasive) surgery (i.e., oesophagectomy) and patient selection have improved survival[2]. However, postoperative recovery is often slow and characterized by significant and long-lasting (i.e., up to 10 years post treatment) impairments in quality of life (QoL)[3]. QoL is typically lowest within the first year after treatment, and is accompanied by high levels of fatigue, eating disorders and decreased physical functioning and fitness[4–8].

Physical exercise, especially supervised exercise training, has the potential to improve cardiorespiratory fitness and patient-reported outcomes in patients with various types of cancer. However, the vast majority of exercise interventions have been evaluated in patients with breast cancer, prostate cancer and haematological malignancies[9–12]. This precludes generalizability of results to cancer types with more complex multimodal

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treatment, such as oesophageal cancer. A recent small randomized controlled trial (RCT) in patients with oesophagogastric cancer showed that a multidisciplinary intervention including exercise was feasible and safe, and indicated beneficial effects on cardiorespiratory fitness[13]. No effects on QoL were found, probably due to the small sample size. A larger RCT, that is adequately powered to evaluate patient-reported outcomes and to confirm positive effects on cardiorespiratory fitness, is currently lacking.

The Physical ExeRcise Following Esophageal Cancer Treatment (PERFECT) multicentre RCT was conducted to investigate effects of a 12-week combined aerobic and resistance exercise programme in patients with oesophageal cancer, in the first year after completion of primary treatment. This article reports on adherence to the exercise programme and the effects of exercise on QoL (primary endpoint), fatigue and cardiorespiratory fitness after completion of the intervention.

Methods

Setting and participants

The PERFECT study design has been published previously[14]. This study adhered to the CONSORT guidelines[15]. The study was conducted in nine Dutch hospitals. Eligible patients were invited to participate by their medical specialist or oncological nurse during a regular outpatient visit. Inclusion criteria were: surgery with curative intent for newly diagnosed, histologically confirmed oesophageal cancer; 4–52 weeks after hospital discharge following surgery; aged 18 years or over; able to read and understand the Dutch language; minimally physically active (up to 150 min/week of moderate–vigorous exercise); Karnofsky Performance Status greater than 60; able to walk 60 m or more. Exclusion criteria were the presence of metastatic oesophageal cancer based on CT-imaging prior to surgical resection, non-radical resection, contra-indications for physical activity (as assessed through the Revised Physical Activity Readiness Questionnaire[16]), and participation in a supervised exercise programme. The study was approved by the Medical Ethics Committee of the UMC Utrecht and the local Ethical Boards of participating hospitals and was conducted in accordance with the Declaration of Helsinki.

After signing written informed consent and completing baseline measurements, concealed computer-generated randomization was used to allocate participants in a 1 : 1 ratio to a 12-week supervised exercise intervention or usual care. Randomization was performed using minimization, stratified by sex, hospital and time since surgery.

Intervention

A 12-week supervised exercise programme was offered to patients randomized to the exercise group, in addition to usual care. Details of the exercise programme have been published elsewhere[14]. Briefly, the programme included two combined aerobic and resistance training exercise sessions per week, supervised by an outpatient (oncology) physiotherapist close to the participant's home address. The 60-minute exercise sessions included a warm-up (5 min), aerobic and resistance training (50 min) (*Table S1*) and a cooling down (5 min) period. The aerobic and resistance exercises were individualized to the participants' fitness levels as assessed by a cardiopulmonary exercise test (CPET) at baseline and repeatedly performed 20-repetition maximum muscle strength tests. In addition to the supervised exercise programme, participants were asked to be physically active for at least 30 min/day on all remaining days of the week, according to the WCRF/AICR guidelines for cancer survivors[17].

Patients in the usual care group received usual care and were requested to maintain their habitual physical activity pattern. After completion of the study, patients were offered exercise advice.

Outcome measures

Participants visited the study centre for outcome assessment at baseline and post intervention (12 weeks). After 24 weeks, participants received the questionnaires by post. Cardiorespiratory fitness was assessed at baseline and post intervention (12 weeks) only. Demographic and clinical data were abstracted from questionnaires and medical records, respectively. Surgery-related postoperative complications were categorized according to the modified Clavien-Dindo classification (MCDC, 2 or greater) and included pulmonary and cardiac complications[18]. Anastomotic leakage, chylothorax and other surgery-related complications were graded according to definitions stated by the Esophagectomy Complications Consensus Group[19]. The risk of malnutrition was assessed using the Patient-Generated Subjective Global Assessment Short Form[20,21].

Primary outcome

Quality of life

QoL, the study's primary outcome, was assessed with the global QoL subscale of the validated 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ, version 3)[22]. This two-item global QoL score helps to avoid an increased type I error that might arise because of multiple testing when making comparisons based on all outcomes of this questionnaire. After initiation of the study, the QLQ-C30 summary score was introduced to provide a conceptually more appropriate summary of QoL compared with the global QoL score, and which is supposed to have better responsiveness to changes over time[23]. Therefore, the QLQ-C30 summary score is now also included as the primary outcome, which is not in accordance with the original study protocol[14]. The summary score was calculated using 13 subscales (see below), excluding the global QoL score and financial difficulties score.

Secondary outcomes

The EORTC-QLQ-C30 incorporates five functional subscales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea and vomiting, and pain) and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). Oesophageal cancer-specific problems were assessed with the validated 25-item oesophagogastric module (QLQ-OG25)[24]. Scores range from 0–100, with higher scores representing a higher response level.

Fatigue

Fatigue was measured using the validated Dutch version of the Multidimensional Fatigue Inventory (MFI)[25]. The MFI is a 20-item questionnaire, designed to measure general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. Scores range from 4–20, with higher scores indicating more fatigue.

Physical fitness

Cardiorespiratory fitness was determined by performing a CPET on a bicycle ergometer with continuous breathing gas analysis under medical supervision. After a 1-min unloaded warm-up, cycling workload was gradually increased with a predetermined 10, 15 or 20 W/min until exhaustion or symptom limitation.

Participants were instructed to cycle at 70–80 revolutions per minute (RPM). The test was terminated when the cycling frequency dropped below 70 RPM or by decision of the sports medicine physician and was followed by a 3-min cooling-down at 20 W. Peak oxygen uptake (VO_{2peak}) was determined by taking the mean of VO_2 values of the last 30 s before exhaustion. Peak workload, peak heart rate, VO_2 and power output were assessed at ventilatory threshold (VT) and respiratory compensation point (RCP)[26].

