Physical functioning in surgical patients with esophageal cancer:

from risk stratification to targeted physiotherapy

Maarten A. van Egmond

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Thesis University of Amsterdam, the Netherlands

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PHYSICAL FUNCTIONING IN SURGICAL PATIENTS WITH ESOPHAGEAL CANCER:

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‘No amount of observations of white swans
can allow the inference that all swans are white,
but the observation of a single black swan
is sufficient to refute that conclusion.’

David Hume

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General introduction

GENERAL INTRODUCTION

Major thoracic and abdominal surgery is associated with a high risk of postoperative complications and a delayed functional recovery.[1-3] Physiotherapists play an important role in improving the patients' physical functioning before and immediately after surgery to enhance postoperative recovery.[3,4] In recent years, there has been increasing evidence that preoperative physical functioning is associated with postoperative outcomes. Research has illustrated that improving preoperative muscle strength and cardiorespiratory fitness leads to a shorter length of stay in patients treated with oncological abdominal surgery, less postoperative pulmonary complications in patients treated with coronary artery bypass graft surgery and increased postoperative cardiorespiratory fitness levels in patients treated with oncological pulmonary surgery.[3,5,6]

As a result, preoperative physiotherapeutic interventions are most commonly performed in different surgical populations to improve preoperative physical functioning, also known as prehabilitation*,* in order to reduce the risk of poor postoperative outcomes.[2,4]

The effectiveness of postoperative physiotherapy has also been well documented in several populations. It has been shown that high-intensity training for patients after lung cancer surgery, leads to improved muscle strength, physical fitness and quality of life.[7] Moreover, it has been reported that early mobilization after thoracic surgery leads to a reduced length of hospital stay and improved physical functioning.[8]

The effects of surgery on physical functioning

Thoracic and abdominal surgery is a major stress factor that negatively affects physical functioning.[2,9,10] The surgically induced catabolic stress response increases metabolic rate to recover homeostasis.[11] This response to surgical stress is initially beneficial and the majority of patients return to their preoperative levels of physical functioning after surgery.[11]

However, in patients with a poor preoperative physical functioning and low physiological reserve, the surgically induced stress response could potentially lead to severe muscle wasting, reduced cardiopulmonary function and increased risk of postoperative complications as a result of metabolic and catabolic processes, leading towards prolonged hospitalization and delayed functional recovery (Figure 1).[2,11]

Despite the developments in surgery and surgical management to reduce these negative effects of surgical stress and the risk of postoperative complications, the incidence of postoperative complications and poor postoperative recovery following major abdominal and thoracic surgery remains high.[4] Besides surgery-related complications, pulmonary and cardiac complications contribute highly to postoperative morbidity and mortality varying from 10 to 40%.[3,10,13] This is not different for patients with esophageal cancer undergoing surgery.

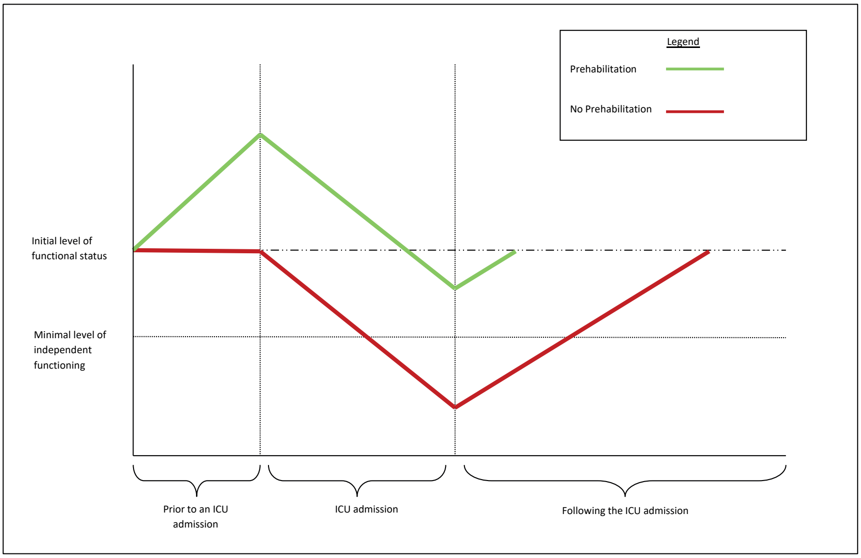

Figure 1. The theoretical model according to Topp et al.[12] on the effects of preoperative physical functioning on postoperative functional recovery

Esophageal cancer

Esophageal cancer is an aggressive malignant disease with an overall estimated 5-years survival of 15 to 20%.[14,15] The incidence of esophageal cancer in The Netherlands has increased from 813 patients per year in 1990 to 2536 patients per year in 2019.[16,17]

For approximately 50% of these patients, surgical resection of the esophagus (esophagectomy) with gastric tube reconstruction and radical lymphadenectomy is the primary curative therapy (Figure 2).[18] Esophagectomy is associated with a high risk of postoperative complications varying from 25 to 60%.[14,15,19,20] Most commonly reported complications are pneumonia, esophago-enteric leak from anastomosis, staple line or localized conduit necrosis and atrial dysrhythmia.[21]

Neoadjuvant chemoradiotherapy usually precedes esophagectomy and leads to better long-term survival than surgery alone.[18] Although loss of body weight and muscle mass could already be present at diagnosis, it is known that neoadjuvant chemoradiotherapy may lead to a significant decrease in lean body mass and fat mass and is a potential risk factor for sarcopenia.[4,23] According to Cruz-Jentoft et al.[24] sarcopenia is defined as '*a progressive and generalized skeletal muscle* *disorder that potentially leads to adverse outcomes including falls, fractures, physical disability and mortality*'. The prevalence of sarcopenia in patients with esophageal cancer awaiting neoadjuvant chemoradiation is 47 to 57% and may increase to 79% after neoadjuvant chemoradiation.[23,25] In disease-free patients, sarcopenia even continues to increase until 1 year postoperatively.[26]

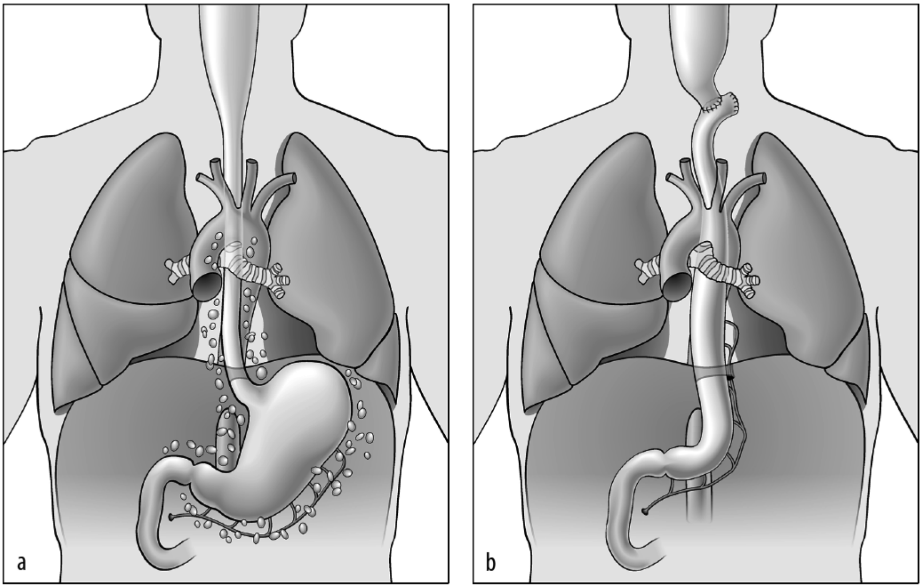

Figure 2. Schematic outline of the preoperative (a) and postoperative (b) situation
A gastric tube has replaced the esophagus and lymph nodes have been removed.[22]
Reproduced with permission from Nederlands Tijdschrift voor Geneeskunde.

Sarcopenia is considered to be an independent predictor of postoperative pulmonary complications, and poor recovery in patients with esophageal cancer and can be influenced by physiotherapy.[27,28]

In addition to sarcopenia, impairments in preoperative physical functioning further contribute to a higher risk of developing postoperative complications and a delayed postoperative recovery in patients treated with esophagectomy.[10]

Physical functioning

Physical functioning is part of the multi-dimensional concept of functional status, defined as '*a patient-oriented health outcome that contains aspects of individual daily functioning, including physical-, psychological-, and social factors*' and is a firm predictor of postoperative complications and postoperative recovery.[29]

Functional status contains aspects of different domains of the International Classification of Functioning, disability and health (ICF).[30] The World Health Organization's ICF-framework objectively explicates functional status and is considered as a standard for describing a patient's level of functioning in daily life. Instead of focusing on mortality and disease, the ICF rather focuses on health and functioning of an individual with a certain health condition in its context.[30]

The ICF describes different domains to illustrate the impact of a patient's health condition on daily life, where body functions, activities and participation refer to functioning and where impairments, limitations and restrictions refer to disability. Furthermore, personal- and environmental factors are described that interact within these domains (Figure 3).[29]

Moreover, health-related quality of life (HRQL) may be affected by cancer treatment.[31] Research has shown that pre-and postoperative physical functioning subscales of HRQL were independent predictors of survival in patients with esophageal cancer.[32] HRQL is not a domain of the ICF, but it also needs to be taken into account to understand a patient's subjective perception of physical functioning and health.[31]

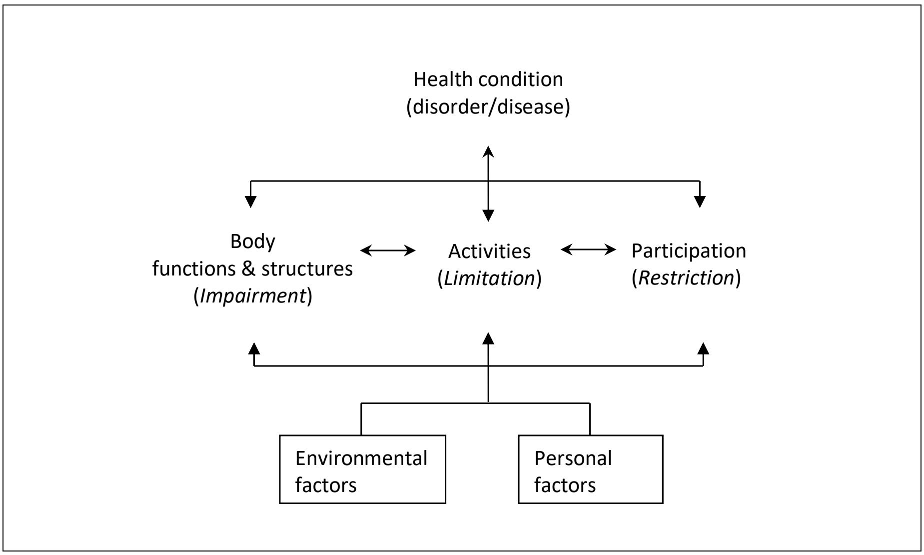

Figure 3. International Classification of Functioning, disability and health (ICF)[29]

Where the evidence for the effectiveness of physical exercise training on postoperative recovery in general is substantial, there is little evidence regarding the effectiveness of physiotherapy in patients diagnosed with esophageal cancer with an indication for surgery.[2,3]

Pre- and postoperative physiotherapy

Pre- and postoperative physiotherapy are key elements of enhanced recovery after surgery (ERAS) pathways that show to be effective in reducing length of hospital stay and complication rates.[33] The main objectives of ERAS pathways for physiotherapists are to optimize preoperative physical functioning, reduce the consequences of surgical stress and postoperative complications and to increase speed of recovery, also after discharge from the hospital. Research has shown that improvement of preoperative muscle strength, respiratory muscle strength, exercise capacity, physical activities and HRQL are all associated with a reduction of postoperative complications and an increased postoperative recovery in major thoracic and abdominal surgery.[3,13,34-36]

However, not every surgical patient will have the same risks of postoperative complications or poor postoperative recovery and therefore preoperative preventive physiotherapy might not be required for everyone, eventually leading towards tailored care.

Postoperative physiotherapy with telerehabilitation

It is known that patients suffering from postoperative complications after esophagectomy may be confronted with fatigue, decreased exercise capacity and impaired walking capacity that could take up to a year.[37,38] Therefore, physiotherapists might play an important role in improving a patient's postoperative physical functioning as well.[2]

Patients with postoperative complications are usually referred to outpatient physiotherapy in a primary care setting to further improve their physical functioning. However, these patients often deal with a temporary loss of mobility that makes it challenging or even impossible to visit a physiotherapist.[39] Moreover, these physiotherapists may be confronted with a lack of knowledge to treat patients after highly complex surgery.[40]

Therefore, these patients could benefit from a relief in burden of care and increased efficiency, by providing them with physiotherapy via telerehabilitation in their home situation instead of conventional 'face-to-face' rehabilitation.

Recent evidence has shown that eHealth applications such as telerehabilitation lead to increased patient satisfaction in different patient populations where clinical effects remain 3 to 6 months after the intervention.[41,42] However, it is not known to what extent physiotherapy with telerehabilitation may be beneficial for patients with esophageal cancer in the postoperative period.

Aims and outline of the thesis

The general aim of this thesis is to evaluate the pre- and postoperative course of physical functioning in patients with esophageal cancer undergoing elective surgery. This knowledge contributes to identifying patients at an increased risk for a delayed postoperative recovery and to develop a tailored pre- and/ or postoperative physiotherapeutic intervention. This intervention could then be offered in the patient's own environment with telerehabilitation under supervision of an experienced physiotherapist.

Chapter 2 describes the association of preoperative physical functioning and postoperative complications in patients with esophageal cancer undergoing elective surgery. Preoperative functional status is a risk factor for developing postoperative complications in major abdominal and thoracic surgery, but this has hardly been evaluated in patients with esophageal cancer undergoing esophagectomy.

Chapter 3 outlines the pre-and postoperative course of physical functioning in patients with esophageal cancer who underwent surgery and describes the course of functional status in patients with and without postoperative complications.

Chapter 4 describes the relation between preoperative muscle mass and handgrip strength, respiratory muscle strength and functional lower extremity strength in patients with esophageal cancer awaiting surgery, prior to neoadjuvant chemoradiation. If an association between muscle mass and muscle strength is found, physiotherapists might be able to measure functional muscle strength as an early predictor for the consequences for functional performance due to decreased muscle mass and eventually sarcopenia.

