Randomized clinical trial

Multicentre randomized clinical trial of inspiratory muscle training *versus* usual care before surgery for oesophageal cancer

K. Valkenet[1], J. C. A. Trappenburg[1], J. P. Ruurda[2], E. M. Guinan[13], J. V. Reynolds[14], P. Nafteux[15], M. Fontaine[16], H. E. Rodrigo[1], D. L. van der Peet[3], S. W. Hania[4], M. N. Sosef[5], J. Willms[6], C. Rosman[7], H. Pieters[8], J. J. G. Scheepers[9], T. Faber[10], E. A. Kouwenhoven[11], M. Tinselboer[12], J. Räsänen[18], H. Ryynänen[19], R. Gosselink[17], R. van Hillegersberg[2] and F. J. G. Backx[1]

Departments of [1]Rehabilitation, Physiotherapy Science and Sports, and [2]Surgery, University Medical Centre Utrecht, Utrecht, Departments of [3]Surgery and [4]Physiotherapy, VU University Medical Centre, Amsterdam, Departments of [5]Surgery and [6]Physiotherapy, Zuyderland Medical Centre, Heerlen, Departments of [7]Surgery and [8]Physiotherapy, Canisius Wilhelmina Hospital, Nijmegen, Departments of [9]Surgery and [10]Physiotherapy, Reinier de Graaf Hospital, Delft, and Departments of [11]Surgery and [12]Physiotherapy, Hospital Group Twente, Almelo, The Netherlands, [13]Discipline of Physiotherapy and [14]Department of Surgery, Trinity Centre for Health Sciences, St James's Hospital, Dublin, Ireland, Departments of [15]Surgery, [16]Physiotherapy and [17]Rehabilitation Sciences, University Hospitals Leuven, Leuven, Belgium, and Departments of [18]Surgery and [19]Physiotherapy, Helsinki University Central Hospital, Helsinki, Finland

Correspondence to: Dr K. Valkenet, Department of Rehabilitation, Physiotherapy Science and Sports, University Medical Centre Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands (e-mail: k.valkenet@umcutrecht.nl; @ValkenetKarin; @UMCUtrecht)

Background: Up to 40 per cent of patients undergoing oesophagectomy develop pneumonia. The aim of this study was to assess whether preoperative inspiratory muscle training (IMT) reduces the rate of pneumonia after oesophagectomy.

Methods: Patients with oesophageal cancer were randomized to a home-based IMT programme before surgery or usual care. IMT included the use of a flow-resistive inspiratory loading device, and patients were instructed to train twice a day at high intensity (more than 60 per cent of maximum inspiratory muscle strength) for 2 weeks or longer until surgery. The primary outcome was postoperative pneumonia; secondary outcomes were inspiratory muscle function, lung function, postoperative complications, duration of mechanical ventilation, length of hospital stay and physical functioning.

Results: Postoperative pneumonia was diagnosed in 47 (39·2 per cent) of 120 patients in the IMT group and in 43 (35·5 per cent) of 121 patients in the control group (relative risk 1·10, 95 per cent c.i. 0·79 to 1·53; $P = 0·561$). There was no statistically significant difference in postoperative outcomes between the groups. Mean(s.d.) maximal inspiratory muscle strength increased from 76·2(26·4) to 89·0(29·4) cmH_2O ($P < 0·001$) in the intervention group and from 74·0(30·2) to 80·0(30·1) cmH_2O in the control group ($P < 0·001$). Preoperative inspiratory muscle endurance increased from 4 min 14 s to 7 min 17 s in the intervention group ($P < 0·001$) and from 4 min 20 s to 5 min 5 s in the control group ($P = 0·007$). The increases were highest in the intervention group ($P < 0·050$).

Conclusion: Despite an increase in preoperative inspiratory muscle function, home-based preoperative IMT did not lead to a decreased rate of pneumonia after oesophagectomy. Registration number: NCT01893008 (https:www.clinicaltrials.gov).

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Introduction

The incidence of oesophageal cancer is increasing worldwide. Oesophagectomy is currently the treatment of choice for advanced locoregional disease[1,2]. Although postoperative recovery has improved owing to the introduction of minimally invasive techniques, centralization of surgery and enhanced recovery programmes, the postoperative complication rate remains high[3]. The most common complication after oesophagectomy is pneumonia[4–6]. Depending on the definition, up to 40 per cent of patients develop this complication[3,4,7]. As pneumonia is a common cause

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of death following oesophagectomy, reducing the risk of pneumonia through targeted interventions may further improve outcome[4,5,8].