Adherence

Adherence to the protocol was evaluated by recording session attendance and adherence to the planned dose/session. Deviations from the scheduled exercise dose were recorded by the physiotherapist. Attendance rates were computed as the number of supervised exercise sessions attended divided by the number of sessions prescribed. The relative dose intensity (RDI), i.e., compliance, was calculated as the ratio of total completed to total planned cumulative dose for three parts of the PERFECT exercise programme: duration of aerobic exercises, intensity of aerobic exercises and muscle strength exercises. The authors calculated the percentages of weeks in which patients adhered to the exercise advice of being physically active for at least 30 min/day, and the Dutch Physical Activity Guidelines, engaging in at least 150 min of exercise per week[27]. Contamination in the control group was assessed using an accelerometer (Actigraph GT3X+ Tri-Axis Accelerometer Monitor) and was defined as an increase of 60 or more minutes of moderate-to-vigorous physical activity per week in the week postintervention compared with baseline[28].

Sample size

The sample size calculation was based on the primary outcome, improvement in global QoL from baseline to post-intervention. Using results from the authors' previous trial[29,30] and taking into account a correlation of 0.4 between baseline and follow-up QoL, power analysis using PASS 2008 software (NCSS Statistical Software, Kaysville, Utah, USA) (http://www.ncss.com/software/pass/) was performed. Assuming a power of 80 per cent (significance level = 0.05), a sample size of 51 patients per group was calculated. It was intended to include 75 patients per group taking into account a drop-out rate of approximately 30 per cent. Since drop-out was found to be lower (approximately 10 per cent) during the study, 57 participants were needed in both the exercise and control group.

Statistical analysis

Descriptive statistics were used to summarize characteristics of the study population. Outcomes assessed at baseline, 12 and 24 weeks (i.e., patient-reported outcome measures) were analysed using intention-to-treat mixed linear regression models, including participants for whom the outcome was observed at two or more time points. The models were adjusted for baseline values of the outcome and stratification factors. Models with different co-variance structures (AR(1) *versus* UN) were compared based on measures of fit using Akaike's information criterion for all outcomes. Outcomes assessed at baseline and 12 weeks (i.e., cardiorespiratory fitness) were analysed as between-group differences in outcomes using ANCOVA, adjusted for baseline values and stratification factors, including participants for whom the outcome was observed at both time points. Modelling assumptions were examined and met. Standardized effect sizes (ESs) were calculated by dividing the adjusted between-group difference of the post-intervention means by the pooled baseline standard deviation. As a predefined explorative analysis, sex, histological subtype of carcinoma, type of surgery (open *versus* minimally invasive) and time since surgery were examined as potential modifiers of the intervention effect. Analyses were performed using SPSS Statistics™ 25.0 (IBM, Armonk, New York, USA). All tests were two-tailed and the significance level was set at $P < 0.05$.

Results

Participants

Between March 2015 and January 2019, 497 patients were assessed for eligibility. In total, 120 of 358 eligible patients (33.5 per cent) were recruited for the study. Reasons for non-participation are shown in *Fig. 1*. Overall, 10 participants were lost to follow-up during the intervention period (exercise group: 7 of 61 patients (12 per cent), control group: 3 of 59 (5 per cent)) and 12 during the follow-up period (exercise group: 6 of 54 (11 per cent), control group: 6 of 56 (11 per cent)), mainly due to cancer recurrence or cancer-related death.

Participants had a mean(s.d.) age of 63.7(8.1) years, were male (86.7 per cent), partnered (89.2 per cent), former smokers (71.7 per cent) and at medium–high risk for malnutrition (70 per cent) (*Table 1*). Most patients were diagnosed with oesophageal adenocarcinoma (76.7 per cent), tumour stage III (53.3 per cent) and treated with neoadjuvant chemoradiotherapy according to the CROSS regimen[1] (81.7 per cent).

Adherence

Participants in the exercise group showed high adherence to the supervised exercise programme. They participated in 96 (i.q.r. 92–100) per cent of the sessions offered. RDI for moderate- to high-intensity endurance exercises, high-intensity endurance exercises, interval training and resistance exercises was 94 (i.q.r. 87–100), 90 (i.q.r. 70–100), 100 (i.q.r. 74–100) and 90 (i.q.r. 81–97) per cent, respectively (*Table 2*). The RDI of the exercise advice, that is, being active 7 days of the week or 5 days/week (Dutch Physical Activity Guidelines[27]) for 12 weeks was 25 (i.q.r. 0–58) and 75 (i.q.r. 17–92) per cent, respectively. Compared with baseline, 10 patients (17 per cent) allocated to usual care increased the time spent on moderate- to high-intensity physical activities for at least 60 minutes (data not shown).

No exercise-related serious adverse events were observed.

Global QoL and QoL summary score

Participants in the exercise group reported a significantly higher global QoL at 12 weeks, compared with baseline (9.3, 95 per cent c.i. 5.1 to 13.6), but no statistically significant between-group differences were observed (3.0, 95 per cent c.i. –2.2 to 8.2; ES = 0.18) (*Fig. 2*, *Table 3*). Compared with controls, participants in the exercise group reported a significantly higher summary score (3.5, 95 per cent c.i. 0.2 to 6.7; ES = 0.26). At 24 weeks, effects were attenuated.

QoL subscales

Compared with controls, participants in the exercise group reported significantly higher role functioning (9.4, 95 per cent c.i. 1.3 to 17.5; ES = 0.40) at 12 weeks. At 24 weeks, the effects were attenuated and no longer significant. No other significant between-group differences were observed at 12 or 24 weeks for the EORTC QLQ-OG25 scales and remaining QLQ-C30 subscales (*Fig. 2*, *Table 3*, *Table S2*).