Chapter 5 contains a systematic review and meta-analysis of randomized controlled trials, controlled clinical trials, quasi-randomized and quasi-experimental designs with comparative controls evaluating the effects of telerehabilitation on postoperative outcomes and quality of life in surgical patients. We also determined if telerehabilitation increased patient satisfaction.

Chapter 6 describes the feasibility and preliminary effectiveness of a 12-week postoperative physiotherapy intervention with telerehabilitation for patients with esophageal cancer treated with esophagectomy and suffering from postoperative complications.

Chapter 7 describes the main findings, strengths and limitations, clinical relevance and recommendations for future research. A summary in English and Dutch will finally conclude the thesis.

1

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Chapter 2

Preoperative functional status is not associated with postoperative surgical complications in low risk patients undergoing esophagectomy

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Diseases of the Esophagus. 2017 Jan 1;30(1):1-7

ABSTRACT

Background: Preoperative functional status is a risk factor for developing postoperative complications (POC) in major abdominal and thoracic surgery, but this has hardly been evaluated in patients with esophageal cancer undergoing esophagectomy. The aim of this prospective cohort study was to determine if preoperative functional status in patients with esophageal cancer is associated with POC.

Methods: From March 2012 to October 2014 patients with esophageal cancer scheduled for esophagectomy at the outpatient clinic of a large tertiary referral center were eligible for the study. We measured inspiratory muscle strength, handgrip strength, physical activities and health-related quality of life as indicators of functional status one day before surgery. POC were scored according to the Clavien-Dindo classification. We used univariate and multivariate backward regression analysis to determine the association between functional status and POC.

Results: We included 94 patients in the study and esophagectomy was performed in 90 patients from which 55 developed POC (61.1%). After multivariate analysis, none of the indicators of preoperative functional status were independently associated with POC [inspiratory muscle strength (OR 1.00; $P = .779$), handgrip strength (OR 0.99; $P = .250$), physical activities (OR 1.00; $P = .174$) and health-related quality of life (OR 1.02; $P = .222$)].

Conclusion: We concluded that preoperative functional status in our study cohort is not associated with POC after esophagectomy.

INTRODUCTION

Esophagectomy, the primary curative treatment for patients with esophageal cancer, is associated with a 60% risk of postoperative complications (POC).[1-3] POC contribute highly to postoperative morbidity and may lead to an increased length of hospital stay, delayed postoperative functional recovery, a reduced quality of life and cost ineffectiveness.[2,4,5]

In major thoracic and abdominal surgery, preoperative functional status has been shown to be a risk factor for POC and subsequently a delayed postoperative functional recovery.[6] Functional status is a multi-dimensional concept defined as *'a patient-oriented health outcome that contains aspects of individual daily functioning including physical, psychological and social factors'*.[7,8] It is essential in achieving and maintaining functional independence, a common prerequisite for hospital discharge and independent functioning and autonomy of an individual in society.[9] Physiotherapeutic treatment, aimed at improvement of preoperative functional status, enables the human body to better withstand external stressors like surgery.[4,9] Several studies reported that an increase of inspiratory muscle strength (IMS) and handgrip strength (HGS), as physical indicators of functional status, reduce POC in major thoracic and abdominal surgery.[10,11] Other indicators of functional status, physical activities (PA) and health-related quality of life (HRQL), are both firm predictors of postoperative outcome and seem to be associated with postoperative morbidity, mortality and length of hospital stay.[12-14]

It is generally known that preoperative improvement of functional status enables the human body to better withstand external stressors like surgery.[4,9] This is called prehabilitation and may lead to a faster postoperative recovery.[9] Although preoperative functional status is associated with a reduction of POC after major abdominal and thoracic surgery, this has hardly been evaluated in patients with esophageal cancer awaiting esophagectomy.[1,5,10,15] To determine whether these patients are at risk for developing POC and poor postoperative functional outcome, preoperative levels of functional status should be carefully evaluated.[6]

If preoperative functional status of patients with esophageal cancer could predict POC, it would enable physiotherapists to identify patients that could benefit from tailored physiotherapeutic treatment to improve preoperative functional status and consequently decrease the risk of POC. Therefore, a valid prediction model is needed.

In this prospective cohort study, we determined associations between IMS, HGS, PA and HRQL as indicators of functional status with POC in patients with esophageal cancer undergoing esophagectomy.

METHODS

Study design and participants

We prospectively recorded data from patients with esophageal cancer scheduled for esophagectomy at the Gastro Intestinal Oncologic Center Amsterdam (GIOCA) of the Academic Medical Center (AMC) in Amsterdam, the Netherlands between March 2012 and October 2014. These patients agreed to be assessed on functional status one day before surgery. For safety reasons, we decided not to assess patients on functional status in case of severe cognitive, functional or nutritional impairments. The Medical Ethics Committee of the Academic Medical Center Amsterdam waived the need for informed consent, because the measurements in this study were performed as part of standard physiotherapeutic care according to and in line with 'Good Clinical Practice'.

Surgical procedures

All patients received chemoradiation therapy before surgery. Open or minimally invasive transthoracic esophagectomy was done in case of a distal esophageal tumor or if signs were present of mediastinal lymph node involvement on the preoperative diagnostic work up. Open transthoracic esophagectomy involved a right posterolateral thoracotomy in the lateral decubitus position with double tracheal intubation and lung block, midline laparotomy, and cervical incision. Minimally invasive transthoracic esophagectomy consisted of a right thoracoscopy in the prone position with single-lumen tracheal intubation, upper abdominal laparoscopy, and cervical incision. After surgery, all patients were admitted to the intensive care unit to be stabilized and detubated.[16]

In frail patients and patients with genuine gastroesophageal (GE) junction tumors without mediastinal lymph node involvement, a transhiatal resection was performed.

Measurements

We prospectively recorded presurgical patient characteristics and the presence of conventional risk factors: gender, American Society of Anesthesiologists (ASA)-physical status score, age, body mass index (BMI), history of smoking, the presence of diabetes, cardiovascular- and pulmonary diseases, pulmonary function and surgical procedure. We described indicators of functional status according to the domains of the International Classification of Functioning, disability and health (ICF).[17] The ICF framework classifies health and health-related components expressed in body functions and structures, activities and participation, as well as personal- and environmental factors. The ICF provides a structure to present this information in a meaningful, interrelated and accessible way and guides effective decision-making within the rehabilitation process.[18] The choice of measurement instruments was based on both psychometric properties and feasibility in clinical practice.

ICF: Body functions

We measured IMS with a micro-medical spirometer (Micro-RPM, Micro Medical Ltd., Rochester, England), which measures maximal inspiratory pressure (MIP) as indicator of IMS and has been shown valid and reliable in surgical populations.[2,15] We calculated the percentage IMS of predicted by using normative values for Caucasian adults, predicted by a regression equation based on age and height.[19]

We used the Jamar® grip strength dynamometer (Lafayette Instrument Company, Lafayette, USA) to measure HGS. This dynamometer is a reliable instrument to predict the total skeletal muscle strength.[15,20-22] We calculated the percentage HGS by using normative values for adults.[23]

ICF: Activities and participation

We measured daily activities with the Longitudinal Ageing Study Amsterdam (LASA) Physical Activity Questionnaire (LAPAQ), in which patients reported their activities of the past 14 days. The LAPAQ is a face-to-face questionnaire that is highly correlated with both the 7-day diary (r = 0.68, P < .001) and moderately to the pedometer (r = 0.56, P < .001), whereas the repeatability is reported as reasonably good (weighted Kappa: 0.65 to 0.75). The LAPAQ appears to be valid and reliable in measuring activities in older people.[15,24]

In addition, patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, (EORTC QLQ-C30), version 3.0 to indicate HRQL. This is a nine multi-item scale including five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, nausea and vomiting); and a global health and quality-of-life scale. Scores range from 0 to 100 with high scores indicating a better HRQL. It is a reliable and valid measurement of the quality of life of patients with cancer in multicultural clinical research settings.[25]

To guarantee optimal inter-rater reliability, we described standardized operating procedures of all measurements. Experienced physiotherapists with extensive clinical expertise executed the standardized measurement protocol and all received an in-depth training of the study protocol, the standardized measures as well as data registration according to 'Good Clinical Practice'.

Outcome measurement

The presence of POC was the outcome measurement of interest. All complications and adverse events within 30 days of surgery or during the in-hospital stay after surgery have been included, as proposed by the Esophagectomy Complications Consensus Group (ECCG).[26] We classified the severity of POC according to the widely used Clavien-Dindo classification of surgical complications. This 5-scale classification reports surgical complications based on the type of therapy required to treat this complication and is an objective, valid, reliable and reproducible classification system.[27,28] We defined POC according to the basic complications list of ECCG, to allow for future comparisons of different surgical approaches and other interventions for esophageal cancer.[26] This complications list distinguishes pulmonary, cardiac, gastrointestinal, urologic, thromboembolic, neurologic/ psychiatric, infection, wound/ diaphragm and other complications.

Statistical analysis

We summarized patient characteristics with descriptive statistics and expressed discrete variables as counts with percentages. Continuous variables were described as mean and standard deviation and in case of a skewed distribution as median (P50) and interquartile range (P25 to P75). We used univariate logistic regression analysis to assess the association of both conventional risk factors and indicators of functional status with POC. Given the small dataset and to avoid missing true predictors, conventional risk factors and indicators of functional status were entered in a multivariate regression model if P-value ≤ .200. We compared the group of patients suffering from POC with the group of patients without POC on aspects of preoperative functional status by using the independent sample T-test or Mann Whitney U-test.

We used backward elimination to create a final multivariate model containing variables with a P-value ≤ .050.

RESULTS

We analyzed data from 94 patients between March 2012 and October 2014 with an indication for esophagectomy. We measured functional status of 92 patients one day before surgery. We missed 2 patients for measurements on preoperative functional status. None of the patients showed severe cognitive, functional or nutritional impairments. During the surgical procedure, resection of the esophagus was not possible in 4 patients and they were subsequently left out in the final analysis. Table 1 presents patient- and surgical characteristics of 94 patients. Mean age (SD) was 63.8 years (9.4) and 74 patients were male.

Pulmonary function was better than predicted (100%) with a forced vital capacity (FVC) of (mean percentage, [SD]) 113.1 [16.0], forced expiratory volume in 1 second (FEV1) of 106.6 [17.5] and inspiratory vital capacity (IVC) of 109.7 [15.3] respectively. The measurements presented in Table 2 show that both IMS and HGS were higher than predicted. HRQL (mean percentage, [SD]) was 83.3 [16.7] on a scale from 0 to 100 with higher scores indicating a better HRQL.

All patients underwent surgery, where 77 patients were operated via a minimally invasive approach (Table 1). Figure 1 shows that 55 patients developed a POC (61.1%). Twenty-six patients suffered from a grade 3a complication or worse according to the Clavien-Dindo Classification for surgical complications and 4 died shortly after surgery. Twenty-eight out of 55 patients with POC developed more than one complication. Table 3 presents the characteristics of POC and it illustrates 19.1% pulmonary complications, 17.0 % cardiac complications and 32.2% gastrointestinal complications.

Univariate analysis of both conventional factors and indicators of functional status revealed that ASA-classification II versus I (OR 0.43, 95% CI 0.14 to 1.29; P = .132), smoking (OR 2.88, 95% CI 0.94 to 8.79; P = .064) and physical activities (OR 1.00, 95 % CI 1.00 to 1.01; P = .162) were significant predictors for POC with a P-value ≤ .200 (Table 4). However, after backward elimination none of them remained significant. We compared the group of patients suffering from POC with the group of patients without POC on aspects of preoperative functional status and found no significant difference (P ≤ .050) between these groups on all aspects of preoperative functional status. The OR of POC in the group with open surgery versus minimally invasive surgery was 0.69 (95% CI 0.21 to 2.24; P = 0.533).

Table 1. Patients and surgical characteristics (94 patients)

	No. of patients*
Gender (male)	74 (78.7)
ASA-classification	
I	19 (20.2)
II	58 (61.7)
III	17 (18.1)
Age at surgery (years), mean (SD)	63.8 (9.4)
60-69 years	35 (37.2)
70-79 years	30 (31.9)
>80 years	1 (1.1)
BMI, mean (SD)	26.5 (3.9)
< 19	1 (1.1)
19-25	29 (30.9)
25.1-30	44 (46.8)
> 30.1	15 (16.0)
Comorbidities	
Cardiovascular	24 (25.5)
COPD	9 (9.6)
DM II	8 (8.5)
Cigarette smoking (yes)	19 (20.2)
Pulmonary function (percentage of predicted), mean (SD)	
FVC	113.1 (16.0)
FEV_1	106.6 (17.5)
IVC	109.7 (15.3)
Chemoradiation	94 (100)
Surgical procedure	
Transhiatal open	3 (3.2)
Transhiatal scopic	11 (11.7)
Transthoracal open	10 (10.6)
Transthoracal scopic	66 (70.2)

* With percentages in parentheses unless indicated otherwise. ASA, American Society of Anesthesiologists; I: healthy person, II: mild systemic disease, III: severe systemic disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; DM II, diabetes mellitus type 2; FVC, functional vital capacity; FEV_1, forced expiratory volume in the first second of expiration; IVC, inspiratory vital capacity.

Table 2. Measurements of preoperative functional status (92 patients)

Indicator of functional status	
MIP (cm H_2O), mean (SD)	92.2 (30.5)
percentage of predicted, mean (SD)	121.5 (40.2)
HGS (kilograms), median (IQR)	42.5 (15.0)
percentage of predicted, mean (SD)	114.0 (20.8)
Physical activities (kcal/day), median (IQR)	855.7 (707.5)
HRQL, median(IQR)	83.3 (16.7)

MIP, maximal inspiratory pressure; HGS, handgrip strength; HRQL, health-related quality of life, where scores range from 0 to 100 with higher scores indicating a better HRQL.