Pulmonary complications can arise from an imbalance between the ventilatory demand and ventilatory capacity provoked by major surgery[9]. By increasing the ventilatory capacity before surgery, this imbalance may be prevented and the cascade leading to a pulmonary complication may be disrupted. Inspiratory muscle training (IMT), a training modality aimed at increasing strength and endurance of the inspiratory muscles, can increase ventilatory capacity[10,11]. Systematic reviews[12–15] of patients undergoing cardiac and upper abdominal surgery have shown that preoperative IMT can decrease the rate of postoperative pneumonia. Whether preoperative IMT is of benefit in patients undergoing oesophagectomy is unclear[16,17]. The aim of this RCT was to assess the effect of a preoperative IMT programme on the rate of postoperative pneumonia in patients undergoing oesophagectomy[18].

Methods

This study was conducted as a single-blind multicentre RCT. The CONSORT 2010 criteria[19] for RCTs were followed. The full study protocol with detailed procedures was published after the start of the trial[18].

Patients diagnosed with oesophageal cancer scheduled for transhiatal, transthoracic or minimally invasive (robot-assisted or conventional) oesophagectomy with gastric tube reconstruction were eligible for inclusion. Other inclusion criteria were: oesophagectomy scheduled at least 2 weeks after the baseline measurement, a good understanding of the instructions of IMT and ability to perform the IMT programme. Exclusion criteria were: unable to communicate in the mother language spoken at the participating centre, age less than 18 years and participation in another trial with similar endpoints[20,21].

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines, and was approved by the independent ethics committees of the participating centres. Written informed consent was obtained from all participating patients. Quality control was performed per centre according to the guidelines of the Dutch Federation of University Medical Centres[22] after the first three included patients and on a yearly base subsequently. The occurrence of serious adverse events that were possibly linked with the IMT intervention had to be reported to the coordinating researcher within 15 days after the event. Complications that were unmistakably related to the surgical or medical treatment were not reported as serious adverse events. The trial was considered low risk and no Data Safety Monitoring Board was installed.

Table 1 Revised Uniform Pneumonia Score

Diagnostic determinant	Value	Score
Temperature (°C)	≥ 36·1 and ≤ 38·4	0
	≤ 36·0 and ≥ 38·5	1
Leucocyte count (× 10^9/l)	≥ 4·0 and ≤ 11·0	0
	< 4·0 or > 11·0	1
Pulmonary radiography	No infiltrate	0
	Diffused (or patchy) infiltrate	1
	Well circumscribed infiltrate	2

A score of 2 points or more with at least 1 point assigned based on pulmonary radiography indicates treatment of suspected pneumonia[4,34].

Recruitment and blinding

Nine centres participated the trial: six in the Netherlands, one in Belgium, one in Ireland and one in Finland. Participants were assigned randomly in a 1 : 1 ratio to usual care or usual care plus IMT. Randomization was concealed and performed with a web-based system. The randomization was stratified by centre, and minimization techniques were applied for the three surgical techniques. Assessors of the baseline and follow-up measurements, and assessors of the postoperative outcomes were blinded for allocation. The physiotherapists guiding the intervention, the participants and the coordinating researcher were not blinded for allocation.

Intervention

Participants allocated to the intervention group received an IMT programme in addition to usual care. When neoadjuvant therapy was administered, IMT started afterwards. Patients were instructed by a physiotherapist. The intervention entailed the use of a tapered flow resistive inspiratory loading device (POWER®breathe K3; POWERbreathe International, Southam, UK) (*Fig. S1*, supporting information), which registers several parameters per training session, including load (cmH_2O), power (W), inhaled volume (litres) and a training index (per cent)[23].