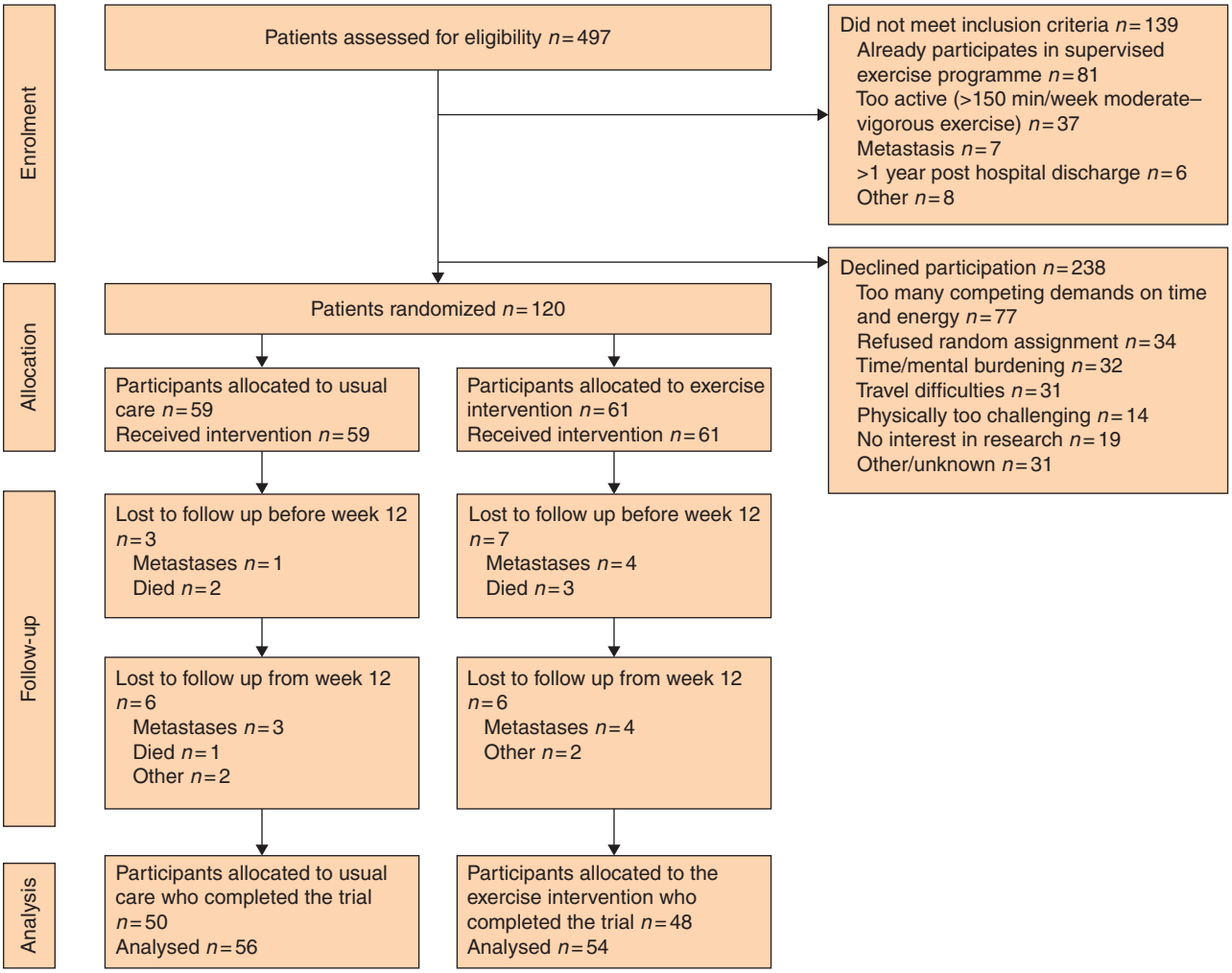

Fig. 1 CONSORT diagram of the PERFECT study.

The study was conducted in nine Dutch hospitals: UMC Utrecht, Utrecht (2015–2019); Hospital Group Twente (ZGT), Almelo (2015–2019); Catharina Hospital, Eindhoven (2015–2019); St. Antonius Hospital, Nieuwegein (2015–2017); IJsselland Hospital, Capelle aan den IJssel (2015–2017); Radboud University Medical Centre, Nijmegen (2015–2019); Amsterdam UMC, Amsterdam (formerly Amsterdam VU Medical Centre (2015–2019) and AMC Amsterdam (2017–2019)); Erasmus MC, Rotterdam (2017–2019).

Fatigue

At 12 and 24 weeks, all participants reported lower levels of fatigue compared with baseline and no significant between-group differences were found (*Fig. 2*, *Table 3*). For physical fatigue, reduced activity and reduced motivation ES was 0.25 or greater in favour of the exercise group at 12 and 24 weeks.

Physical fitness

At 12 weeks, VO_{2peak} (0.13 l/min, 95 per cent c.i. 0.04 to 0.22; ES = 0.26) and peak power output (16.9 W, 95 per cent c.i. 9.0 to 24.7; ES = 0.36) were significantly higher in the exercise group compared with usual care (*Table 4*). For VO_2 and power output at VT, significant differences in favour of the exercise group of 0.12 l/min (95 per cent c.i. 0.03 to 0.21; ES = 0.36) and 11.8 W (95 per cent c.i. 2.4 to 21.2; ES = 0.37) were observed. Significant differences in favour of the exercise group were found for VO_2 at the RCP (0.13 l/min, 95 per cent c.i. 0.01 to 0.25; ES = 0.29), but not for power output.

Subgroup analyses

In general, similar exercise effects on QoL and fatigue were found for all subgroups at 12 and 24 weeks (*Fig. 3*, *Tables S3–S6*). Men randomized to the exercise group reported a significantly higher QoL summary score at 12 weeks compared with control (4.4, 95 per cent c.i. 0.9 to 7.9; ES = 0.33), whereas no effect was found in women. Compared with controls, participants in the exercise group, who had undergone open surgery, reported significantly lower levels of physical fatigue at 12 weeks (–7.1, 95 per cent c.i. –10.5 to –3.7; ES = 1.85) and significantly higher global QoL at 24 weeks (18.5, 95 per cent c.i. 0.6 to 36.3; ES = 1.00). Participants in the exercise group diagnosed with a squamous cell carcinoma reported a significantly lower global QoL at 24 weeks, compared with control (–9.3, 96 per cent c.i. –16.6 to –2.1; ES = 0.56). For QoL and fatigue, larger ESs were found in favour of participants in the exercise group who participated at least 6 months post surgery, although these were not significant.