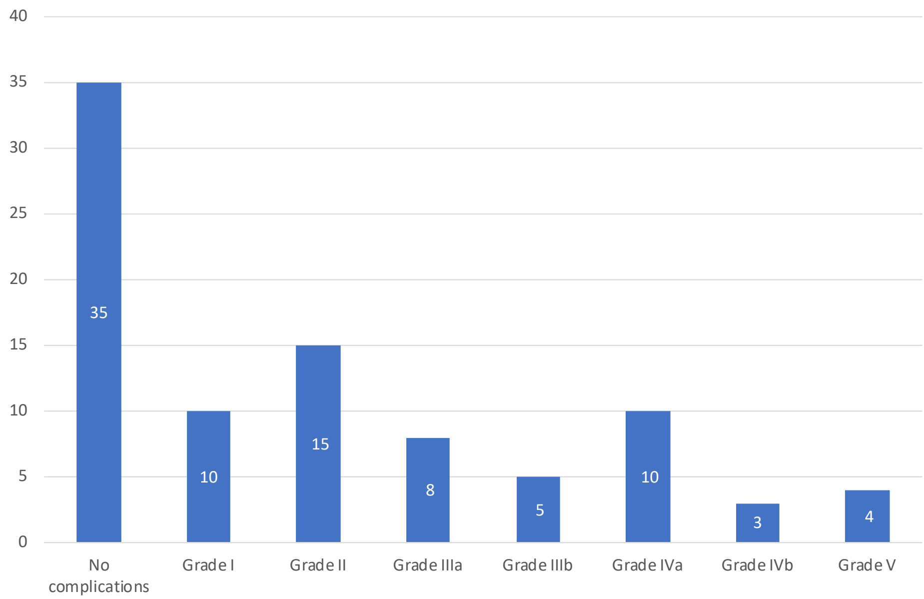

Figure 1. Frequency of postoperative complications according to the Clavien-Dindo classification (90 patients)

Grade I: Any deviation from the normal postoperative course without pharmacologic treatment or surgical, endoscopic, and radiological interventions; Grade II: Requiring pharmacologic treatment with drugs other than ones allowed for grade I complications; Grade III: Requiring surgical, endoscopic, or radiologic intervention not under general anesthesia (IIIa), under general anesthesia (IIIb); Grade IV: Life-threatening complications requiring IC/ ICU management, single-organ dysfunction (including dialysis) (IVa), multiorgan dysfunction (IVb); Grade V: Death of a patient.

Table 3. Postoperative complications and hospitalization (90 patients)

	No. of events*
Postoperative complications	
Pulmonary	18 (19.1)
Cardiac	16 (17.0)
Gastrointestinal	29 (32.2)
Urologic	2 (2.2)
Thromboembolic	3 (3.3)
Neurologic/ psychiatric	10 (11.1)
Infection	10 (11.1)
Wound/ diaphragm	0 (0.0)
Other	23 (25.6)
Hospitalization	
ICU stay (days), median (IQR)	1 (2)
Readmission < 30 days	9 (9.6)
In-hospital mortality	4 (4.3)

* With percentages in parentheses unless indicated otherwise. ICU, intensive care unit.

Table 4. Univariate and multivariate stepwise backward logistic regression analysis for associations of conventional risk factors and indicators of preoperative functional status with POC

	Univariate analysis		Multivariate analysis	
	Odds Ratio	*P*-value †	Odds Ratio	*P*-value
Conventional risk factors				
Gender	0.57 (0.20 1.59)	.280		
ASA-classification				
II vs. I	0.43 (0.14, 1.29)	.132	0.49 (0.16, 1.56)	.226
III vs. I	0.66 (0.17, 2.59)	.550		
Age	1.02 (0.97, 1.06)	.507		
BMI	0.95 (0.85, 1.05)	.318		
DM II	1.45 (0.33, 6.45)	.626		
Cardiovascular disease	0.80 (0.31, 2.01)	.628		
COPD	1.78 (0.42, 7.58)	.437		
Smoking	2.88 (0.94, 8.79)	.064	3.11 (0.91, 10.65)	.071
Pulmonary function (percentage of predicted)				
FVC	1.00 (0.98, 1.03)	.886		
FEV_1	0.99 (0.97, 1.02)	.620		
IVC	1.00 (0.97, 1.02)	.712		
Type of surgery				
Transthoracal open *versus* transhiatal open	5.33 (0.34, 82,83)	.232		
Transhiatal scopic *versus* transhiatal open	1.33 (0.09, 20.11)	.835		
Transthoracal scopic *versus* transhiatal open	2.71 (0.23, 31.44)	.424		
Indicators of functional status				
MIP (% pred)	1.00 (0.99, 1.01)	.779		
HGS dom (% pred)	0.99 (0.97, 1.01)	.250		
Physical activities (kcal/day)	1.00 (1.00, 1.01)	.162	1.00 (1.00, 1.01)	.174
HRQL	1.02 (0.99, 1.05)	.222		

Values in parentheses are 95% confidence intervals. ASA, American Society of Anesthesiologists; BMI, body mass index; DM II, diabetes mellitus type 2; FVC, functional vital capacity; FEV1, forced expiratory volume in the first second of expiration; IVC, inspiratory vital capacity; MIP, maximal inspiratory pressure; HGS, handgrip strength; HRQL, health-related quality of life; †All variables with a *P*-value < .200 in univariate analysis were entered in a multivariate model.

DISCUSSION

The results of our study suggest that that IMS, HGS, PA and HRQL as part of functional status are not associated with POC in our cohort of patients with esophageal cancer undergoing esophagectomy. Although 55 out of 90 patients developed POC, there was no association found with preoperative functional status.

Our findings seem to be contrary to findings related to other thoracic and abdominal surgical populations. Hulzebos et al.[10] demonstrated that higher IMS decreased the incidence of postoperative pulmonary complications in the high-risk category of coronary artery bypass graft (CABG) patients. Also, Dronkers et al.[15] indicated physical activity as a preoperative predictor of postoperative outcome in patients scheduled for major abdominal surgery.

There might be three reasons why preoperative functional status in our study cohort was not found to be associated with POC.

First, gastrointestinal complications represented 32.2% of POC in our study cohort. We suggest that these types of complications are due to surgical procedures and are not related to preoperative functional status.

Second, the incidence of postoperative pulmonary complications in our study cohort was relatively low compared to other types of complications (Table 3). Decreased pulmonary function and IMS are known to be risk factors for postoperative pulmonary complications.[2] This was illustrated in a study of Feeney et al.[2] where preoperative pulmonary function of patients with an esophagectomy was lower than predicted (FVC: 90.3%, FEV1: 89.7% respectively). However, our study clearly revealed that pulmonary function was higher than predicted: FVC 114.8%, FEV1 109.2%, IVC 111.0% respectively. Moreover, our study showed higher preoperative IMS than their predicted normative values as well. Pulmonary function and functional status are highly interrelated and, therefore, it could be suggested that preoperative functional status in our study cohort was much better compared to other surgical populations and, therefore, led to less postoperative pulmonary complications.[9] It should also be taken into account that patients with a chronic cardio-pulmonary disease tend to be longer inactive preoperatively, subsequently leading to decreased pulmonary function, and functional status compared to our study cohort, where the disease is relatively recently diagnosed and treated by surgery.

Third, the type of surgery might also have affected the incidence of postoperative pulmonary complications (Table 1). A majority (77 patients) underwent minimally invasive surgery. This may have led to a lower incidence of postoperative pulmonary complications.[29] However, in our study cohort there was no significant difference in the occurrence of complications between open and minimally invasive surgery.

This study has some intrinsic limitations.
First, we have only analyzed patients who agreed to have functional status measured and patients who were indicated for surgery only if both their preoperative pulmonary function and general condition was good enough to allow surgery. The selection of relatively healthy patients for surgery, who subsequently had on average a high preoperative functional status, could have resulted in lower discriminative power between functional status and the incidence of POC.

Second, a majority of the patients suffered from gastrointestinal complications (32.2 %), which is unlikely to be related to preoperative functional status, where only 18 out of 90 patients suffered from a postoperative pulmonary complication. It could be assumed that the high rate of gastrointestinal complications confounded the overall study conclusion. The sample size within the subgroup of postoperative pulmonary complications was too low to perform a stratified analysis to the association between preoperative functional status and postoperative pulmonary complications without a subsequent risk of a Type 2 error.

Third, functional status contains more aspects than we investigated, but we only chose these indicators with good clinical applicability, that have been shown to have an association with POC in other surgical populations. Although aerobic capacity is a risk factor for postoperative outcome, we decided not to include this variable in our study due to the lack of consistency in measuring it.[4]

The reason to use a questionnaire to measure PA instead of a more objective measurement tool like an activity monitor was done by means of feasibility. Several questionnaires have been validated to assess PA in older adults, but all showed limitations on psychometric properties and content.[30]

First, the LAPAQ is interviewer-administered, which requires training for its application in practice. We solved this by providing in depth training to assessors.

Second, in previous research the LAPAQ was compared with a diary and pedometer, which were used as validation instruments. Neither the diary nor the pedometer was able to accurately measure PA or validate the findings of the LAPAQ. This problem however, also holds true for other questionnaires. Nevertheless, the LAPAQ appears to be a promising tool for measuring PA in patients with major abdominal surgery.[12]

Moreover, Siebeling et al.[30] revealed in their study that LAPAQ underestimates PA. If this finding would be transferred to our population, we could conclude that the reported PA are lower than real, which supports the relatively good functional status of our investigated cohort.

From our study, we conclude that despite the high rate of POC, preoperative functional status in our cohort of patients with an esophagectomy probably does not predict POC, irrespective of the surgical procedure. Therefore, preoperative functional status should not always be considered as a risk factor for postoperative complications in high-risk surgical populations per se, but depends on patient- and surgery specific characteristics (i.e. the initial levels of preoperative functional status, the presence of comorbidities, type of surgery and the nature of POC as well).

On average, our study cohort scored high on aspects of preoperative functional status, despite the fact that such patients are considered to have a high-risk for developing postoperative complications and a delayed functional recovery. This has also recently been illustrated by a study of Dettling et al.[31] where preoperative training of inspiratory muscles in a comparable esophageal cancer population did not lead to an expected postoperative reduction of POC. The researchers stated that these patients benefited less from inspiratory muscle training than other surgical populations with decreased pulmonary function.

Therefore, our study shows that a high incidence of POC is not necessarily related to high levels of preoperative functional status and we question whether increasing preoperative functional status in these relatively fit patients would contribute to a reduced chance of poor postoperative functional recovery. This might be different in other esophago-gastric cancer patients and, therefore, our study emphasizes the need to carefully assess preoperative functional status and relate this to patient- and surgery specific characteristics, before indicating a preoperative training program.

We hypothesize that only patients with a low initial preoperative functional status or the presence of comorbidities or other risk factors might benefit from a preoperative training program in order to improve postoperative recovery (Better in- Better out).[32] Additional research to investigate the association in esophagectomy patients with a low preoperative functional status and postoperative pulmonary complications is, therefore, highly recommended.

Despite the fact that our study does not show an association between preoperative functional status and POC, we would recommend comparing the association between preoperative functional status and postoperative functional recovery in esophagectomy patients with and without POC. This might answer the question whether people with a high initial preoperative functional status will recover faster in case they develop a POC.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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Chapter 3

The pre- and postoperative course of functional status in patients undergoing esophageal cancer surgery

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ABSTRACT

Introduction: To optimally target physiotherapy treatment, knowledge of the pre- and postoperative course of functional status in patients undergoing esophagectomy is required. The aim of this prospective longitudinal study was to investigate the course of functional status in patients with esophageal cancer before and after esophagectomy.

Materials and methods: Functional status outcome measures of patients with esophageal cancer who underwent surgery between March 2012 and June 2016 were prospectively measured at 3 months and at 1 day before surgery and at 1 week and at 3 months after surgery. Analysis of repeated measurements with the mixed model approach was used to study changes over time.

Results: Hundred fifty-five patients were measured at 3 months and at 1 day before surgery, of which 109 (70.3%) at 1 week and 60 (38.7%) at 3 months after surgery. Mean (SD) age at surgery was 63.5 years (9.3), and 122 patients (78.7%) were male. The incidence of postoperative complications was 83 (53.5%). Three months postoperatively, functional status measures returned to baseline levels, except from handgrip strength (beta [95% CI] -6.2 [-11.3 to -1.1]; *P* = .02) and fatigue (4.7 [0.7 to 8.7]; *P* = .02). No differences were observed in the course of functional status between patients with and without postoperative complications.

Conclusion: Functional status of patients undergoing esophagectomy returned to baseline values three months after surgery, despite the high incidence of postoperative complications. This requires rethinking the concept of prehabilitation, where clearly not all patients benefit from high functional status to prevent postoperative complications.

INTRODUCTION

The surgical treatment of esophageal cancer after neoadjuvant chemotherapy consists of curative esophagectomy with gastric tube reconstruction and is associated with a high rate of postoperative complications, up to 60%, and an increased length of hospital stay and poor functional outcome.[1-6] In addition to surgery-related complications, pulmonary and cardiac complications contribute highly to postoperative morbidity.[2,4,7]

Impairments in preoperative functional status have been identified as independent risk factors of postoperative complications and delayed postoperative recovery in major abdominal and thoracic surgery.[1,2,5] It is also known that increased preoperative functional status has positive effects on postoperative recovery.[8,9]

Physiotherapists play an important role in optimizing functional status both preceding and following esophagectomy. Traditionally, physiotherapy treatment aims at improving postoperative recovery, but gradually, more emphasis has been placed on preoperative physiotherapeutic interventions to improve physical activity (respiratory and cardiovascular capacity and muscle strength), enabling the human body to better withstand external stressors such as surgery.[7,9,10] This is called prehabilitation, and several studies have demonstrated that it leads to a faster postoperative recovery in cardiothoracic surgical populations.[8,9,11,12]

Physiotherapeutic prehabilitation has been recommended for the preoperative management of patients with esophageal cancer, but evidence of the effectiveness of specific interventions remains unclear.[10] After surgery, functional status decreases significantly in high-risk surgical populations and tends to recover during the postoperative period with postoperative physiotherapy.[8] However, there is a lack of evidence concerning how functional status develops over time in the pre- and postoperative course of patients with esophageal cancer. Moreover, it is currently unclear how changes in functional status relate to postoperative recovery. It could be hypothesized that patients in poor preoperative condition are not able to adequately respond to the negative effects of surgery, resulting in a delayed postoperative recovery and an increase in morbidity and mortality. In addition, patients suffering from postoperative complications will take longer to recover and regain their functional status, especially if their preoperative functional status is low.

Therefore, the main objective of this prospective longitudinal study was to investigate the course of functional status in patients with esophageal cancer before and after esophagectomy. The second objective was to investigate whether the course of functional status was different between patients with and without postoperative complications.