Patients had to perform 30 breaths twice daily, 7 days a week, for 2 weeks or longer until the date of surgery[11,24,25]. Starting inspiratory load was aimed at 60 per cent of the baseline maximum inspiratory pressure, and was tailored on an individual basis during training. After each training session, patients reported their rate of perceived exertion ('How intense was this training session?') on a scale from 0 (no exertion) to 10 (maximum exertion) in their training diary[26,27]. When a rate of perceived exertion below 7 was scored, patients were instructed to increase the inspiratory

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Table 2 Baseline characteristics of participants

	Intention to treat		Per protocol
	Control ($n = 121$)	Intervention ($n = 120$)	Intervention (n = 95)
Age (years)*	62·7(8·9)	63·7(7·5)	63·1(7·5)
Sex ratio (M : F)	97 : 24	89 : 31	68 : 27
BMI (kg/m^2)*	26·5(5·2)	26·7(4·8)	26·4(4·5)
Paid worker	41 of 119 (34·5)	30 of 119 (25·2)	24 of 94 (26)
High school or university education	37 of 93 (40)	33 of 92 (36)	28 of 73 (38)
Living alone	20 of 117 (17·1)	12 of 119 (10·1)	11 of 94 (12)
Prehabilitation programme	13 (10·7)	12 (10·0)	11 (12)
Co-morbidity			
COPD	14 (11·6)	19 (15·8)	14 (15)
Pneumonia in past 8 weeks	3 of 120 (2·5)	5 of 116 (4·3)	3 of 93 (3)
Productive cough in past 5 days	26 of 120 (21·7)	19 of 117 (16·2)	16 of 94 (17)
Current smoker	20 of 120 (16·7)	19 (15·8)	17 (18)
Cardiac history	35 of 119 (29·4)	25 of 119 (21·0)	18 of 94 (19)
Diabetes mellitus type 2	13 (10·7)	14 (11·7)	9 (9)
ASA fitness grade			
0–I	11 of 117 (9·4)	11 of 112 (9·8)	8 of 89 (9)
II	72 of 117 (61·5)	66 of 112 (58·9)	53 of 89 (60)
III–IV	34 of 117 (29·1)	35 of 112 (31·3)	28 of 89 (31)
Tumour and treatment			
Tumour location			
Cervical–upper third	4 of 118 (3·3)	2 of 118 (1·7)	1 of 93 (1)
Middle third	14 of 118 (11·9)	19 of 118 (16·1)	14 of 93 (15)
Lower third	62 of 118 (52·5)	66 of 118 (55·9)	55 of 93 (59)
Junction	38 of 118 (32·2)	31 of 118 (26·3)	23 of 93 (25)
Tumour type			
Adenocarcinoma	84 of 118 (71·2)	91 of 115 (79·1)	73 of 91 (80)
Squamous cell carcinoma	30 of 118 (25·4)	23 of 115 (20·0)	17 of 91 (19)
Other	4 of 118 (3·4)	1 of 115 (0·9)	1 of 91 (1)
Neoadjuvant treatment			
None	15 (12·4)	16 of 119 (13·4)	14 (15)
Chemotherapy	12 (9·9)	10 of 119 (8·4)	8 (8)
Chemoradiotherapy, CROSS	80 (66·1)	84 of 119 (70·6)	66 (69)
Chemoradiotherapy, other	14 (11·6)	9 of 119 (7·6)	7 (7)
Perioperative antibiotics	118 of 119 (99·2)	120 (100)	95 (100)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). COPD, chronic obstructive pulmonary disease; CROSS, ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study.

load of their training device by 5 per cent. Patients also reported the parameters of the training device after each session.

All patients in the intervention group received one baseline face-to-face instruction by the physiotherapist at the outpatient clinic. In addition, they received a training diary and an instruction video where the appropriate use of the inspiratory muscle trainer was illustrated step by step. Patients then continued training at home, and the physiotherapist contacted them by telephone after 3 days. When the training was not followed as instructed, the physiotherapist made a follow-up appointment at the outpatient clinic to repeat the face-to-face instruction. Subsequently, adherence to the training and training progress was evaluated by weekly scheduled telephone interviews with the patient.

Compliance

To evaluate compliance with the IMT intervention, the number of trained sessions, training parameters and training intensity were registered and compared with the protocol.

Usual care

Usual care was not standardized, owing to the pragmatic character of the PREPARE (preoperative inspiratory muscle training to prevent postoperative pneumonia in patients undergoing esophageal resection) trial. Thus, all participants received usual care according to local policies[18]. As a requirement for participation in the trial, IMT could not be part of usual care procedures during the trial.