Discussion

This large exercise RCT shows that patients after oesophagectomy are well able to attend a 12-week supervised exercise programme and adhere to moderate- to high-intensity exercises. The combined aerobic and resistance training resulted in small improvements in QoL summary score, QoL role functioning and

Table 1 Baseline characteristics of participants in the PERFECT study

	All participants (*n* = 120)	Intervention (*n* = 61)	Control (*n* = 59)
Age (years)†	63.7(8.1)	64.3(7.8)	63.1(8.5)
Sex			
Male	104 (86.7)	52 (85)	52 (88)
Female	16 (13.3)	9 (15)	7 (12)
Educational level			
Low	32 (26.7)	16 (26)	16 (27)
Middle	59 (49.2)	29 (48)	30 (51)
High	29 (24.2)	16 (26)	13 (22)
Marital status			
Couple	107 (89.2)	55 (90)	52 (88)
Single	12 (10)	5 (8)	7 (12)
Widow	1 (0.8)	1 (2)	0 (0)
Work status			
Paid work	47 (39.2)	26 (43)	21 (36)
Sick leave	32 (68.1)	18 (69)	14 (67)
No paid work/retired	73 (60.1)	35 (57)	38 (64)
BMI (kg/m^2)†	24.9(3.5)	24.8(3.2)	25.0(3.8)
Malnutrition risk‡			
Low risk	31 (25.8)	16 (26)	15 (25)
Medium risk	45 (37.5)	23 (38)	22 (37)
High risk	39 (32.5)	21 (34)	18 (31)
Smoking			
Yes	10 (8.3)	3 (5)	7 (12)
No	24 (20.0)	12 (20)	12 (20)
Former	86 (71.7)	46 (75)	40 (68)
Cancer type			
Adenocarcinoma	92 (76.7)	49 (80)	43 (73)
Squamous cell carcinoma	20 (16.7)	9 (15)	11 (19)
Adenosquamous	1 (0.8)	0 (0)	1 (2)
Other	7 (5.8)	3 (5)	4 (7)
Tumor stage			
I	16 (13.3)	10 (16)	6 (10)
II	39 (32.5)	16 (26)	23 (39)
III	64 (53.3)	34 (56)	30 (51)
Co-morbidities			
Yes	49 (40.8)	21 (34)	28 (47)
No	71 (59.2)	40 (66)	31 (53)
Type of surgery			
Open oesophagectomy	11 (9.2)	5 (8)	6 (10)
Minimally invasive oesophagectomy	109 (90.8)	56 (92)	53 (90)
Thoraco-laparoscopic	55 (45.8)	31 (51)	24 (41)
Transhiatal-laparoscopic	7 (5.8)	2 (3)	5 (8)
Robot-assisted	47 (39.2)	23 (38)	24 (41)
Complications after surgery			
Pulmonary complications			
Pneumonia	23 (19.2)	13 (21)	10 (17)
Pneumothorax	4 (3.3)	3 (5)	1 (2)
Other	8 (6.7)	4 (7)	4 (7)
Cardiac complications			
Atrial fibrillation	18 (15.0)	7 (11)	11 (19)
Wound infection			
Cervical	2 (1.7)	1 (2)	1 (2)
Abdominal	1 (0.8)	0 (0)	1 (2)
Anastomotic leakage			
Type II (non-surgical intervention)	3 (2.5)	0 (0)	3 (5)
Type III (surgical intervention)	6 (5.0)	2 (3)	4 (7)
Chylothorax			
Type II (total parental nutrition)	5 (4.2)	3 (5)	2 (3)
Type III (operative)	1 (0.8)	1 (2)	0 (0)
Other	12 (10.0)	4 (7)	8 (14)
Time since surgery			
0–5 months	81 (67.5)	41 (67)	40 (68)
6–12 months	39 (32.5)	20 (33)	19 (32)
(Neo)adjuvant treatment			
Chemotherapy	7 (5.8)	1 (2)	6 (10)
Chemoradiotherapy	96 (80.0)	50 (82)	46 (78)
Chemoradiotherapy + immunotherapy	2 (1.7)	1 (2)	1 (2)
No (neo)adjuvant treatment	15 (12.5)	9 (15)	6 (10)

*Values in parentheses are percentages unless indicated otherwise; †values are mean(s.d.). ‡The risk of malnutrition was assessed using the PG-SGA SF, with a score lower than 4 indicating a low risk, 4–8 medium risk, and greater than 8 high risk.

Table 2 Ratio of the completed exercise dose to the planned exercise dose (relative dose intensity)

	Total group ($n = 61$)
Relative dose intensity	**Median percentage (i.q.r.)**
Resistance exercise training	
Leg	90 (81–99)
Arms	92 (79–98)
Shoulders	92 (75–96)
Back	92 (81–100)
Core	91 (67–96)
Moderate- to high-intensity endurance training	
Duration	94 (84–100)
Intensity	95 (85–100)
High-intensity endurance training	
Duration	90 (70–100)
Intensity	90 (69–100)
Interval training	100 (66–100)
Exercise advice	
Percentage of weeks being active on 7 days/week	25 (0–58)
Percentage of weeks being active on 5 days/week	75 (17–92)

cardiorespiratory fitness at 12 weeks. The intervention did also reduce levels of fatigue, albeit not significantly. Intervention effects on QoL were attenuated after 24 weeks.

The almost 100 per cent attendance and RDI reported in this study, shows that patients were highly motivated and able to complete both resistance and moderate- to high-intensity aerobic exercise training after oesophagectomy. Generally, attendance at an exercise programme, offered after cancer treatment, ranged from 62–78 per cent[32], which highlights the high acceptability of the supervised PERFECT exercise programme. The studies in this review consisted mainly of patients with breast cancer, who overall have fewer co-morbidities compared with oesophageal cancer survivors[33]. Whereas caregivers often are hesitant to advise patients with co-morbidities or in suboptimal condition to exercise[34], our results show that a supervised exercise programme, such as PERFECT, is very well tolerated. Also, compared with the general Dutch population (47.1 per cent in 2018)[35], adherence to the Dutch Physical Activity Guideline during the intervention was high (75 per cent).