MATERIALS AND METHODS

Participants

From 2012 to 2016, patients with esophageal cancer scheduled for esophagectomy at the Department of Surgery of the Amsterdam University Medical Centers were eligible for the study. Patients were excluded from the study when the initial indication for surgery was withdrawn or if metastasized disease was diagnosed after neoadjuvant therapy.

Study design and ethics

In this prospective cohort study, pre- and postoperative examinations of functional status were systematically performed. These measurements took place 3 months and 1 day preoperatively (T1 and T2) and 1 week and 3 months postoperatively (T3 and T4). The measurements performed in this study were part of physiotherapeutic care and performed in line with ‘Good Clinical Practice’. Therefore, the Medical Ethics Committee of the Amsterdam University Medical Centers waived the need for informed consent (W11-147 # 11.17.1012).

Patient characteristics

Pre-surgical baseline characteristics were recorded from both medical records and preoperative physical examination. Postoperative complications were prospectively recorded and defined by the Clavien-Dindo classification of surgical complications.[13]

Measurements

The main outcome measures were prospectively collected and recorded and contained measurements of musculoskeletal and cardiovascular functions, activities and participation, which are major components of functional status, according to the domains of the International Classification of Functioning, disability and health (ICF). The ICF framework guides effective decision-making within the rehabilitation process.[14,15] The choice of measurement instruments was based on both psychometric properties and clinical relevance.

ICF: Body functions

Handgrip strength (HGS) was measured with a hand held dynamometer, which is a reliable instrument to predict the total skeletal muscle strength.[3,16-18] The outcomes were compared with normative values of adults as described by Spruit et al.[19]

Proximal muscle strength of the lower extremities was assessed the with the functional 30-second chair stand test (30CST). This test was validated and found to be reliable in older adults.[3,18,20] Outcomes were compared with normative values for men and women older than age 60 years.[21]

Maximal inspiratory pressure (MIP) was measured as an indicator of inspiratory muscle strength with a micro-medical spirometer that has been described as valid and reliable.[2,3] Normative values for Caucasian adults were used based on age, sex and height.[22]

Fatigue was measured with the multidimensional fatigue inventory (MFI), which is composed of 20 items and organized into five scales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. The MFI has good internal consistency and construct validity.[18,23]

ICF: Activities and participation

Walking capacity was measured with the 2-minute walk test (2MWT). This test measured the distance a patient was able to walk quickly on a flat, hard surface in a period of 2 minutes.[24,25] The 2MWT correlates highly with the 6-minute walk test, and the intraclass correlation coefficient that indicates the test-retest reliability is 0.82 (95% CI: 0.76 to 0.87).[26] Normative reference values stratified by sex and age were used, as described by Bohannon.[27]

Self-reported activities of daily life (ADL) were assessed with the Longitudinal Ageing Study Amsterdam (LASA) Physical Activity Questionnaire (LAPAQ), in which patients reported their activities during the past 14 days.[28] The LAPAQ appears to be valid and reliable for measuring activities in older people.[3,28]

Health-related quality of life (HRQL) was measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), version 3.0. It is a reliable and valid measure of the quality of life of patients with cancer in multicultural clinical research settings.[29]

Statistical analysis

All data were entered and analysed in the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL), version 25.0 for Windows. Statistical tests were two-sided and considered significant with an $\alpha \leq .05$.

Linear mixed model analyses were used to analyse the course of functional status over time and to analyse the differences in course over time between patients with and without postoperative complications.

RESULTS

Aspects of functional status were assessed of 155 patients with an indication for esophagectomy at T1 and T2 (100%), of which 109 patients were assessed at T3 (70.3%) and 60 at T4 (38.7%). The mean age at surgery was (SD) 63.5 years (9.3), and 122 patients (78.7%) were male. Pulmonary function was better than predicted with a forced vital capacity of (mean, [SD]) 114.4 [16.6], forced expiratory volume in 1 second of 107.4 [19.0] and inspiratory vital capacity of 110.4 [16.3]. All patients received neoadjuvant therapy. The majority of patients (72.3%) underwent a minimally invasive transthoracic esophagectomy. Table 1 presents all patient characteristics at the different time points.

One week after surgery (T3), 46 patients could not be assessed for functional status due to postoperative complications (12.9%), refusal to further cooperate (5.8%) or feeling too weak to be assessed (3.2%). See Table 2 for further details. At T4 (3 months postoperatively), another 49 patients were not able to be assessed due to loss to follow-up (20.2%), the presence of complications (5.5%), the inability to be assessed due to sickness (5.5%) and refusal to further cooperate (6.4%). A detailed analysis of the patients who were lost to follow-up at T3 and T4 revealed that these patients did not systematically differ in baseline characteristics from the patients who completed all measurements but the proportion of patients lost to follow up at T3 with a postoperative complication Clavien-Dindo grade 3a, 4a and 4b was higher (Table 1).

The mean level of HGS, proximal muscle strength of the lower extremities and MIP before surgery (T1 and T2) was higher than predicted when adjusted for sex and age. From T1 to T2 walking capacity, HRQL, and ADL significantly improved and patients experienced significantly less fatigue. At T3, proximal muscle strength of the lower extremities and MIP were significantly decreased compared to T2, whereas HGS remained more or less unchanged. At T4, all mean functional status measures returned to baseline levels, but patients had significantly less HGS and experienced more fatigue (Table 3). Figure 1 shows the graphical representation of the course of measurements of functional status over time.

The incidence of postoperative complications was 83 (53.5%) and was registered as one or more postoperative complications per patient, and this group had a significantly longer hospital stay with a median (IQR) of 17 (9 to 30) days ($P \leq .01$) (Figure 2). No differences in the measurements of functional status between patients with and without complications at the different time points (Table 4) were observed, apart from 2MWT at T3, which was significantly lower in the group with postoperative complications.

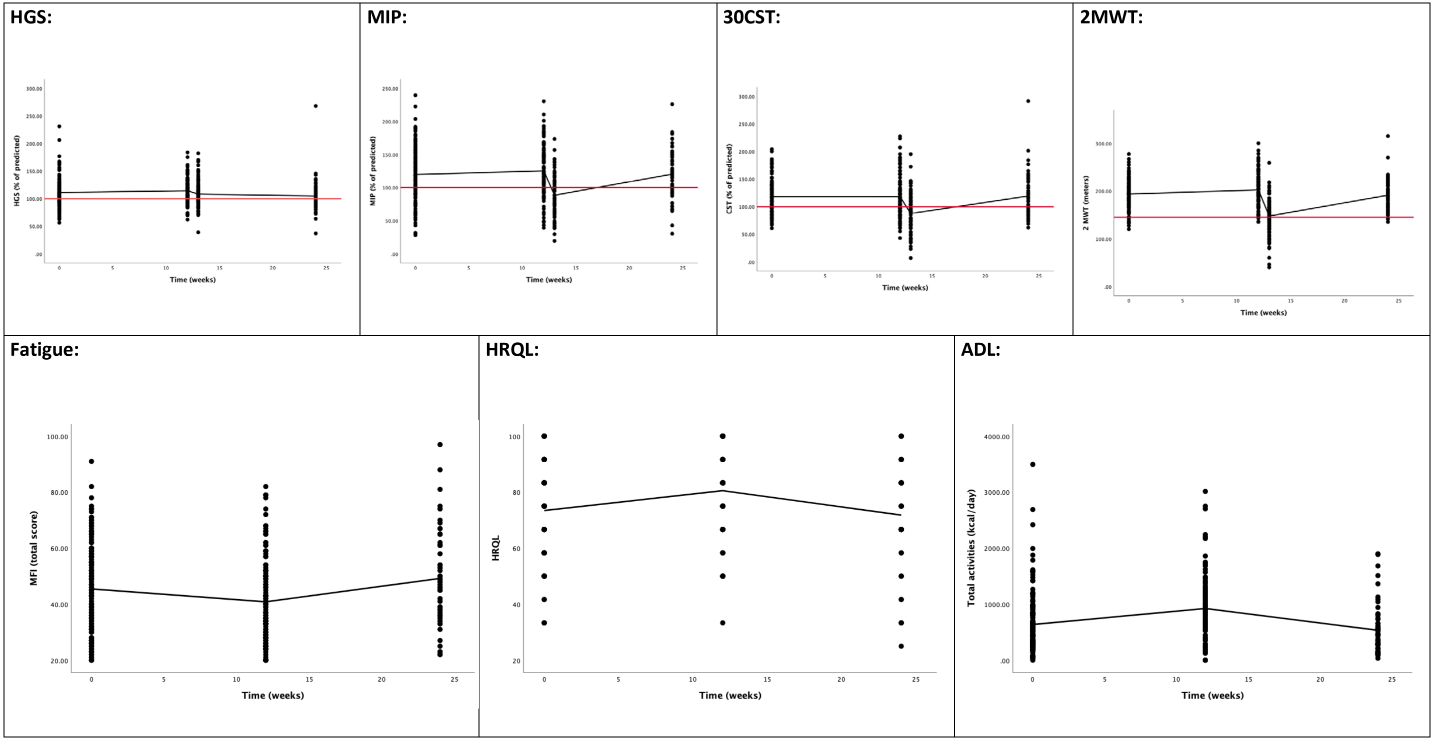

Figure 1. Course of functional status of patients with esophageal cancer undergoing esophagectomy

Functional status measurements are presented as a percentage of the predicted value unless otherwise stated. Red lines represent normative values if available. Abbreviations: MIP, maximal inspiratory pressure; HGS, handgrip strength; 30CST, 30-second chair stand test; 2MWT, 2-minute walk test; MFI, Multidimensional Fatigue Inventory: scores range from 20 to 100 with a higher score representing more fatigue, reduced activity/ motivation; HRQL, health-related quality of life: scores range from 0 to 100 with high scores indicating a better HRQL. ADL, activities of daily life: total amount of activities in kilocalories a day.

Table 1. Patient characteristics

Characteristics	T1 (N = 155)	T2 (N = 155)
Sex (Male)	122 (78.7)	122 (78.7
ASA-classification		
I		33 (21.3)
II		98 (63.2)
III		24 (15.5)
Age (years), mean (SD)	62.7 (8.8)	63.5 (9.3)
BMI, mean (SD)	26.2(4.3)	26.4 (4.0)
Comorbidities		
Cardiovascular	29 (18.7)	29 (18.7)
COPD	11 (7.1)	11 (7.1)
DM II	10 (6.5)	10 (6.5)
Cigarette smoking (yes)	40 (25.8)	40 (25.8)
Pulmonary function (percentage of predicted), mean (SD)		
FVC	114.4 (16.6)	114.4 (16.6)
FEV_1	107.3(19.0)	107.4 (19.0)
IVC	110.4 (16.3)	110.4(16.3)
Surgical procedure		
Transhiatal open		6 (3.9)
Transhiatal minimally invasive		13 (8.4)
Transthoracal open		20 (12.9)
Transthoracal minimally invasive		112 (72.3)
Clavien-Dindo postoperative complications		
I		19 (12.1)
II		22 (14.0)
IIIa		17 (10.8)
IIIb		7 (4.5)
IVa		14 (8.9)
!Vb		4 (2.5)
V		5 (3.2)

Characteristics of patients measured at different time points and patients who were lost to follow-up at T3 and T4. * With percentages in parentheses unless indicated otherwise. ASA, American Society of Anesthesiologists; I: healthy person, II: mild systemic disease, III: severe systemic disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; DM II, diabetes mellitus type 2; FVC, functional vital capacity; FEV_1, forced expiratory volume in the first second of expiration; IVC, inspiratory vital capacity; LtFU, Loss to follow up.

	T3 (N = 109)	*LtFU T3 (n = 46)*	T4 (N = 60)	*LtFU T4 (n = 49)*
	88 (80.7)	*36 (75.0)*	48 (80.0)	*45 (77.6)*
	20 (18.3)	*13(28.2)*	15 (25.0)	*7 (14.3)*
	69 (63.3)	*30 (65.2)*	32 (53.3)	*35 (71.4)*
	20 (18.3)	*3 (6.5)*	13 (21.7)	*7 (14.3)*
	63.7 (8.8)	*61.6 (8.8)*	63.6 (8.8)	*63.3 (9.5)*
	26.1 (4.3)	*26.4 (4.1)*	24.7 (3.7)	*25.9 (3.2)*
	19 (17.9)	*10 (20.8)*	11 (18.3)	*20 (34.5)*
	7 (6.6)	*4 (8.3)*	7 (11.7)	*4 (7.1)*
	6 (5.7)	*5 (10.4)*	2 (3.3)	*4 (6.9)*
	26 (24.3)	*14 (29.2)*	10 (16.7)	*14 (24.1)*
	114.7 (15.5)	*113.5 (19.1)*	113.3 (15.2)	*115.47 (14.5)*
	108.2 (17.9)	*104.6 (21.5)*	109.5 (15.2)	*106.66 (16.8)*
	111.0 (15.4)	*108.8 (18.5)*	109.9 (14.3)	*104.92 (30.0)*
	4 (3.7)	*3 (6.3)*	4 (6.7)	*1 (2.0)*
	9 (8.4)	*3 (6.3)*	8 (13.3)	*5 (10.2)*
	11 (10.3)	*9 (18.8)*	6 (10.0)	*1 (2.0)*
	83 (77.6)	*29 (60.4)*	42 (70.0)	*42 (85.7)*
	14 (12.8) (12.8)	*5 (10.4)*	7 (12.1)	*8 (13.8)*
	16 (14.7)	*5 (10.4)*	9 (15.5)	*9 (15.5)*
	8 (7.3)	*9 (18.8)*	5 (8.6)	*4 (6.9)*
	5 (4.6)	*2 (4.2)*	3 (5.2)	*2 (3.4)*
	7 (6.4)	*8 (16.7)*	6 (10.3)	*2 (3.4)*
	2 (1.8)	*2 (4.2)*	1 (1.7)	*1 (1.7)*
	-	-	-	*5 (10.4)*

Postoperative complications according to the Clavien-Dindo classification Grade I: Any deviation from the normal postoperative course without pharmacologic treatment or surgical, endoscopic, and radiological interventions; Grade II: Requiring pharmacologic treatment with drugs other than ones allowed for grade I complications; Grade III: Requiring surgical, endoscopic, or radiologic intervention not under general anesthesia (IIIa), under general anesthesia (IIIb); Grade IV: Life-threatening complications requiring IC/ICU management, single-organ dysfunction (including dialysis) (IVa), multiorgan dysfunction (IVb); Grade V: Death of a patient.