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Table 3 Surgical and tumour characteristics of participants

	Intention to treat		Per protocol
	Control (*n* = 121)	Intervention (*n* = 120)	Intervention (*n* = 95)
Surgical approach		(*n* = 119)	(*n* = 94)
Transhiatal	20 (16·5)	14 (11·8)	11 (12)
Transthoracic, left	10 (8·3)	16 (13·4)	13 (14)
Transthoracic, right	91 (75·2)	89 (74·8)	70 (74)
Surgical technique			
Open	47 (38·8)	44 (36·7)	35 (37)
MIO, laparoscopic	53 (43·8)	50 (41·7)	42 (44)
MIO, robot-assisted	21 (17·4)	26 (21·7)	18 (19)
Anastomosis	(*n* = 120)	(*n* = 115)	(*n* = 90)
Cervical	58 (48·3)	58 (50·4)	44 (49)
Thoracic	62 (51·7)	57 (49·6)	46 (51)
pT status	(*n* = 115)	(*n* = 115)	(*n* = 92)
pT0	12 (10·4)	13 (11·3)	11 (12)
pT1	19 (16·5)	20 (17·4)	17 (18)
pT2	17 (14·8)	20 (17·4)	17 (18)
pT3	64 (55·7)	59 (51·3)	45 (49)
pT4	3 (2·6)	3 (2·6)	2 (2)
pN status	(*n* = 116)	(*n* = 115)	(*n* = 92)
pN0	68 (58·6)	63 (54·8)	55 (60)
pN1	32 (27·6)	32 (27·8)	24 (26)
pN2	12 (10·3)	15 (13·0)	10 (11)
pN3	4 (3·4)	5 (4·3)	3 (3)
Single lung ventilation	99 of 118 (83·9)	108 of 118 (91·5)	86 of 94 (91)
Blood loss (ml)*	455(599)	405(427)	397(443)
Duration (h:min)*	5:57(1:45)	6:04(1:47)	5:57(1:37)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). MIO, minimally invasive oesophagectomy.

Respiratory muscle function and lung function

Respiratory muscle function and lung function measurements were performed by the blinded physiotherapist at five consecutive time points: baseline (T0), before surgery (T1), and during hospital stay on postoperative day 3 (T2), day 6 (T3) and day 9 (T4). The respiratory muscle function values included maximum inspiratory pressure and inspiratory muscle endurance, and were assessed with handheld devices (respectively POWER®breathe KH1 and modified K2; POWERbreathe International). Maximum inspiratory pressure was measured at the mouth during a forceful inspiratory manoeuvre at residual volume. Inspiratory muscle endurance was assessed with an inspiratory load of 70 per cent of the maximum inspiratory pressure until task failure[18]. The pulmonary function values included forced expiratory volume in 1 s and forced vital capacity, and were assessed using a portable spirometer (Micro™ I; CareFusion, Hoechberg, Germany).

Physical functioning

Quality of life, physical activity level and fatigue were assessed with questionnaires at baseline (T0) and 4 weeks after surgery (T5). The EuroQol-5D (EQ-5D-3L™; EuroQol Group, Rotterdam, The Netherlands) and Short Form 12 (SF-12®; Quality Metric, Lincoln, Rhode Island, USA) questionnaires were used to assess quality of life[28–31]; the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) questionnaire (Netherlands National Institute for Public Health and the Environment, Bilthoven, The Netherlands) was used to measure physical activity[32]; and the Multidimensional Fatigue Inventory (MFI-20)[33] was used to measure fatigue. Dates of first day out of bed were obtained from the medical records.

Primary endpoint

The rate of postoperative pneumonia was measured by the revised Uniform Pneumonia Score[34]. This scoring system uses the variables temperature, leucocyte count and chest X-ray findings to determine whether treatment of pneumonia is indicated (*Table 1*)[4,34]. Chest X-ray was performed according to unstandardized local routine care policies. On the days when a chest X-ray was performed, the local researcher assessed the variables of the Uniform Pneumonia Score.

Secondary endpoints

Secondary endpoints included postoperative complications (anastomotic leak, chyle leak, wound infection, sepsis, vocal cord paralysis, delirium/confusion, and cardiac, neurological or thromboembolic events), prescription of antibiotics for suspected pneumonia, in-hospital mortality, length of hospital stay (overall and ICU stay), mechanical ventilation time (number of hours spent on the mechanical ventilator during and directly after the primary operation) and the number of reintubations. Other secondary endpoints included respiratory muscle function and lung function, and physical functioning.