The authors found that patients reported a significantly higher QoL summary score after completion of the supervised exercise programme compared with that reported by patients receiving usual care. Previous studies in patients with different types of cancer have shown that the summary score is more sensitive to changes compared with global QoL[36] and

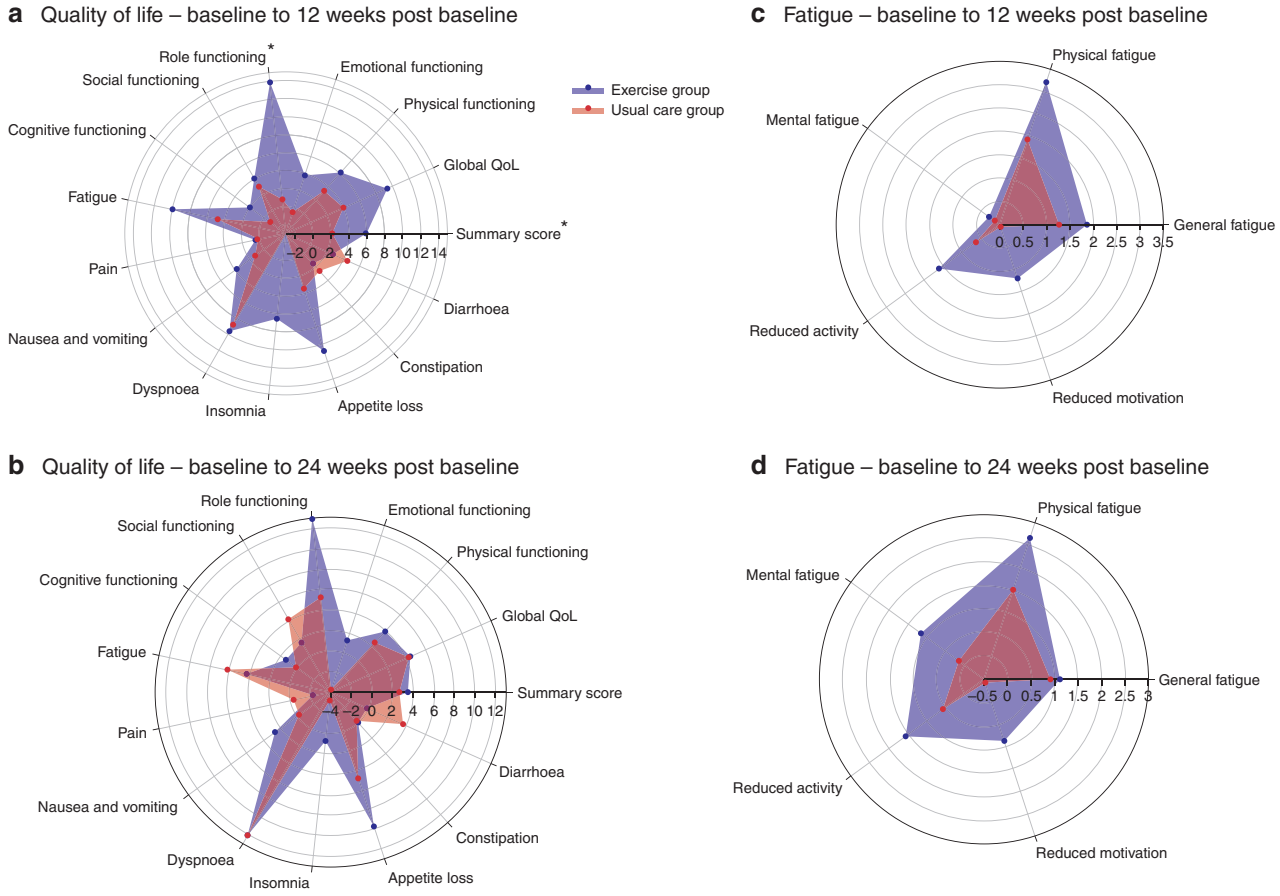

Fig. 2 Radar plots demonstrating changes from baseline to 12 and 24 weeks post baseline in quality of life and fatigue scores for participants randomized to the exercise and usual care groups.

An asterisk indicates a statistically significant between-group difference. It should be noted that the scale of all QoL-symptom outcomes and fatigue outcomes were inverted to facilitate interpretability. An increase from baseline to 12 or 24 weeks post-baseline now indicates an improvement for all outcomes.