Table 2. Reasons for loss to follow-up

Reasons for loss to follow-up*	T3	T4
Total patients not measured	46 (29.6)	49 (46.8)
Deceased	0 (0)	5 (4.6)
No show, reason unknown	0 (0)	20 (20.2)
Planning reasons	4 (2.6)	0 (0)
Unable to test due to complications	20 (12.9)	6 (5.5)
Too weak/sick to be tested	5 (3.2)	6 (5.5)
Unspecified refusal to cooperate	9 (5.8)	7 (6.4)
No resectable tumor	2 (1.3)	0 (0)
Psychosocial reasons	1 (0.6)	0 (0)
Unspecified personal circumstances	2 (1.3)	3 (2.8)
Metastasis	3 (1.9)	2 (1.8)

* With percentages in parentheses.

In the group of patients suffering from postoperative complications, most of the functional status measures at T4 returned to baseline levels (beta [95% CI]: 30CST (-0.4, [-10.2 to 9.3]; *P* = .93), MIP (-6.7, [-15.9 to 2.4]: *P* = .15), ADL (-70.3, [-284.6 to 144.0]; *P* = .52), 2MWT (-8.8, [-18.7 to 1.1]; *P* = .08), HRQL (-4.7, [-10.3 to 0.9]; *P* = .10), but these patients had significantly less HGS (beta [95% CI]: (-9.0, [-17.3 to -0.7]; *P* = .03) and experienced more fatigue (7.2, [2.1 to 12.2]; *P* = .006).

Table 3. Differences in functional status outcomes

Measurements	T1	T2	Δ T2-T1 (95% CI)
HGS	111.0 (25.9)	114.3 (21.7)	2.6 (-1.3 to 6.5)
MIP	119.7 (40.6)	125.4 (38.5)	4.1 (-0.6 to 8.7)
30CST	118.1 (28.9)	117.0 (38.2)	0.3 (-4.69 to 5.25)
2MWT (m)	193.6 (29.2)	202.3 (35.6)	9.4 (4.0 to 14.7)
MFI fatigue, median (IQR)	45.5 (26.3)	40.8 (23.8)	-4.7 (-7.6 to -1.7)
EORTC QLQ C30 quality of life (%) median (IQR)	73.4 (15.7)	80.5 (14.2)	7.1 (3.9 to 10.3)
LAPAQ (Kcal/day) median (IQR)	475.4 (550.2)	864.5 (671.0)	364.0 (177.6 to 550.3)

Functional status measurements are presented as a percentage of the predicted value in means ± standard deviation (SD), unless otherwise stated. Abbreviations: MIP, maximal inspiratory pressure; HGS, handgrip strength; 30CST, 30-second chair stand test; 2MWT, 2-minute walk test; MFI, multidimensional fatigue inventory: scores range from 20 to 100 with a higher score representing more fatigue, reduced activity/ motivation;

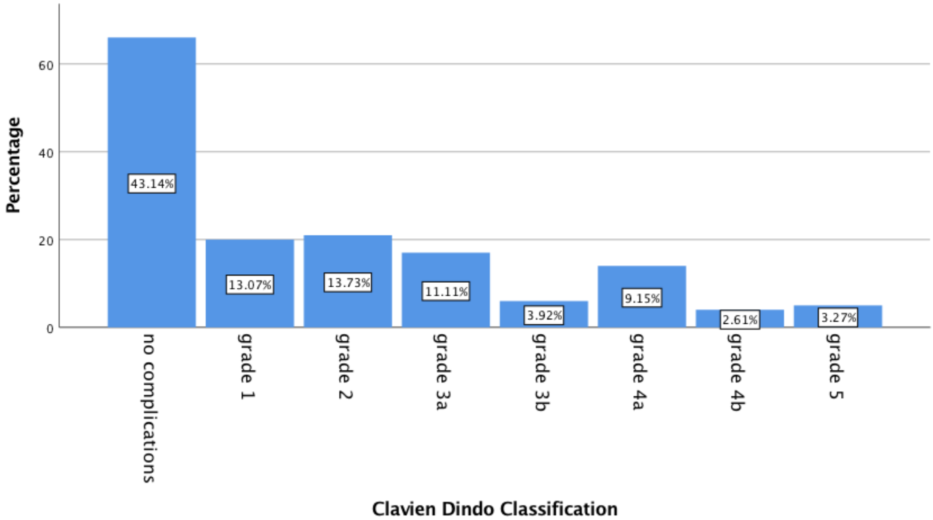

Figure 2. Postoperative complications according to the Clavien Dindo classification (N = 155)

Grade I: Any deviation from the normal postoperative course without pharmacologic treatment or surgical, endoscopic, and radiological interventions; Grade II: Requiring pharmacologic treatment with drugs other than ones allowed for grade I complications; Grade III: Requiring surgical, endoscopic, or radiologic intervention not under general anesthesia (IIIa), under general anesthesia (IIIb); Grade IV: Life-threatening complications requiring IC/ICU management, single-organ dysfunction (including dialysis) (IVa), multiorgan dysfunction (IVb); Grade V: Death of a patient.

P-value	T3	Δ T3-T1 (95% CI)	*P*-value	T4	Δ T4-T1 (95% CI)	*P*-value
.19	108.2 (23.3)	-2.8 (-6.8 to 1.3)	.18	104.8 (30.1)	-6.2 (-11.3 to -1.1)	.02
.09	88.4 (33.6)	-37.2 (-43.0 to -31.4)	<.001	120.4 (38.1)	-4.4 (-10.5 to 1.8)	.16
.91	87.6 (34.0)	-32.2 (-37.7 to -26.7)	-.70	119.1 (38.1)	-2.3 (-8.8 to 4.2)	.48
.001	147.5 (37.2)	-48.4 (-54.0 to -42.7)	<.001	191.2 (34.4)	-5.7 (-12.6 to 1.2)	.10
.002	-	-	-	49.2 (17.1)	4.7 (0.7 to 8.7)	.02
<.001	-	-	-	71.8 (18.1)	-2.5 (-6.7 to 1.8)	.25
<.001	-	-	-	453.0 (539.4)	136.8 (-106.8 to 380.5)	.27

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30: scores range from 0 to 100 with high scores indicating a better quality of life. LAPAQ, LASA physical activity questionnaire: total amount of activities in kilocalories per day. *P*-value ≤ .05 is considered significant.

Table 4. The differences in aspects of functional status in patients with postoperative complications compared to patients without postoperative complications at different time points

	T1 (95% CI)	*P*-value	T2 (95% CI)
HGS	4.0 (-3.9 to 11.9)	.32	-1.4 (-9.9 to 7.2)
MIP	-7.9 (-20.4 to 4.6)	.21	-3.6 (-16.7 to 9.5)
30CST	-2.4 (-13.2 to 8.5)	.67	3.9 (-7.7 to 15.5)
2MWT	0.7 (-10.1 to 11.6)	.89	6.6 (-5.1 to 18.3)
ADL	126.4 (-47.0 to 299.8)	.15	164.1 (-23.5 to 351.8)
Fatigue	0.3 (-5.0 to 5.6)	.92	-2.8 (-8.4 to 2.9)
HRQL	-2.8 (-7.8 to 2.3)	.28	-2.7 (-5.8 to 5.3)

Regression coefficients represent the difference in functional status between the group with and without complications at T1, 2, 3 and 4. *P*-value ≤ 0.05 is considered significant. Abbreviations: MIP, maximal inspiratory pressure; HGS, handgrip strength; 30CST, 30-second chair stand test; 2MWT, 2-minute walk test; HRQL, health-related quality of life.

P-value	T3 (95% CI)	*P*-value	T4 (95% CI)	*P*-value
.75	-6.5 (-15.4 to 2.3)	.15	-1.5 (-12.2 to 9.2)	.79
.59	-8.7 (-23.6 to 6.2)	.25	-13.0 (-28.3 to 2.3)	.10
.51	-11.6 (-24.2 to 1.0)	.07	1.4 (-13.0 to 15.7)	.85
.27	-23.3 (-35.6 to -11.0)	<.001	-6.21 (-20.6 to 8.2)	.40
.09	Not tested	-	128.6 (-141.0 to 398.2)	.35
.34	Not tested	-	5.8 (-2.1 to 13.6)	.15
.92	Not tested	-	-7.0 (-15.0 to 0.9)	.08

DISCUSSION

This is the first prospective study that systematically described the course of functional status of patients undergoing esophagectomy from 3 months before until 3 months after surgery. This study showed that functional status of patients with esophageal cancer treated with esophagectomy was on average higher compared to normative values at 3 months and at 1 day before surgery and returned to baseline levels 3 months postoperatively with an expected decline directly after surgery. Although patients had significantly less HGS at T4 than at baseline and experienced more fatigue, the differences could be clinically interpreted as minimal. The same pattern was observed in patients who suffered from postoperative complications.

Furthermore, this study showed that the course of functional status between patients with and without postoperative complications was not different. The length of hospital stay was clearly longer for patients suffering from postoperative complications, but 3 months after surgery, there was no difference in functional status between patients with and without postoperative complications.

These results are surprising because patients with esophageal cancer are considered high-risk for developing postoperative complications with a delayed postoperative recovery.[2,4,7] The incidence of postoperative complications in our study cohort was 53.5%, but despite this, all patients recovered to their baseline functional status 3 months after surgery. This seems contradictory to the results of several studies that described the positive effects of improved preoperative functional status on postoperative outcomes in comparable surgical populations.[1,3,4,30]

In a recent study by Minnella et al.[31], the effects of a prehabilitation intervention on functional capacity were investigated in patients with esophageal cancer undergoing surgery. A significant improvement in functional capacity was found in patients who received a prehabilitation intervention, although no differences were found with respect to the incidence of postoperative complications, length of hospital stay and readmission rates.[31]

Hulzebos et al.[30] demonstrated that preoperative inspiratory muscle training decreased the incidence of postoperative pulmonary complications and length of hospital stay compared to usual care in patients undergoing coronary artery bypass graft (CABG).

However, preoperative pulmonary function in their study cohort was on average 20% lower than predicted, while it was up to 15% higher than predicted in our study cohort.[30,32] Besides, a majority of our study cohort (72.3%) underwent minimally invasive surgery from which is known that it leads to a lower incidence of postoperative pulmonary complications. [33] Moreover, in our study cohort, fewer patients with chronic obstructive pulmonary disease (COPD) and diabetes mellitus type 2 (DM II) were present (COPD 7.1% vs. 19.4%, DM II 6.5% vs. 43.9% in the CABG group). Functional status is highly dependent on cardiorespiratory components. Therefore, it could be stated that the initial preoperative functional status of our study cohort was much higher compared to other surgical populations.[9]

Tew et al.[34] stated in their clinical guidelines on preoperative training in major non-cardiac surgery that every patient with an indication for surgery should be provided with preoperative exercise training to increase physiological and functional status. An increased physiological and functional status helps patients to better withstand the negative effects of surgery, such as postoperative pulmonary complications.[7]

Based on the results of our study, however, it might be questioned whether preoperative exercise training to increase preoperative physiological and functional status is beneficial for all patients with an indication for esophagectomy, because preoperative functional status was on average higher than normative values and did not change between 3 months preoperatively and 1 day preoperatively. It could be hypothesized that little improvement in physiological and functional status is to be expected with preoperative training if functional status is already high, and therefore, these patients should not be provided with prehabilitation. Moreover, there seems to be no relationship between preoperative functional status and postoperative recovery in our study cohort. This is in line with a study by Valkenet et al.[35] who did not find any significant improvements in aerobic capacity, HGS, knee extension strength and elbow flexion strength after a preoperative exercise program in a comparable group of cancer patients scheduled for elective gastrointestinal surgery. The authors suggested that the results could be due to the relatively short training period, but the high fitness levels of these patients could also be an explanation for the lack of effectiveness. Dettling et al.[36] demonstrated in a comparable esophageal cancer population that preoperative inspiratory muscle training did not lead to an expected postoperative reduction of pneumonia and concluded that these patients seemed to benefit less from inspiratory muscle training than other surgical populations. Moreover, it could be questioned whether esophageal surgery-related complications, such as anastomotic leakage, could be prevented with increased preoperative functional status. Although prehabilitation is also aimed at improving postoperative recovery after postoperative complications, this study surprisingly showed no difference in recovery between patients with and without postoperative complications.

This raises the question of whether and when postoperative exercise training should be indicated. A review by Hoogeboom et al.[8] stated that training should start as early as 4 hours after surgery, and the exercise therapy should be tailored to the individual needs of the patient to improve postoperative recovery. To identify these needs and to determine if physiotherapy is indicated, it is essential to assess functional status.

This study has some limitations.
First, only 155 patients were included in this study who consented to have their functional status measured out of 449 patients treated with esophagectomy between 2012 to 2016 (34.5%). However, the included patients did not substantially differ in baseline characteristics from the overall population (Appendix A). In addition, patients were indicated for surgery only if their preoperative pulmonary function and general condition was good enough for surgery and if metastases were not present. This may explain the high mean values of functional status throughout the pre- and postoperative course. However, the rate of postoperative complications was still high, and there were also a substantial number of patients who scored below normative values of functional status and still returned to baseline levels 3 months after surgery.

Second, there was a high number of patients who could not be assessed, mainly during the postoperative course. It could be argued that the patients with postoperative complications or low physical fitness levels were among these patients. However, a detailed analysis revealed that the patients lost to follow-up did not systematically differ in baseline characteristics and functional status at T1. The proportion of patients lost to follow up at T3 with a postoperative complication Clavien-Dindo grade 3a, 4a and 4b was higher compared to the patients measured at T3 and T4, so it could be argued that the postoperative course of functional status may have been different for this group. However, due to the low numbers of patients within each classification grade, it was statistically impossible to analyze the course of functional status of each subgroup. Moreover, severe complications (IIIa and worse) were also present in the patients that completed all measurements.

Third, functional status was compared to currently available normative values presented in the peer-reviewed literature. Within physiotherapy, there is a lack of consistency in interpreting these normative values because they have either been based on the means and standard deviations of comparable normative samples or on values from regression equations. The latter should be preferred because it provides continuous norms rather than discrete norms formed by age bands where the consequences of an individual's raw score can change suddenly as he transfers from one band to another.[37] Another disadvantage of categorizing normative values by demographic characteristics is that it leads to small sample sizes and subsequently wide standard deviations. This could have led to an incorrect interpretation of high versus low functional status. However, these normative values are widely used in physiotherapy practice to indicate functional status and are therefore used in this study as well.