Sample size calculation

The sample size was calculated based on an expected reduction of 50 per cent in the rate of postoperative pneumonia[11]. Presuming a 30 per cent rate of postoperative pneumonia after oesophageal resection in the control arm, and using a significance level of 0·05 and a power of 80 per cent, 118 patients were required in each arm[1,16,35]. Taking into account a 5 per cent in-hospital mortality rate after surgery, 124 patients per arm needed to be included.

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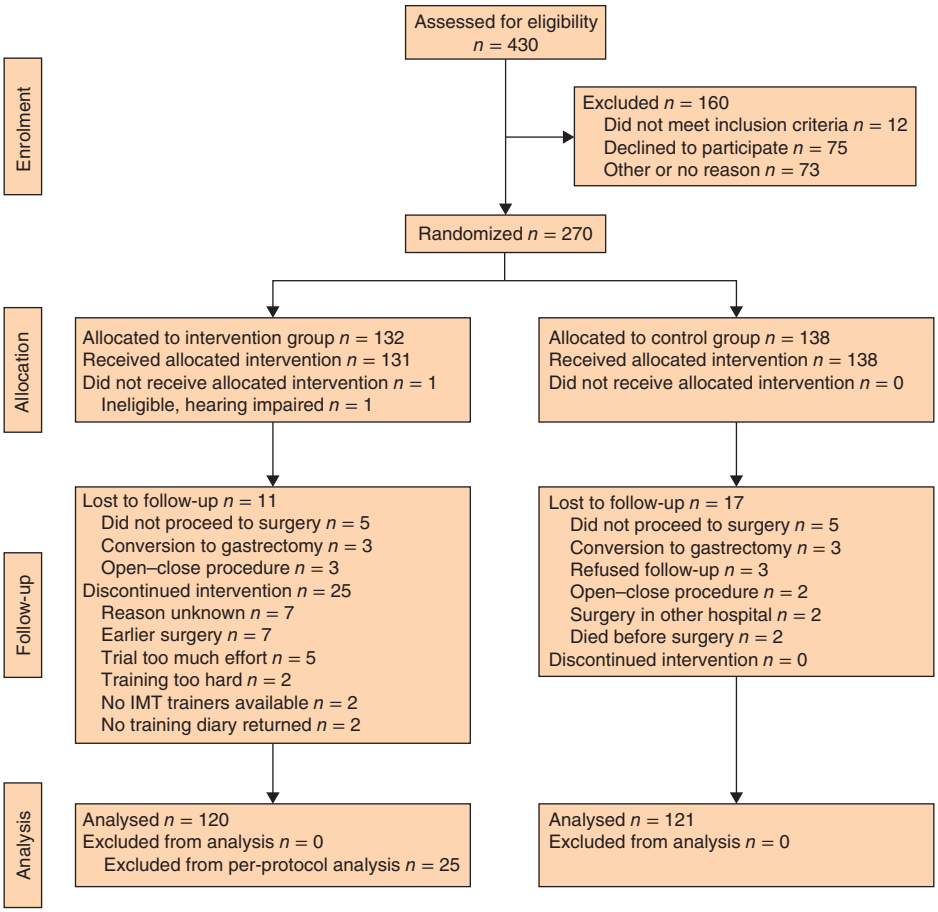

Fig. 1 CONSORT flow diagram for the trial. IMT, inspiratory muscle training

Statistical analysis

Data analyses were performed in accordance with the modified intention-to-treat (ITT) principle and the per-protocol principle[36,37]. Patients were excluded from per-protocol analysis when they were allocated to the intervention group but did not start IMT, or had trained for less than 2 weeks.

Descriptive statistics were used to analyse baseline demographic variables. Log-binomial regression analyses were performed to calculate the relative risk (RR) for all dichotomous outcomes[38–42]. The continuous outcome variables duration of mechanical ventilation and length of stay were analysed using Cox proportional hazards regression models.

For the repeated measurements of respiratory muscle function, lung function and the physical functioning questionnaires, the differences between groups were analysed using multivariate linear regression at the different time points. The comparison for within-group differences for preoperative respiratory muscle function and lung function measurements, as well as the scores from the questionnaires for quality of life, physical activity and fatigue, were performed with paired-samples *t* tests.