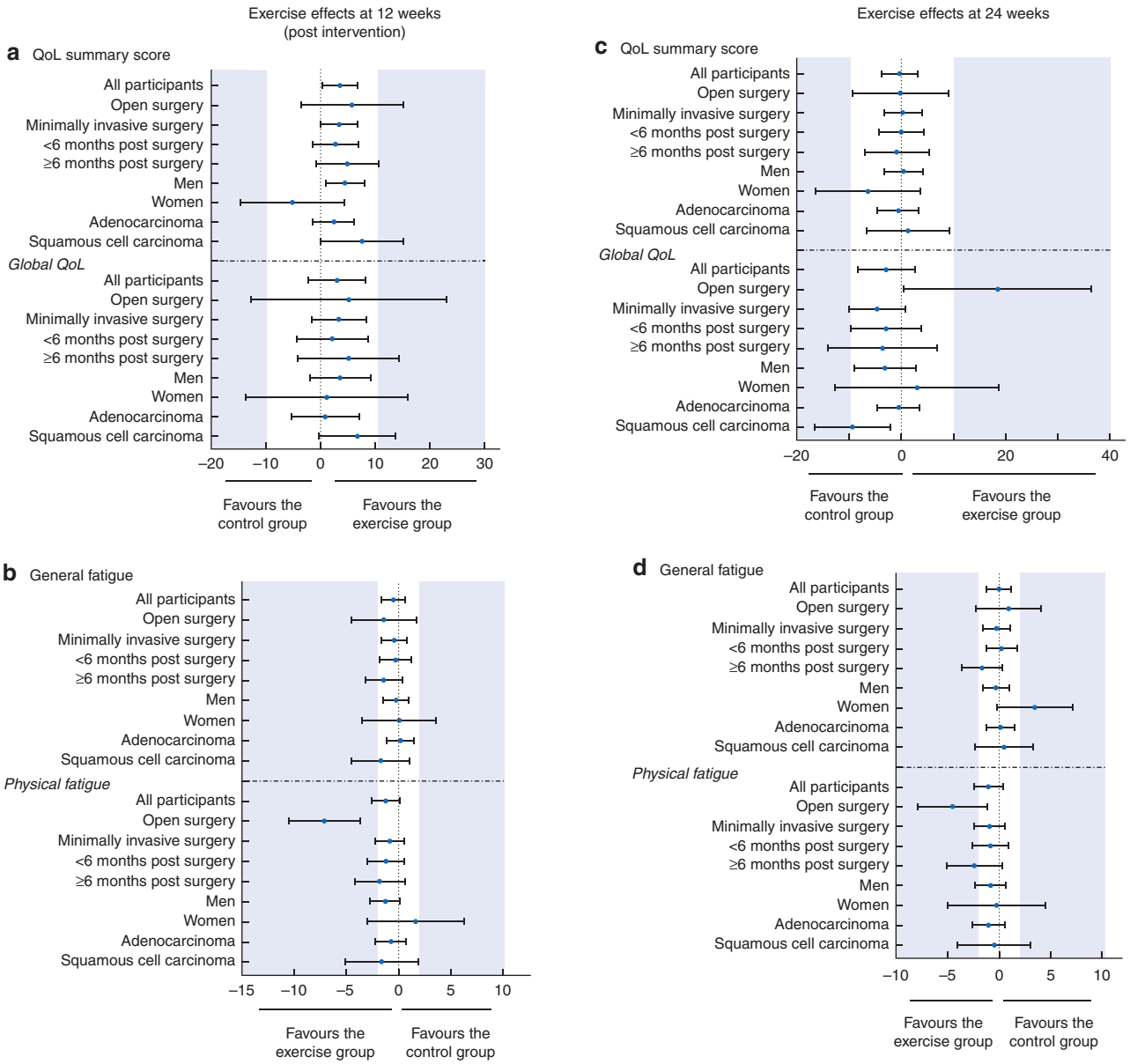

Fig. 3 Effects of the 12-week exercise intervention on QoL and fatigue 12 and 24 weeks post baseline for all participants and stratified for sex, type of surgery, subtype of carcinoma and time since surgery.

Intention-to-treat mixed linear regression models were used to calculate differences between the exercise and usual care group at 12 and 24 weeks. Models were adjusted for the baseline value of the outcome and stratification factors. Between-group differences were based on participants for whom measurements at 12 or 24 weeks were available (EX: open surgery $n = 5$; minimal invasive $n = 49$; <6 months $n = 36$; ≥6 months $n = 18$, men $n = 46$; women $n = 8$, adenocarcinoma $n = 45$ and squamous cell carcinoma $n = 8$, UC: open surgery $n = 6$; minimal invasive $n = 50$; <6 months $n = 39$; ≥6 months $n = 17$; men $n = 49$; women $n = 7$; adenocarcinoma $n = 41$; squamous cell carcinoma $n = 10$). Blue zones show the cut-off for clinically relevant (i.e., ≥10 points for QoL[32] and ≥2 for fatigue[51]) changes. Between-group differences are shown with corresponding 95 per cent confidence intervals. Confidence intervals not including 0 are considered statistically significant.

that it has a strong prognostic value for overall survival[37]. Moreover, it is believed that the summary score takes all factors into consideration that might influence a patient's QoL, whereas this cannot be detected by a single global QoL question. Importantly, supervised exercise exerts its effect on quality of life not only through physical fitness and health, but also through social, mental and cognitive factors (e.g., improvements in social environment and self-concept)[38]. It is not one of these factors alone, but the interplay between all factors that contributes to successful rehabilitation in cancer patients.

Compared with the general European population, participants reported a poorer QoL at baseline, especially in terms of role functioning[39]. Role functioning comprises the ability of an individual to engage in activities that are typical for their age and social setting[40], which is perceived to remain substantially impaired into cancer survivorship[41]. We found that patients who participated in a 12-week supervised exercise intervention experienced significantly and clinically relevant higher role functioning compared with patients receiving usual care. These results indicate that patients are capable of engaging in physical and social activities. This is an important finding, since a recent mixed methods study observed that the majority of cancer patients find the impact of the disease and its symptoms on everyday life most clinically important[42].

Patients had improved global QoL and levels of fatigue following the intervention, although between-group differences were

Table 3 Effects of the PERFECT exercise intervention on quality of life and on all dimensions of fatigue