In many studies, the importance of determining a patient's physiological and functional status to successfully recover from surgery has been emphasized.[8,11] Although our study illustrates that functional status returned to baseline values postoperatively and that the course did not systematically differ for patients with and without postoperative complications, it does not imply that this also holds true for the individual patient. Therefore, an individual assessment of functional status both pre- and postoperatively is still required. A valid prediction model should be constructed based on preoperative functional status or other conventional risk factors to determine whether patients indicated for esophagectomy are at high risk for developing postoperative complications.[6]

This model may then be able to differentiate which patients should be referred to a physiotherapist to obtain tailored care to improve pre- and postoperative functional status and thereby reduce the chance of a poor postoperative outcome.

CONCLUSIONS

This study shows that functional status of high-risk surgical patients undergoing esophagectomy returned to baseline values three months after surgery, despite the high incidence of postoperative complications. This requires rethinking the concept of prehabilitation, where clearly not all patients benefited from high functional status to prevent postoperative complications. Therefore, this study illustrates the importance of first evaluating the pre- and postoperative course of functional status of high-risk surgical patients and of timing and tailoring the physiotherapy treatment to a patient's individual needs before referring them for pre- or postoperative physiotherapy.

CONFLICT OF INTEREST STATEMENT

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MIvBH is consultant for Medtronic and Mylan, in areas unrelated to the present study.

All other authors declare no conflicts of interest.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.08.005.

Appendix A. **Patient characteristics of patients with esophageal resection between 2012-2016 compared to the study cohort**

Characteristics*	N = 449	N = 155	*P*-value
Sex (Male)	336 (74.8)	122 (78.7)	
ASA-classification			
I	160 (35.6)	33 (21.3)	
II	206 (45.9)	98 (63.2)	
III	83 (18.5)	24 (15.5)	
Age (years), mean (SD)	63.6 (9.0)	63.5 (9.3)	.506
BMI, mean (SD)	25.9 (4.5)	26.4 (4.0)	.250
Comorbidities			
Cardiovascular	182 (40.5)	29 (18.7)	
COPD	24 (5.4)	11 (7.1)	
DM II	43 (9.6)	10 (6.5)	
Pulmonary function (percentage of predicted), mean (SD)			
FEV1/ VCmax (percentage of predicted), mean (SD)	95.1 (12.3)	94.0 (11.8)	.264
Surgical procedure			
Transhiatal open	20 (4.5)	6 (3.9)	
Transhiatal minimally invasive	43 (9.6)	13 (8.4)	
Transthoracal open	31 (6.9)	20 (12.9)	
Transthoracal minimally invasive	333 (74.2)	112 (72.3)	
Clavien-Dindo postoperative complications			
I	55 (12.2)	19 (12.1)	
II	62 (13.8)	22 (14.0)	
IIIa	52 (11.6)	17 (10.8)	
IIIb	7 (1.6)	7 (4.5)	
IVa	59 (13.1)	14 (8.9)	
IVb	20 (4.5)	4 (2.5)	
V	21 (4.7)	5 (3.2)	

Appendix A. **Continued**

Characteristics of included participants, compared to all patients treated with esophagectomy between 2012-2016. * With percentages in parentheses unless indicated otherwise. ASA, American Society of Anesthesiologists; I: healthy person, II: mild systemic disease, III: severe systemic disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; DM II, diabetes mellitus type 2; FVC, functional vital capacity; FEV_1, forced expiratory volume in the first second of expiration. Postoperative complications according to the Clavien-Dindo classification Grade I: Any deviation from the normal postoperative course without pharmacologic treatment or surgical, endoscopic, and radiological interventions; Grade II: Requiring pharmacologic treatment with drugs other than ones allowed for grade I complications; Grade III: Requiring surgical, endoscopic, or radiologic intervention not under general anesthesia (IIIa), under general anesthesia (IIIb); Grade IV: Life-threatening complications requiring IC/ICU management, single-organ dysfunction (including dialysis) (IVa), multiorgan dysfunction (IVb); Grade V: Death of a patient.

Chapter 4

Muscle strength is associated with muscle mass in patients with esophageal cancer awaiting surgery

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ABSTRACT

Background and purpose: Decreased muscle mass and muscle strength are independent predictors of poor postoperative recovery in patients with esophageal cancer. If there is an association between muscle mass and muscle strength, physiotherapists are able to measure muscle strength as an early predictor for poor postoperative recovery due to decreased muscle mass. Therefore, in this cross-sectional study we aimed to investigate the association between muscle mass and muscle strength in predominantly older patients with esophageal cancer awaiting esophagectomy, prior to neoadjuvant chemoradiation.

Methods: In patients with resectable esophageal cancer eligible for surgery between March 2012 and October 2015, we used computed tomography scans to assess muscle mass and compared them with muscle strength measures (handgrip strength, inspiratory- and expiratory muscle strength, 30-second chair stand test). We calculated Pearson correlation coefficients and determined associations with multivariate linear regression analysis.

Results and discussion: A tertiary referral center referred 125 individuals to physiotherapy who were eligible for the study; we finally included 93 individuals for statistical analysis. Multiple backward regression analysis showed that gender (95% CI 2.05 to 33.82), weight (95% CI 0.39 to 1.02), age (95% CI (-0.91 to -0.04), left handgrip strength (95% CI 0.14 to 1.44) and inspiratory muscle strength (95% CI 0.08 to 0.38) were all independently associated with muscle surface area at L3. All these variables together explained 66% of the variability (R^2) in muscle surface area at L3 ($P < .01$).

Conclusions: This study shows an independent association between aspects of muscle strength and muscle mass in patients with esophageal cancer awaiting surgery and physiotherapists could use the results to predict muscle mass based on muscle strength in preoperative patients with esophageal cancer.

INTRODUCTION

Esophagectomy is the primary option for curative treatment in patients with esophageal cancer and is associated with a high rate of mortality and morbidity.[1,2] A majority of these patients will be confronted with dysphagia and weight loss during the course of their disease.[3-5] This may lead to decreased muscle mass and muscle strength and eventually to sarcopenia, a multifactorial syndrome characterized by chronic inflammation, inactivity, malnutrition and weight loss which leads to decreased muscle mass and general loss of muscle function, leading to adverse outcomes such as increased complication rates, delayed functional recovery, low quality of life and high mortality.[6-10]

A loss of muscle mass may reflect high metabolic stress due to systemic inflammation in patients with esophageal cancer. The imbalance between anabolic and catabolic activity within muscle leads to a loss of muscle mass with increased muscle protein degradation as a consequence.[11] Hormones, tumor-derived factors, inactivity and malnutrition also contribute to a loss of muscle mass, negatively affecting the metabolic response to gastrointestinal surgery and increasing the risk of complications following surgery.[12] The prevalence of sarcopenia in patients with esophageal cancer awaiting neoadjuvant chemoradiation varies between 47 and 57% increasing from 53% to 79% after neoadjuvant chemoradiation.[13,14] Moreover, sarcopenia is an independent predictor of postoperative pulmonary complications, because it does not only affect general muscle strength, but also respiratory muscle strength. Reduced respiratory muscle strength leads to an ineffective cough and increases the risk of postoperative pneumonia and atelectasis.[3,10,13] Therefore, it is important to assess patients on decreased muscle mass and muscle strength before neoadjuvant chemoradiation, since early tailored exercise therapy and nutritional support may prevent patients from developing sarcopenia with consequences for functional performance.[15]

To diagnose decreased muscle function, both muscle mass and muscle strength need to be assessed.[9] Muscle mass is usually measured with dual x-ray absorptiometry (DXA), computed tomography (CT), or magnetic resonance imaging (MRI).[16,17] Physiotherapists are unable to measure muscle mass directly, but they are able to quantify aspects of muscle strength and endurance by hand held dynamometry and muscle strength measures.

The association between muscle mass and muscle strength is not self-evident because, although the loss of muscle mass is associated with the decline in muscle strength, muscle strength decline may be more rapid than the loss of muscle mass, while muscle mass is maintained or even increased.[18,19] Many studies have shown an association between muscle mass and muscle strength, but there are no studies that investigated this association in patients with esophageal cancer scheduled for esophagectomy.[18-21]

If there is an association between muscle mass and muscle strength in preoperative patients with esophageal cancer prior to neoadjuvant chemoradiation, physiotherapists may be able to determine which patients are at risk for decreased muscle function and its functional consequences by measuring muscle strength. These patients may benefit from preoperative exercise training and nutritional support to increase muscle strength as well as functional status contributing to better postoperative outcomes.

Therefore, the purpose of this study was to investigate the association between muscle mass and muscle strength in patients with esophageal cancer awaiting potentially curative esophagectomy, before neoadjuvant chemoradiation.

METHODS

Study design and participants

For this cross-sectional study, all patients with an indication for curative-intent esophagectomy at the Gastro Intestinal Oncologic Center Amsterdam (GIOCA) of the Academic Medical Center (AMC) in Amsterdam were eligible for this study between March 2012 and October 2015. Only patients, who agreed to have their muscle strength measured preoperatively were referred to the physiotherapy department and included in this study. We did not apply cut-off scores for muscle strength to be included in the study. We excluded patients for assessment of muscle strength if severe cognitive, functional or neurological impairments would make reliable assessment outcomes impossible. We measured all patients 3 months preoperatively, before neoadjuvant chemoradiation. The Medical Ethics Committee of the AMC waived the need for informed consent, because the measurements in this study were part of standard care.

Measurements

Clinical characteristics

We prospectively recorded clinical characteristics and the presence of conventional risk factors: age, gender, height, weight, body mass index (BMI), the presence of diabetes type II, cardiovascular- and pulmonary diseases and pulmonary function.

Body composition

All included patients underwent computed tomography scans (CT-scans) before neoadjuvant chemoradiation. We used CT-scans meeting the following criteria to assess for the muscle surface areas:

1. The vertebral spine was entirely visible at the level of the third lumbar vertebra (L3);
2. The whole cross-section of the body was displayed on the image at the level of L3;
3. The CT-scan was displayed in the portal venous phase;
4. The quality of the CT-scan was high enough to be able to distinguish different tissues.

We assessed cross-sectional muscle surface areas (cm^2) at the level of L3, because tissue areas in this region are significantly related to whole-body muscle mass (Figure 1).[22,23] We selected plain images and we obtained measurements of the psoas, paraspinal, transverse abdominal, internal and external oblique and rectus abdominis muscles using computer software SliceOmatic 5.0 (Tomovision, Montreal, Canada). We used Hounsfield unit thresholds of −29 to 150 to differentiate muscle from other tissues.[24] We computed cross-sectional areas (cm^2) for the muscle by summing tissue pixels and multiplying by the pixel surface area. We corrected cross-sectional muscle areas for height to calculate the L3 muscle index expressed in cm^2/m^2.

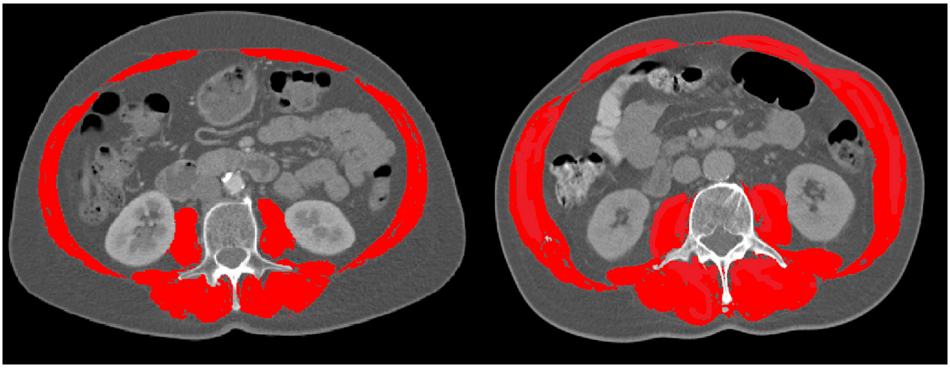

Figure 1. CT scans at the third lumbar vertebra level of a male patient with normal skeletal muscle mass (right) and decreased muscle mass (left)
Skeletal muscle surface areas are highlighted in red.

By international consensus, we considered people sarcopenic if the total muscle tissue area measured at the third lumbar level (L3) was less than 52.4 cm^2/m^2 body surface area for men and 38.5 cm^2/m^2 for women measured with CT imaging.[17]

Muscle strength

We measured the highest value of handgrip strength (HGS) on the right and left side with the Jamar® grip strength dynamometer (Lafayette Instrument Company, Lafayette, USA). This dynamometer is a reliable instrument to predict the total skeletal muscle strength.[25-28] We calculated the percentage HGS of predicted by using normative values for adults, taking gender, age, height and measurement side into account.[29]

We measured maximal inspiratory and expiratory pressure (MIP/ MEP) as indicators of respiratory muscle strength reporting the highest value, with a micro-medical spirometer (Micro-RPM, Micro Medical Ltd., Rochester, England). These measurements are described as valid and reliable.[25,30] We calculated the percentage MIP and MEP of predicted by using normative values, predicted by a regression equation based on age, gender and height.[31]

We assessed functional lower extremity strength with the 30-second chair stand test (30CST). During this test, the patient had to stand up from a chair without support of the arms and sit again, repeating this during 30 seconds, registered as counts. This test was validated and reliable in older adults.[25,28,32] We described normative values for men and women older than 60 years old.[33]

We described standardized operating procedures (SOPs) of all measurements in order to guarantee uniformity and accuracy in operationalization as well as prerequisites for inter-rater reliability. Trained and experienced physiotherapists executed the standardized measurement protocol. All physiotherapists received an in-depth training of the study protocol, the standardized measures as well as data registration.

Statistical analysis

We entered and analyzed all data in the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL), version 21.0. We checked data for completeness and skewness with the Shapiro-Wilk test. We summarized baseline characteristics with descriptive statistics, where discrete variables were expressed as counts with percentages, ordinal variables as median and interquartile ranges (P25-75) and continuous variables as mean and standard deviation and in case of a skewed distribution as median and interquartile range.

For evaluating the relation between muscle mass and muscle strength, we compared data using Pearson correlation coefficients (r), interpreted according to Zou et al[34] (rating $r = 0.5$ as moderate and $r = 0.8$ as strong). We built linear regression models on skeletal muscle area at L3 with each aspect of muscle strength as an exploratory variable, adjusted for age, gender, height, and weight.