All analyses were adjusted for centre. Multivariable linear regression analyses were additionally adjusted for baseline parameters[43]. A two-sided *P* value of less than 0·050 was regarded as significant. IBM SPSS® statistics software version 22 (IBM, Armonk, New York, USA) was used for all data analyses.

Results

Between 6 September 2013 and 23 May 2016, 270 patients were randomized of whom 241 were included in the final analyses (120 patients in the IMT group and 121 in the control group). Baseline and surgical characteristics of the patients are shown in *Tables 2* and *3*. Six centres entered patients during the entire study period, two joined in April 2014 and one centre joined in October 2015. The median

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Table 4 Multivariable analysis of complications and postoperative course

	Intention to treat				Per protocol		
	Control (n = 121)	Intervention (n = 120)	RR†	P§§	Intervention (n = 95)	RR	P§§
Complications							
Death in hospital	3 (2·5)	5 (4·2)	1·67 (0·40, 6·87)	0·478	4 (4)	1·68 (0·38, 7·41)	0·489
Pneumonia§	43 (35·5)	47 (39·2)	1·10 (0·79, 1·53)	0·561	38 (40)	1·13 (0·80, 1·59)	0·501
Antibiotics for suspected pneumonia	40 (33·3)	47 (39·2)	1·19 (0·84, 1·66)	0·326	38 (40)	1·21 (0·85, 1·73)	0·292
Pulmonary, other¶	40 of 120 (33·3)	41 of 118 (34·7)	1·04 (0·73, 1·49)	0·818	33 of 94 (35)	1·05 (0·72, 1·53)	0·786
Cardiac	27 of 120 (22·5)	23 of 118 (19·5)	0·87 (0·53, 1·42)	0·570	17 of 94 (18)	0·80 (0·47, 1·39)	0·432
Complication, other#	17 of 120 (14·2)	26 of 118 (22·0)	1·56 (0·89, 2·72)	0·121	21 of 94 (22)	1·58 (0·88, 2·83)	0·125
Anastomotic leak	17 of 119 (14·3)	18 of 118 (15·3)	1·07 (0·58, 1·98)	0·834	13 of 94 (14)	0·97 (0·49, 1·90)	0·924
Positive sputum culture	15 (12·4)	12 (10·0)	0·81 (0·39, 1·66)	0·557	9 (9)	0·76 (0·35, 1·68)	0·501
Chyle leak	11 of 120 (9·2)	13 of 118 (11·0)	1·20 (0·56, 2·58)	0·637	9 of 94 (10)	1·04 (0·45, 2·43)	0·919
Vocal cord paresis	10 of 118 (8·5)	4 of 118 (3·4)	0·40 (0·13, 1·25)	0·114	3 of 94 (3)	0·38 (0·11, 1·34)	0·131
Infection, other**	9 of 119 (7·6)	10 of 118 (8·5)	1·12 (0·47, 2·67)	0·796	7 of 94 (7)	0·99 (0·38, 2·56)	0·975
Sepsis	6 of 119 (5·0)	5 of 117 (4·3)	0·85 (0·26, 2·72)	0·780	5 of 93 (5)	1·07 (0·33, 3·41)	0·913
Infection, wound	5 of 119 (4·2)	8 of 117 (6·8)	1·63 (0·55, 4·86)	0·381	6 of 93 (6)	1·53 (0·48, 4·91)	0·468
Neurological	4 of 120 (3·3)	6 of 116 (5·2)	1·55 (0·45, 5·39)	0·488	4 of 93 (4)	1·29 (0·33, 5·06)	0·714
Delirium/confusion	3 (2·5)	9 (7·5)	3·03 (0·83, 10·97)	0·092	7 (7)	2·97 (0·78, 11·27)	0·109
Bleeding	1 of 120 (0·8)	3 of 118 (2·5)	3·05 (0·32, 29·25)	0·332	2 of 94 (2)	2·55 (0·23, 28·11)	0·442
Thromboembolic	1 of 119 (0·8)	2 of 118 (1·7)	2·02 (0·18, 22·22)	0·565	1 of 94 (1)	1·27 (0·08, 20·29)	0·867
Postoperative course							
Mechanical ventilation (h)*	8:06(4:08)	8:55(7:56)††	1·03 (0·67, 1·59)‡	0·898	9:05(8:43)	1·05 (0·66, 1·67)‡	0·830
LOS, total (days)*	20·5(20·9)	18·4(18·0)	0·77 (0·51, 1·18)‡	0·231	17·8(18·7)	0·73 (0·47, 1·14)‡	0·166
LOS, ICU (days)*	3·1(6·6)	3·3(7·5)‡‡	0·91 (0·56, 1·38)‡	0·658	3·5(8·2)‡‡	0·94 (0·60, 1·46)‡	0·782
Readmission ICU	20 (16·5)	12 (10·0)	0·62 (0·34, 1·17)‡	0·138	9 (9)	0·57 (0·28, 1·15)	0·113
Reintubation	17 of 117 (14·5)	15 of 114 (13·2)	0·91 (0·47, 1·73)‡	0·763	14 of 90 (16)	1·07 (0·56, 2·06)	0·838