		Baseline	Baseline to 12 weeks (post intervention)			Baseline to 24 weeks		
			Within-group differences	Between-group differences		Within-group differences	Between-group differences	
		Mean(s.d.)	Mean (95% c.i.)	Mean (95% c.i.)	ES	Mean (95% c.i.)	Mean (95% c.i.)	ES
EORTC QLQ C-30								
Summary score	EX	80.63(13.94)	5.89 (3.32, 8.47)*	3.51 (0.24, 6.77)*	0.26	3.48 (–0.41, 4.62)	–0.29 (–3.72, 3.15)	0.02
	UC	82.05(12.76)	2.10 (0.03, 6.93)*	Reference		2.68 (–0.72, 6.07)	Reference	
Global QoL	EX	67.48(17.19)	9.32 (5.08, 13.56)*	3.01 (–2.19, 8.21)	0.18	4.44 (–0.91, 9.80)	–2.86 (–8.37, 2.65)	0.17
	UC	71.05(16.26)	4.01 (–0.19, 8.20)	Reference		4.38 (–0.97, 9.72)	Reference	
Physical functioning	EX	82.97(14.19)	6.09 (2.89, 9.29)*	3.18 (–1.37, 7.73)	0.23	3.89 (–0.28, 8.06)	1.83 (–2.92, 6.57)	0.13
	UC	81.36(13.83)	3.36 (0.20, 6.52)*	Reference		2.43 (–1.74, 6.61)	Reference	
Emotional functioning	EX	82.51(22.29)	3.79 (–0.63, 8.21)	1.16 (–4.62, 6.94)	0.06	1.25 (–4.51, 7.00)	0.93 (–5.12, 6.98)	0.05
	UC	86.86(17.45)	–0.52 (–4.89, 3.85)	Reference		–3.80 (–9.53, 1.93)	Reference	
Role functioning	EX	70.77(24.09)	13.91 (7.27, 20.55)*	9.38 (1.28, 17.48)*	0.40	12.88 (4.95, 20.82)*	3.94 (–4.66, 12.54)	0.17
	UC	75.71(22.81)	0.83 (–5.75, 7.41)	Reference		5.21 (–2.77, 13.18)*	Reference	
Social functioning	EX	83.61(21.62)	4.05 (–0.76, 8.86)	0.99 (–4.52, 6.50)	0.04	1.55 (–4.58, 7.68)	–3.23 (–9.09, 2.64)	0.14
	UC	81.92(24.03)	3.02 (–1.74, 7.77)	Reference		4.15 (–1.96, 10.26)	Reference	
Cognitive functioning	EX	87.70(20.28)	1.94 (–1.82, 5.70)	3.97 (–1.43, 9.36)	0.21	1.33 (–3.66, 6.32)	2.11 (–3.44, 7.66)	0.11
	UC	85.03(17.60)	–0.89 (–4.60, 2.82)	Reference		0.10 (–4.86, 5.07)	Reference	
Fatigue	EX	35.34(22.45)	–9.89 (–14.69, –5.10)*	–4.62 (–10.77, 1.53)	0.22	–4.27 (–10.55, 2.02)	3.29 (–3.22, 9.80)	0.16
	UC	31.26(19.63)	–4.75 (–9.49, –0.02)*	Reference		–6.24 (–12.53, 0.05)	Reference	
Pain	EX	9.56(18.12)	–0.45 (–5.34, 4.45)	–1.24 (–7.28, 4.80)	0.07	2.26 (–3.89, 8.40)	1.52 (–4.88, 7.92)	0.08
	UC	13.56(19.93)	–0.22 (–5.06, 4.63)	Reference		0.33 (–4.59, 5.68)	Reference	
Nausea and vomiting	EX	14.48(20.85)	–3.77 (–8.33, 0.80)	–0.52 (–5.43, 4.39)	0.03	–2.66 (–8.31, 2.99)	–1.01 (–6.27, 4.24)	0.05
	UC	10.37(16.79)	–1.20 (–5.71, 3.32)	Reference		0.25 (–5.42, 5.93)	Reference	
Dyspnoea	EX	23.50(23.71)	–9.56 (–14.80, –4.31)*	–5.21 (–12.10, 1.69)	0.20	–12.05 (–18.93, –5.17)*	–3.08 (–10.34, 4.17)	0.12
	UC	31.07(27.43)	–8.74 (–13.92, –3.56)*	Reference		–13.08 (–19.93, –6.23)*	Reference	
Insomnia	EX	25.68(32.81)	–6.54 (–13.07, –0.02)*	–4.14 (–12.38, 4.09)	0.14	–0.78 (–9.19, 7.63)	–1.11 (–7.56, 9.78)	0.04
	UC	16.95(26.38)	2.69 (–3.80, 9.18)	Reference		3.18 (–5.20, 11.56)	Reference	
Appetite loss	EX	31.15(34.70)	–10.77 (–17.25, –4.29)*	–0.81 (–8.70, 7.07)	0.03	–9.74 (–18.12, –1.37)*	2.20 (–6.06, 10.44)	0.07
	UC	17.51(27.77)	–3.48 (–9.83, 2.88)	Reference		–4.76 (–13.13, 3.61)	Reference	
Constipation	EX	6.56(16.92)	–1.52 (–5.53, 2.50)	2.00 (–2.66, 6.67)	0.12	0.06 (–4.85, 4.97)	3.97 (–0.98, 8.93)	0.24
	UC	6.21(16.83)	–2.63 (–6.60, 1.35)	Reference		0.22 (–4.01, 4.46)	Reference	
Diarrhoea	EX	13.11(21.21)	–2.68 (–8.51, 3.15)	1.44 (–5.38, 8.26)	0.06	0.13 (–7.09, 7.35)	2.66 (–4.58, 9.91)	0.11
	UC	16.95(26.38)	–5.49 (–11.22, 0.25)	Reference		–3.72 (–10.97, 3.53)	Reference	
Financial difficulties	EX	6.01(12.85)	–1.65 (–5.57, 2.28)	–2.00 (–7.18, 3.19)	0.12	1.55 (–3.59, 6.69)	–2.77 (–8.22, 2.69)	0.16
	UC	8.47(20.96)	–0.79 (–4.68, 3.11)	Reference		3.44 (–1.68, 8.55)	Reference	
Multidimensional Fatigue Inventory (MFI)								
General fatigue	EX	11.84(3.41)	–1.86 (–2.73, –0.98)*	–0.50 (–1.66, 0.66)	0.14	–1.11 (–2.27, 0.03)	–0.03 (–1.26, 1.19)	0.01
	UC	11.42(3.89)	–1.27 (–2.13, –0.41)*	Reference		–0.91 (–2.04, 0.23)	Reference	
Physical fatigue	EX	12.43(3.89)	–3.21 (–4.23, –2.19)*	–1.22 (–2.58, 0.15)	0.30	–2.65 (–3.96, –1.35)*	–1.03 (–2.45, 0.40)	0.25
	UC	12.17(4.30)	–1.92 (–2.92, –0.91)*	Reference		–1.50 (–2.80, –0.21)*	Reference	
Mental fatigue	EX	8.77(4.26)	–0.29 (–1.01, 0.43)	–0.02 (–1.03, 0.99)	0.01	–1.16 (–2.15, –0.18)*	–0.87 (–1.92, 0.18)	0.20
	UC	8.73(4.34)	–0.14 (–0.84, 0.57)	Reference		–0.16 (–1.13, 0.81)	Reference	
Reduced activity	EX	11.00(3.87)	–1.62 (–2.57, –0.66)*	–1.19 (–2.51, 0.12)	0.29	–1.56 (–2.80, –0.33)	–1.10 (–2.47, 0.28)	0.26
	UC	11.34(4.46)	–0.64 (–1.58, 0.30)	Reference		–0.57 (–1.79, 0.66)	Reference	
Reduced motivation	EX	9.34(3.50)	–1.21 (–2.01, –0.41)*	–0.93 (–2.10, 0.25)	0.26	–0.88 (–1.94, 0.18)	–1.06 (–2.29, 0.16)	0.29
	UC	8.98(3.79)	–0.05 (–0.84, 0.74)	Reference		0.42 (–0.63, 1.46)	Reference	

Between-group effects were assessed using mixed models including the measurements obtained at 12 and 24 weeks, adjusted for sex, hospital and time since surgery, and the value of the outcome variable at baseline. Within-group effects were assessed using mixed models including the measurements obtained at baseline, 12 and 24 weeks, adjusted for sex, hospital and time since surgery, and the value of the outcome variable at baseline. Baseline results and within-group differences were based on participants having baseline measurements (61 intervention and 59 usual care). Between-group differences were based on participants for whom measurements at 12 or 24 weeks were available (54 intervention and 56 usual care). According to Cohen, ES < 0.2 indicate no difference, ES of 0.2–0.5 indicates a small difference, ES of 0.5–0.8 indicates a medium difference and ES 0.8 or more indicates a large difference[31]. ES, effect size; EX, exercise group; UC, usual care group.
*indicates significant differences ($P < 0.05$).

not significantly different. Nevertheless, the ESs for global QoL and physical fatigue are in line with previous studies[9,10]. The ES of the present study might be diluted for several reasons. First, patients were not selected on low baseline levels of QoL and fatigue (i.e., had a broad range of baseline levels of global QoL/fatigue), whereas it is known that exercise effects are larger in individuals who need it (i.e., with poor baseline values)[43]. Second, these effects might have been contaminated by the adoption of exercise behaviour by the usual care group[28]. Indeed, 10 patients allocated to usual care increased the time spent on moderate- to high-intensity physical activities for at least 60 minutes compared with baseline. Third, response shift, which refers to the change in one's self-evaluation of QoL, might mask the effect of the exercise intervention on global QoL[44]. Therefore, the authors added the recently developed QoL summary scale to the primary outcome, which is more responsive to changes over time. Indeed, they observed significant changes for this scale.