Consecutively, we forced all variables in one multiple linear regression model and with backward elimination we created a final regression model.

We tested all hypotheses 2-tailed with a significance level set to .050 and we considered regression coefficients significantly different if the 95% confidence intervals (CI) were not overlapping.

RESULTS

Between March 2012 and October 2015, 226 patients with a resectable esophageal carcinoma (cT0-4aN0-3M0) were eligible for this study. Finally, 125 patients agreed to be measured on muscle strength before neoadjuvant chemoradiation and a tertiary referral center subsequently referred them to the physiotherapy department. From these 125 patients, 93 CT-scans were eligible to compute muscle surface areas. Reasons for exclusion of the CT-scans were: No high dose CT available in portal phase on level L3 (n = 17), not able to assess due to low dose CT (n = 10), L3 was not properly scanned (n = 1), muscle was not fully depicted on CT (n = 2), CT was taken in wrong phase (n = 1) and CT could not be taken from server for analysis (n = 1). Therefore, we finally included 93 patients for statistical analysis. The majority of patients were male (82.8%) and mean age (SD) was 61.1 years (9.4). BMI was (mean, [SD] 25.9 [54.2]) and 3 out of 93 individuals (3.2%) had a nasogastric feeding tube preoperatively. Pulmonary function was better than predicted (100 %) with a forced vital capacity (FVC) of (mean percentage, [SD]) 115.3 (16.5), forced expiratory volume in 1 second (FEV1) of 107.2 (19.5) and inspiratory vital capacity (IVC) of 111.3 (15.8) respectively (Table 1).

Table 1. Baseline patient characteristics[a] (N = 93 patients)

Characteristics	Total (N = 93)[a]	Male (n = 77)[b]	Female (n = 16)[b]
Age, y	61.1 (9.4)	61.5 (17.0)	59.4 (15.0)
Height, cm	176.2 (8.0)	178.0 (10.0)	169.0 (9.5)
Weight, kg	80.5 (14.9)	82.1 (21.6)	67.4 (19.3)
Body mass index, kg/m^2	25.9 (4.2)	25.8 (5.6)	23.9 (6.3)
< 19	3 (3.2) [c]	3 (3.9) [c]	-
19.1-25	39 (40.9) [c]	30 (39) [c]	9 (56.3) [c]
25.1-30	38 (40.0) [c]	33 (42.9) [c]	5 (31.3) [c]
> 30.1	13 (14.0) [c]	11 (14.3) [c]	2 (12.5) [c]
Comorbidities			
Cardiovascular	20 (21.5)[c]	19 (24.7)[c]	1 (6.3)[c]
Chronic obstructive pulmonary disease	7 (7.5)[c]	6 (7.8)[c]	1 (6.3)[c]
Diabetes mellitus type II	3 (3.2)[c]	2 (2.6)[c]	1 (6.3)[c]
Muscle surface area at L3, cm^2	151.5 (31.9)	159.8 (36.8)	106.5 (15.9)
L3 muscle index, cm^2/m^2	76.4 (12.8)	79.6 (14.5)	59.6.(9.5)
Pulmonary function, percentage of predicted			
Forced vital capacity	115.3 (16.5)	116.5 (19.7)	111.8 (35.4)
Forced expiratory volume$_{1\ second}$	107.2 (19.5)	109.7 (23.2)	102.2 (36.5)
Inspiratory vital capacity	111.3 (15.8)	111.4 (19.2)	103.3 (29.8)

[a] Mean (standard deviation) is shown
[b] Median (interquartile range) is shown
[c] Number (percentage) is shown

All scores on muscle strength of our study cohort were all on average higher than predicted, compared with normative values. Our study cohort scored (mean, [SD]) 109.7 [19.5] percent of the predicted right HGS, 110.8 [19.9] percent of the predicted left HGS, 123.0 [42.1] percent of the predicted MIP, 108.4[(32.5] percent of predicted MEP and 119.0 [29.6] of functional lower extremity strength (Table 2). Based on the cut-off values for sarcopenia on L3 muscle index, 2 male individuals in our cohort were sarcopenic.[17] Pearson correlation coefficients between aspects of muscle strength and both skeletal muscle mass area at L3 and L3 muscle index were all significantly positive on a $P < .01$ (Table 3).

Table 2. Scores on functional muscle strength[a]

Aspects of functional muscle strength	Total (N = 93)	Male (n = 77)	Female (n = 16)
Right handgrip strength, kg	42.4 (10.5)	45.7 (7.9)	26.5 (5.0)
Percentage of predicted	109.7 (19.5)	111.3 (18.7)	102.1 (22.3)
Left handgrip strength, kg	40.43 (10.0)	43.5 (7.5)	24.8 (4.5)
Percentage of predicted	110.8 (19.9)	111.9 (19.2)	105.5 (22.6)
Maximal inspiratory pressure, mmHg	95.6 (33.0)	103.0 (30.2)	60.3 (20.3)
Percentage of predicted	123.0 (42.1)	132.4 (38.6)	78.2 (25.8)
Maximal expiratory pressure, mmHg	129.6 (43.8)	138.4 (42.3)	87.7 (20.2)
Percentage of predicted	108.4 (32.5)	112.1 (33.3)	91.1 (21.6)
30-second chair stand test, counts	18.4 (4.8)	19.1 (4.7)	14.9 (3.5)
Percentage of predicted	119.0 (29.6)	121.8 (30.0)	105.7 (23.8)

[a]Means (standard deviations) are shown.

Table 3. Correlations between aspects of functional muscle strength, skeletal muscle mass at L3 and muscle index L3[a]

	Skeletal muscle mass L3		Muscle Index L3	
	r	95% CI	*r*	95% CI
Skeletal muscle mass L3	1	-	0.87	0.83 to 0.91
Right handgrip strength	0.68	0.53 to 0.79	0.55	0.36 to 0.68
Left handgrip strength	0.68	0.55 to 0.79	0.54	0.37 to 0.68
Maximal inspiratory pressure	0.62	0.46 to 0.73	0.55	0.38 to 0.67
Maximal expiratory pressure	0.56	0.42 to 0.68	0.48	0.33 to 0.64
30 second chair stand test	0.35	0.17 to 0.51	0.45	0.28 to 0.59

[a] Pearson correlation coefficients are significant at a $P \leq .01$ level (2-tailed), *r*; Pearson correlation coefficient

Results from linear regression analysis showed that the regression coefficients [95% CI] of right HGS (0.92 [0.29 to 1.54]), left HGS (1.02 [0.36 to 1.67]), MIP (0.26 [0.11 to 0.42]), MEP (0.15 [0.04 to 0.27]) and 30CST (1.53 [0.58 to 2.48]) were each significantly associated with skeletal muscle mass area at L3, adjusted for age, height, weight and gender.

Multiple backward regression analysis showed that gender, weight, age, left HGS and MIP were all independently associated with muscle surface area at L3 (Table 4). All these variables together explained 66% of the variability (R^2) in muscle surface area at L3 ($P < .01$).

Table 4. Results after multiple backward linear regression analysis of functional muscle strength on muscle surface area (N = 93)

Exploratory variable	Regression coefficient (95% CI)	*P*-value[a]
Gender	17.93 (2.05 to 33.82)	.03
Weight	0.71 (0.39 to 1.02)	< .01
Age	-0.48 (-0.91 to -0.04)	.02
Left HGS	0.79 (0.14 to 1.44)	<.01
MIP	0.23 (0.08 to 0.38)	< .01

Abbreviations: HGS, handgrip strength; MIP, maximal inspiratory pressure. [a]$P < .05$ is considered significant.

DISCUSSION

In this study we investigated the relation between muscle mass and muscle strength in patients with esophageal cancer awaiting esophagectomy, before neoadjuvant chemoradiation. The study results show a significantly high association between muscle mass on CT-scan and muscle strength, expressed as right and left HGS, MIP, MEP and 30CST.

To our knowledge, this is the first study that showed an independent association between aspects of muscle strength and muscle mass in patients with esophageal cancer awaiting surgery, corrected for clinical characteristics. Patients with esophageal cancer are likely to develop a loss of muscle mass and weight, eventually leading to loss of muscle function and subsequently decreased functional performance and poor long-term outcome.[4] Previous studies have mainly reported on functional outcome measures related to sarcopenia. Cruz-Jentoft et al.[9] provided an overview of measurable variables and their cut-off points for sarcopenia. For example, muscle strength estimated by HGS lower than 30 kilograms for men and 20 kilograms for women was considered as an indirect measure for sarcopenia. The direct relation with muscle mass was, however, lacking.

Only dual x-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI) are able to measure muscle mass directly. Despite its accuracy, these technologies are very expensive or they inflict high radiation exposure.[16,17] Therefore, we need methods to easily and rapidly assess muscle mass in a clinical setting with minimal patient burden to identify patients with decreased muscle mass. This selected population then may benefit from a tailored physiotherapeutic and nutritional treatment regimen to prevent them from functional decline.[9,35] These treatment programs should contain progressive resistance exercise training leading to an increased muscle protein mass, maximal voluntary muscle strength and muscle fiber hypertrophy.[36]

In our opinion, the main strength of this study is that physiotherapists could use the results to predict muscle mass based on muscle strength and its functional consequences in preoperative patients with esophageal cancer.[10,15] This study has some limitations. Although the association between muscle strength and muscle mass is obvious, we cannot use the results to predict sarcopenia.

First of all, despite the reported prevalence of sarcopenia in preoperative patients with esophageal cancer, only 2 male patients (2%) in our cohort were sarcopenic.[4,14,17]

One of the main reasons for this low amount of sarcopenic patients could be that we only analyzed patients in this study that agreed to have their muscle strength measured preoperatively. This group of included patients (N = 125) was smaller than the total amount of patients that was indicated for curative-intent surgery (N = 226). That could have caused a selection of relatively healthy patients. However, additional analysis of the patients not included in this study showed no additional cases of sarcopenia.

Second, there are still concerns in the conceptualization of sarcopenia leading to various definitions and cut-off values, which may have led to an underestimation of sarcopenic patients in this study cohort.[37] Recent research suggested that not only changes in skeletal muscle mass, but also ectopic fat infiltration in skeletal muscle (myosteatosis) negatively affects muscle function and seems to interact with sarcopenia. However, with CT it is not possible to directly measure the lipid content or detect the location of intramyocellular and extramyocellular fat tissue.[35]

Third, while each variable was independently associated with muscle mass, there is still 34% of the variability unexplained. Besides the lack of physical activity and muscle strength, also protein metabolism and nutrition explain the loss of muscle mass.[36] Prolonged metabolism due to aggressive tumor biology leads to systemic inflammation and consecutively to muscle wasting.[38] We did not take these mechanisms into account in this study and should be subject of further studies.

CONCLUSIONS

This study contributes to the physiotherapeutic assessment of muscle function in relation to muscle mass and the possible functional consequences, as well as perspectives for tailored functional muscle training in preoperative patients with esophageal cancer. For future research, we should further investigate the predictive value of muscle strength for the presence of sarcopenia and the functional consequences in a cohort of both sarcopenic and non-sarcopenic patients, taking the continuous developments of defining and conceptualizing sarcopenia into account.

If physiotherapists are able to identify patients who are at risk for decreased muscle function and eventually sarcopenia, it allows them to provide these high-risk patients with a physiotherapeutic intervention to increase muscle mass and muscle strength, which may subsequently improve postoperative recovery and functional outcome.

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Chapter 5

The effectiveness of physiotherapy with telerehabilitation in surgical patients: a systematic review for intervention studies and meta-analysis

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ABSTRACT

Background: Over the last few years, telerehabilitation services have developed rapidly, and patients value benefits such as reduced travelling barriers, flexible exercise hours, and the possibility to better integrate skills into daily life. However, the effects of physiotherapy with telerehabilitation on postoperative functional outcomes compared with usual care in surgical populations are still inconclusive.

Objectives: To study the effectiveness of physiotherapy with telerehabilitation on postoperative functional outcomes and quality of life in surgical patients.

Data sources: Relevant studies were obtained from MEDLINE, EMBASE, CINAHL, the Cochrane Library, PEDro, Google Scholar and the World Health Organization International Clinical Trials Registry Platform.

Study selection: Randomized controlled trials, controlled clinical trials, quasi-randomized studies and quasi-experimental studies with comparative controls were included with no restrictions in terms of language or date of publication.

Data extraction and synthesis: Methodological quality was assessed using the Cochrane risk of bias tool. Twenty-three records were included for qualitative synthesis. Seven studies were eligible for quantitative synthesis on quality of life, and the overall pooled standardized mean difference was 1.01 (95% confidence interval 0.18 to 1.84), indicating an increase in favor of telerehabilitation in surgical patients.

Limitations: The variety in contents of intervention and outcome measures restricted the performance of a meta-analysis on all clinical outcome measures.

Conclusions: Physiotherapy with telerehabilitation has the potential to increase quality of life, is feasible, and is at least equally effective as usual care in surgical populations. This may be sufficient reason to choose physiotherapy with telerehabilitation for surgical populations, although the overall effectiveness on physical outcomes remains unclear.

INTRODUCTION

Delayed postoperative recovery is one of the main problems after surgery.[1] Postoperative complications contribute highly to postoperative morbidity, and may lead to increased length of hospital stay and mortality, and reduced cost-effectiveness.[2-4] In surgical patients, handgrip strength, inspiratory muscle strength, physical activities and quality of life (QoL) are risk factors for postoperative complications and poor postoperative functional recovery.[5,6] Physiotherapists play an important role in reducing and preventing the decrease in physiological and functional capacity due to surgery by physical exercise training, and maintenance of physical activity levels over the pre- and postoperative course. These interventions are potentially effective for postoperative functioning.[7]

Health systems are currently engaged in a process of innovation to improve efficacy and efficiency in healthcare services.[8,9] Telerehabilitation is one of these developments, defined as *'the delivery of rehabilitation services to patients at a distance using information and communication technologies'*.[10] Telerehabilitation may contain assessment, education, monitoring and exercise interventions.[9,10] Over the last few years, telerehabilitation services have developed rapidly, and have the potential to be a more cost-effective alternative for outpatient assessment and treatment in hospital due to the ability to reach people in remote areas or at home. Telerehabilitation interventions have been used with success in areas of preventive care and management of chronic diseases, where patients positively valued benefits such as reduced travelling barriers, flexible exercise hours and the possibility to better integrate skills into daily life. Telerehabilitation interventions decrease travelling costs, are significantly less time consuming and are generally more convenient.[11] People also have the opportunity to train more intensively than is possible at a healthcare institution. The feasibility and acceptability of such technology have demonstrated significant patient and clinician satisfaction and improvements in QoL.[9,12,13] Physiotherapy or exercise interventions can be streamed through telerehabilitation, and are valuable in the pre- and postoperative phase for surgical patients.