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Relative risk (RR), except ‡hazard ratio. §Pneumonia according to revised Uniform Pneumonia Score[4,34]; ¶pneumothorax, pulmonary embolism, respiratory insufficiency, pulmonary oedema, pleural empyema, pleural effusion; #hyperglycaemia, hypoglycaemia, gastroparesis, wound dehiscence, spleen infarction, kidney insufficiency, decubitus, jejunostomy blockage, alcohol withdrawal, anaemia, ileus; **systemic inflammatory response syndrome, abscess, fever or infection of unknown origin; ††one extreme outlier (493 h) excluded; ‡‡one extreme outlier (166 days) excluded. LOS, length of stay. §§*Versus* control.

number of included patients per participating centre was 20 (range 9–60). In the per-protocol analyses, 25 patients were excluded (*Fig. 1*). No serious adverse events were reported during the trial.

Primary endpoint

Postoperative pneumonia was diagnosed in 47 of 120 patients (39·2 per cent) in the intervention group and in 43 of 121 (35·5 per cent) in the control group (RR 1·10, 95 per cent c.i. 0·79 to 1·53; $P = 0·561$) (*Table 4*).

Secondary outcomes

There were no statistically significant differences between groups for complications or other postoperative outcomes (*Table 4*). Mean(s.d.) maximum inspiratory muscle strength increased from 76·2(26·4) to 89·0(29·4) cmH_2O ($P < 0·001$) in the intervention group and from 74·0(30·2) to 80·0(30·1) cmH_2O in the control group ($P < 0·001$). Preoperative inspiratory muscle endurance increased from 4 min 14 s to 7 min 17 s in the intervention group ($P < 0·001$) and from 4 min 20 s to 5 min 5 s in the control group ($P = 0·007$). The increases were higher in the intervention group than in the control group ($P < 0·050$) (*Table S1*, supporting information). The mean(s.d.) training load increased from 42(18) cmH_2O at the start of the intervention period to 53(21) cmH_2O at the end ($P < 0·001$). The mean(s.d.) training load over the whole training period was 51(20) cmH_2O, power was 6·9(4·5) W, inhaled volume 2·3(1·0) litres and training index 75(27) per cent. There were no significant differences between groups in lung function parameters (*Table S1*, supporting information). For both groups, the median time between surgery and first time out of bed was 1 (range 0–62) day. Quality of life, fatigue and physical activity level measures 4 weeks after surgery showed no significant differences between the IMT and control groups (*Table S2*, supporting information).

According to the ITT analysis, there was a median of 27 (range 8–97) days between the baseline measurement and surgery. Participants in the intervention group trained

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for a median of 21 (0–74) days and 35 (0–130) sessions. Of the 120 patients allocated to the intervention group, 95 (79·2 per cent) trained for the prescribed 2 weeks or longer (range between centres 57–100 per cent), 65 (54·2 per cent) followed at least 80 per cent of the planned training sessions (range between centres 40–83 per cent), and 1591 (39·6 per cent) of the total of 4014 sessions were trained at the prescribed intensity with a rate of perceived exertion of 7 or more (range between centres 5–79 per cent) (*Table S3*, supporting information).