The PERFECT exercise intervention had beneficial effects on both maximal and submaximal cardiorespiratory fitness, suggesting the importance of supervised exercise after oesophageal cancer treatment with regard to physical recovery. Multimodality treatment of oesophageal cancer causes short- and long-term impairments in VO_{2peak}[45,46]. Evidence indicates that poor VO_{2peak} is associated with a high symptom burden (i.e., fatigue and lower

Table 4 Effects of the PERFECT exercise intervention on cardiorespiratory fitness

		Baseline	Baseline to 12 weeks (post-intervention)		
			Within-group differences	Between-group differences	
		Mean(s.d.)	Mean (95% c.i.)	Mean (95% c.i.)	ES
Cardiorespiratory fitness					
Peak VO_2 (l/min)	EX	1.73(0.51)	0.19 (0.12, 0.26)*	0.13 (0.04, 0.22)*	0.26
	UC	1.75(0.49)	0.06 (0.003, 0.12)*	Reference	
Peak VO_2 (ml/min/kg)	EX	22.55(5.46)	2.75 (1.81, 3.69)*	1.80 (0.62, 2.99)*	0.33
	UC	22.35(5.34)	0.86 (0.12, 1.59)*	Reference	
Peak power output (Watt)	EX	154.75(47.55)	20.28 (14.58, 25.98)*	16.89 (9.03, 24.74)*	0.36
	UC	150.61(47.32)	2.92 (–2.30, 8.13)	Reference	
VO_2 at VT (l/min)	EX	1.13(0.37)	0.14 (0.08, 0.20)*	0.12 (0.03, 0.21)*	0.36
	UC	1.16(0.30)	0.01 (–0.06, 0.08)	Reference	
VO_2 at VT (ml/min/kg)	EX	14.75(3.95)	2.25 (1.40, 3.09)*	1.81 (0.58, 3.03)*	0.48
	UC	14.94(3.63)	0.23 (–0.64, 1.09)	Reference	
Power output at VT (Watt)	EX	76.47(34.46)	15.22 (8.65, 21.78)*	11.81 (2.38, 21.23)*	0.37
	UC	78.90(29.33)	1.40 (–5.93, 8.73)	Reference	
VO_2 at RCP (l/min)	EX	1.55(0.46)	0.25 (0.17, 0.33)*	0.13 (0.01, 0.25)*	0.29
	UC	1.59(0.43)	0.11 (0.02, 0.19)*	Reference	
VO_2 at RCP (ml/min/kg)	EX	19.95(4.87)	3.56 (2.60, 4.52)*	1.71 (0.20, 3.22)*	0.14
	UC	22.72(18.97)	1.43 (0.33, 2.53)*	Reference	
Power output at RCP (Watt)	EX	127.43(40.98)	22.19 (14.41, 29.96)*	8.53 (–4.37, 21.43)	0.21
	UC	126.93(39.94)	10.96 (1.44, 20.47)*	Reference	

Within- and between-group effects were assessed using ANCOVA including the measurements obtained at baseline and 12 weeks, adjusted for sex, hospital and time since surgery, and the value of the outcome variable at baseline. Baseline results and within-group differences were based on participants having baseline measurements (61 intervention and 59 usual care). Between-group differences were based on participants for whom measurements at 12 or 24 weeks were available (54 intervention and 56 usual care). According to Cohen, ES less than 0.2 indicates no difference, ES of 0.2–0.5 indicates a small difference, ES of 0.5–0.8 indicates a medium difference and ES of 0.8 or more indicates a large difference[31]. ES, effect size; EX, exercise group; UC, usual care group; VO_2, oxygen uptake; VT, ventilatory threshold; RCP, respiratory compensation point. *Indicates significant differences ($P < 0.05$).

QoL) and an increased risk of overall- and cancer-specific mortality[47]. The significant results observed at the submaximal level are highly relevant, since most activities in daily life are performed on a submaximal level.

Most positive intervention effects were attenuated at 24 weeks. This might be explained by the fact that participants allocated to the exercise intervention did not continue exercising at the same intensity and that controls slightly improved their physical activity behaviour. It would be helpful to gain more insight into the patients' barriers and facilitators to physical exercise to enable the development of more effective and targeted exercise interventions or advice designed to promote long-term behaviour change. Possibly, involving telemedicine, adding educational sessions and behavioural change techniques to the intervention could help participants maintain a physically active lifestyle after completion of an exercise programme[48].

The present study has some limitations. The recruitment rate was rather low (33.5 per cent), which might hamper generalizability. Due to (self-)selection by the patient and/or treating physician, patients who were enrolled had relatively favourable characteristics (e.g., 53.3 per cent of all participants had grade 2 or above surgical complications *versus* 64.5 per cent of all patients receiving an oesophagectomy in The Netherlands)[49]. Patients in greatest need of an exercise intervention (i.e., with higher fatigue levels, more (severe) complications and co-morbidities) were less likely to participate. Based on the exploratory subgroup analysis, it may be assumed that patients who have had open surgery might benefit more from an exercise intervention, since they are more in need of one (i.e., have a lower QoL). However, results of the subgroup analysis should be interpreted with caution due to small subgroups. The study's exercise intervention did not include a dietary component, although this study population is at risk of malnutrition. Usual care by a dietician was provided to both study groups. Future exercise programmes should study whether including a structured dietary intervention would result in larger effects of the exercise intervention. Strengths of the present study include a well designed multicentre RCT including a large sample size and limited loss to follow-up, the use of valid outcome measures and excellent adherence to the supervised exercise programme. The attendance and RDI were extensively monitored, resulting in reliable and accurate data. Additionally, the PERFECT study used a pragmatic design by delivering the intervention at different sites with different physiotherapists, increasing the external generalizability.

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Supplementary material

Supplementary material is available at *BJS* online.

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