Post hoc analyses

There were no significant differences in the rate of pneumonia between IMT and control arms for the following subgroups: patients who had minimally invasive or open surgery, patients aged 70 years or more, patients with chronic obstructive pulmonary disease, those with an ASA fitness grade of 3 or above, and patients with baseline maximum inspiratory muscle strength of 70 cmH_2O or below.

A subgroup analysis of training progression (*Table S4*, supporting information) showed that the preoperative increase in maximum inspiratory muscle strength was not associated with the rate of pneumonia.

Discussion

This study shows that a home-based high-intensity IMT programme resulted in increased inspiratory muscle strength and endurance capacity. However, this did not lead to a reduction in the rate of postoperative pneumonia in patients following oesophagectomy for cancer. The effect of preoperative IMT on inspiratory muscle function parameters is comparable with the results reported in other preoperative IMT studies (*Table S5*, supporting information)[11,16,17,44–48]. In contrast to the present study, one other well powered RCT[11] investigating preoperative IMT reported a 50 per cent reduction in the postoperative rate of pneumonia. However, this was a single-centre trial investigating a supervised IMT programme in patients undergoing cardiac surgery[11].

The objective of the PREPARE trial was to investigate the effectiveness of an IMT intervention in the context of daily care practice. A multicentre design with a pragmatic approach was chosen; thus usual care was not standardized and possible heterogeneity between centres was accepted. The homogeneity of study procedures was optimized by providing all centres with the same documentation, equipment, education and guidance, and by stratifying per centre. Although single-centre research has better homogeneity regarding usual care, multicentre studies provide better reflection of real life, thereby increasing the external validity of the study.

The choice was made for a mainly unsupervised training programme as weekly home visits by a physiotherapist are difficult to achieve[11,18]. Although adherence to the prescribed number of training sessions was fairly good (67·5 per cent according to the ITT analysis), the number of patients training at the prescribed intensity was low (28·3 per cent according to the ITT analysis) and only 39·6 per cent of all training sessions were performed at the prescribed intensity. Nevertheless, the increase of inspiratory muscle function was comparable to that found in other studies[11,16,46,47], and thus differences in the amount of supervision do not fully explain the failure to improve postoperative outcomes.

Oesophagectomy is a major operation involving a 4–8-h anaesthesia and mechanical ventilation time. As a consequence, up to 75 per cent of patients develop postoperative complications[7]. It was hypothesized that IMT would decrease the rate of pneumonia by preventing the imbalance of ventilatory demand and capacity as a result of improved preoperative capacity[9]. Considering the high impact of surgery itself and the associated complications, it could be argued that a relatively small intervention such as IMT is insufficient to have an impact on the postoperative course in this patient group. Furthermore, research[49] has shown that dissection of the pulmonary branches of the vagal nerve during oesophagectomy might be a relevant contributor to the development of postoperative pneumonia.

Most patients scheduled for oesophagectomy were eligible for the PREPARE trial, irrespective of their preoperative respiratory status and physical condition. It is known that a diminished preoperative health status is in general associated with worse postoperative outcomes[50–52]. However, it was considered that including only frail patients would not be valid given the high overall complication rates. The fact that recent research[53] has shown that preoperative status does not appear to be related to postoperative outcomes after oesophagectomy supports this decision and questions whether the rationale for aiming prehabilitation programmes only at frail patients is applicable to oesophagectomy.

The rate of pneumonia in the PREPARE trial was on the high side (37·3 per cent) compared with rates reported from other studies (range 2–39 per cent)[7]. Pneumonia is defined differently in different studies, and the majority of definitions include isolation of a pathogen from a sputum culture[7]. The rate of pneumonia in the present study, defined according to the revised Uniform Pneumonia

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Score[34], corresponds well with the number of times that antibiotics were prescribed to treat pneumonia, suggesting that this scoring system identifies the indication for treatment of pneumonia adequately. Furthermore, the internal and external validity of this scoring system has found to be excellent[34], making it an interesting tool for use in scientific trials.

Given the findings of the present study, standard prescription of IMT before oesophagectomy is not advisable, and IMT programmes aiming to reach high training intensities should probably include supervised elements. Future prehabilitation research may need to focus on the optimal mix of supervised and unsupervised sessions in combination with the best possible balance between feasibility and the received training stimulus. Improved reporting of details on training adherence and compliance in trial reports is important to increase knowledge of responders and non-responders and to create more insight in the successful and unsuccessful elements of training interventions.

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