There is evidence showing the positive effects of physiotherapy with telerehabilitation on clinical outcomes in cancer patients, cardiac patients, and patients with musculoskeletal disorders and depression.[14,15] Moreover, the effects of telerehabilitation on QoL seem to be promising.[16] How- ever, research that demonstrates the effects of physiotherapy with telerehabilitation on postoperative functional outcomes and QoL compared with conventional care in surgical populations is still inconclusive.[16]

Therefore, this systematic review aimed to study the effectiveness of physiotherapy with telerehabilitation on postoperative functional outcomes and QoL in surgical patients. The secondary objective was to determine whether telerehabilitation in surgical patients increased patient satisfaction.

METHODS

Data sources and searches

MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL), PEDro (www.pedro.org.au), Google Scholar (http://scholar.google.com) and the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp) were searched for eligible studies following the Cochrane Handbook for Systematic Reviews of Interventions.[17] Grey literature was searched using Open Grey (www.opengrey.eu). The following keywords and Medical Subject Headings (MeSH) combined with Boolean operators were used: 'Physical Therapy Modalities'[Mesh] OR 'Exercise Therapy'[Mesh] OR physiotherap*[tiab] OR exercise*[tiab] AND 'Telemedicine'[MAJR] OR 'Telecommunications'[MAJR] OR telehealth[tw] AND 'Surgical Procedures Operative'[MeSH] AND randomized controlled trial[pt] OR controlled clinical trial[pt]. All databases were searched from their inception to November 2016. Appendix A shows the full electronic search.

The references of included studies were checked for other relevant publications in order not to miss any unpublished or ongoing trials. Also, the proceedings and developments of the American Telemedicine Association were followed with care.

Study selection

Randomized controlled trials, controlled clinical trials, quasi-randomized studies and quasi-experimental studies with comparative controls were included with no restrictions in terms of language or date of publication.

Adults aged > 18 years with an indication for thoracic, upper abdominal or orthopedic surgery were included in this review.

Studies on telerehabilitation were included if the intervention contained aspects of physical exercise or exercise therapy combined with health education or intentions to change health-related behavior. All modalities of the pre- and postsurgical intervention (type, duration, frequency and intensity of the treatment strategies) were taken into consideration. The control intervention was considered as usual care, face-to-face contact or no care. Telerehabilitation that combined incidental face-to-face contact to clinically assess patients on aspects of functional status were included if the intervention was conducted with telerehabilitation.

Studies were excluded if the intervention did not contain physical exercise or exercise therapy via telerehabilitation.

The functional outcome measures were based on the International Classification of Functioning, disability and health (ICF).[18] In this framework, health and health-related components are classified in domains, expressed as body functions and structures, activities and participation, and personal and environmental factors.[19]

Studies in the different ICF domains that measured any postoperative functional outcome, which represent the effectiveness of telerehabilitation programs, were included in this review. In the domain of body functions and structures, pain, fatigue, joint range of motion, muscle strength, coordination, stamina, and inspiratory and expiratory muscle strength were measured, whereas in the activity and participation domain, limitations in activities of daily living, mobility, employment, education, social and vocational activities, and any other patient-reported outcome measures were measured.[20]

Measurements of QoL performed with questionnaires were also taken into account. Secondary outcome measures included patient satisfaction.

Data extraction and quality assessment

The titles and abstracts of articles identified by the search strategy were screened by two authors (ME and TV), and when there was insufficient information for inclusion, the full text article was obtained. If necessary, the corresponding authors were contacted for additional information. Reasons for exclusion were recorded.

Two authors (ME and TV) extracted study data independently and recorded them on a modified data extraction form for intervention studies according to the guidelines of the Cochrane Collaboration.[21] In cases of disagreement, a third author (MS) was consulted to make a final decision.

Two authors (ME and TV) assessed the risk of bias for each included study independently using the Cochrane Collaboration's tool for assessing the risk of bias (Figure A, see online supplementary material).[22] Discrepancies were resolved through discussion. In cases of disagreement, a third author (MS) was consulted to make a final decision.

Data synthesis and analysis

A meta-analysis was conducted using Cochrane Review Manager (RevMan) software if studies were similar in terms of included patients, intervention and outcome measures. The overall effect size was calculated using the standardized mean difference because the data of all included studies were continuous. Heterogeneity with the I^2 statistic was assessed, with a percentage 40% representing no heterogeneity of importance and a percentage 75% representing considerable heterogeneity.[23] A random effects model was used, taking into account the heterogeneity of patients across studies. If meta-analysis was not possible, a narrative overview of the findings was presented, including tabular summaries of extracted data.

Where data were missing, the authors attempted to contact the study authors. An intention-to-treat analysis was conducted where possible. Otherwise, data were analyzed as reported. Loss to follow-up information was documented and assessed as a source of potential bias. Subgroup analysis has been executed on type of surgery, time of intervention (pre- or postoperatively), type and duration of intervention (mono- or multidisciplinary, consultation, monitoring, training), type of communication technology, the healthcare provider and the method of implementation (as new care for something that did not exist before or in addition to existing care). Due to the small number of studies included in each subgroup, heterogeneity was not assessed, and it was not possible to assess reporting bias using funnel plots. Selective outcome reporting was assessed using the Cochrane risk of bias tool.[23]

RESULTS

Study selection

The search strategy yielded 1031 results. After removing duplicates, 799 records remained and were initially screened. Fifty-five records were found to be eligible for full screening, of which 23 records were included for qualitative synthesis (Figure 1). Full details of these studies can be found in Table 1. Nineteen of the included studies were randomized controlled trials [8,24-41], of which two were non-inferiority studies[33,34], two were pilot studies[25,38] and one was a feasibility study.[31] Two studies had quasi-experimental designs with comparative controls[42,43], one was a prospective controlled trial[16], and one was a multisite, two-group experimental study with repeated measures.[44]

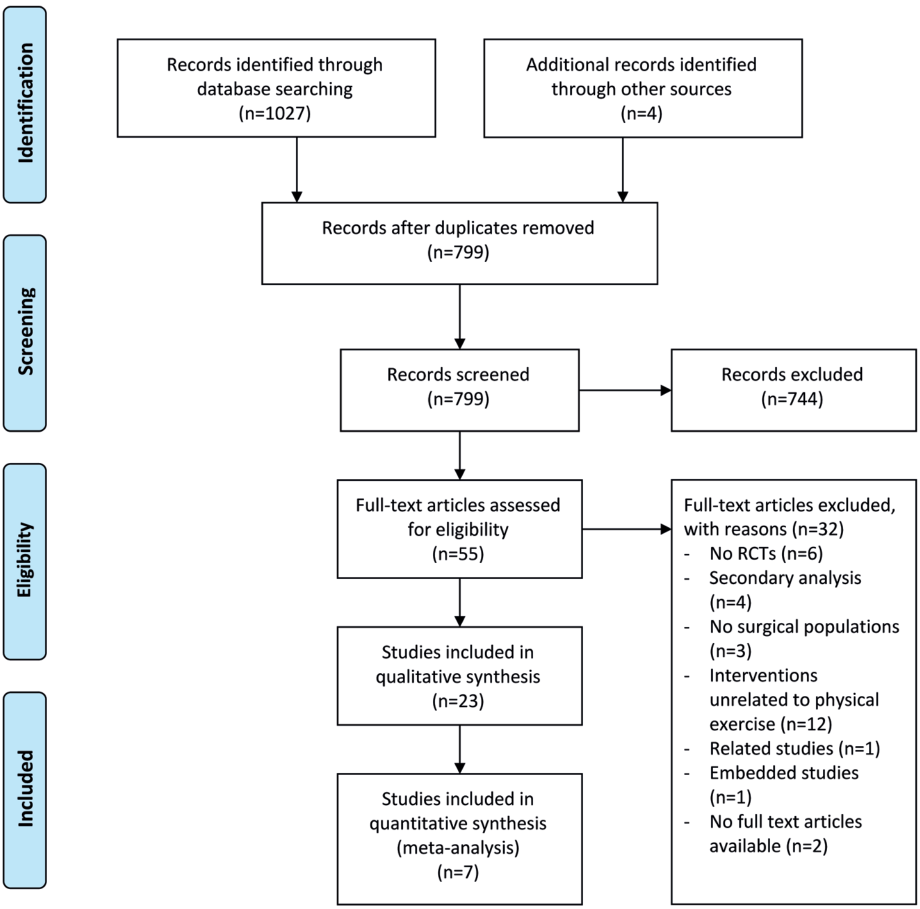

Figure 1. PRISMA flowchart

Table 1. Summary of study characteristics

Study	Design	Objective	Participants			Intervention
			N (male/ female)	Characteristics	I: n [age (SD)] C: n [age (SD)]	Treatment
CARDIAC SURGERY						
Arthur 2002	RCT	Effectiveness of a monitored, home-based programme	242 (197/45)	Patients after CABG surgery	I: 120 [64.2 (9.4)] C: 122 [62.5 (8.8)]	Home: exercise consultations and exercise training
Barnason 2006	Pilot RCT	Effectiveness of a home communication intervention	50 (28/22)	Patients after CABG surgery	Not specified	Home health care plus communication intervention
Hartford 2002	RCT	Effectiveness of a telephone based intervention	131 (113/ 18)	Patients after CABG surgery and their partners	I: 63 [62.7 (9.1)] C: 68 [63.0 (8.2)]	Information and support by telephone
Kortke 2006	Quasi-experimental design with comparative controls	Evaluation of a telemedically monitored intervention	170 (157/13)	Patients after cardiac surgery	I: 100 [57.6 (8.4)] C: 70 [55.2 (1.2)]	An ambulatory rehabilitation with telemedical monitoring
Lee 2013	RCT	Effectiveness of home-based exercise with wireless monitoring	55 (44/11)	Patients with a diagnosis of ACS and having undergone PCI	I: 26 [54.3 (8.9)] C: 29 [57.8 (7.5)]	Wireless monitored home based exercise training

Control	Outcomes: Primary	Outcomes: Secondary	Results[a]	Conclusion
Hospital: supervised exercise sessions	Peak oxygen uptake	· QoL (SF36) · Social support	· Peak VO_2 was not significant · Social support 6 months: 36.0 (SD 4.9) vs 34.6 (SD 6.4); *P* = *.05* · QoL: 51.2 (SD 6.4) vs 48.6 (SD 7.1); *P* = *.004*	Low-risk CABG surgery patients may be served as well or better with a monitored, home-based exercise programme than with an institution-based programme
Home health care	· Physiologic Functioning · Psychosocial Functioning (MOS-SF36)	Not specified	· General health function: F 8.41, *P* = *<0.01* · Physical: F 9.42, *P* = *< 0.001* · Role-physical: F 5.74, *P < .05* · Mental health function: F 7.97, *P < 0.001*	Findings demonstrate the potential benefit of using home communication intervention to augment outcomes of patients undergoing CABG
Usual care	Anxiety (BAI)	n/a	Greater than minimal anxiety: (39% vs 57%) (Chi^2 = 4.174, df = 1, *P < .041*)	The Intervention effect is most present in the early period after discharge– the time most affected by reduced lengths of stay
Regular conventional in-hospital rehabilitation	· Physical performance · QoL (SF36)	· Complication · Costs	All items had increased with statistical significance in favor of the intervention	An ambulatory rehabilitation improves physical performance, QoL, and is safe and cheap
Ordinary medical therapy, diet control, and exercise at home on their own	· Exercise Capacity · QoL (SF36)	Not specified	· Exercise capacity: increase in metabolic equivalent of the tasks (+2.47 vs +1.43, *P* = *.021*) maximal exercise time (+169.68 vs +88.31 second, *P* = *.012*) · QoL: +4.81 vs +0.89, *P* = *.022*	The finding that patients were able to reduce their anxiety by using the wireless monitoring equipment during exercise at home is considered clinically meaningful

Table 1. Continued

Study	Design	Objective	Participants			Intervention
			N (male/ female)	Characteristics	I: n [age (SD)] C: n [age (SD)]	Treatment
Tranmer 2004	RCT	Effectiveness of a telephone based intervention	200 (152/48)	Patients after cardiac surgery	I: 102 [63.8 (38.7-87.1)][c] C: 98 [66.6 (41.9-82.6)][c]	Active and on-going follow-up via telephone at home
Rollman 2009	RCT	Effectiveness of a telephone-based intervention	302 (177/125)	Patients after CABG surgery with depression	I: 150 [64 (10.8)] C: 152 [64 (11.2)]	Telephone contact with a workbook
ORTHOPAEDIC SURGERY						
Eriksson 2009	Quasi-experimental designs with comparative controls	Exploration of video communication in home rehabilitation	22 (5/17)	Patients after shoulder hemi-arthroplasty replacements	I: 10 [70 (53–85)][c] C: 12 [73 (50–86)][c]	Supervised telemedicine at home
Jones 2011	RCT	Efficacy of a telephone-based Intervention	102 (40/62)	Patients after arthroscopy	I: 52 [45.9 (13.3)] C: 50 [47.1 (12.2)]	Intervention by telephone
Langford 2015	Randomized controlled feasibility study	Feasibility of a telephone-based intervention	30 (11/19)	Community-dwelling adults after recent hip fracture	I: 15 [83 (8)] C: 15 [82 (10)]	Usual care plus an in-hospital educational session

	Outcomes		Results[a]	Conclusion
Control	Primary	Secondary		
Preoperative and discharge preparation	· QoL (SF36) · Symptom Distress (MSAS)	· Utilization of health care · Health care contacts · Home care use	· Physical component score: MD 0.04 (95% CI –1.99 to 2.08) *P = .97* · Mental component score: MD–1.25 (95% CI, –4.54 to 2.04) *P = .45* There were no significant differences in QoL and symptom distress	The provision of a telephone-based intervention following cardiac surgery is feasible
No treatment advice .	Generic Mental QoL (SF36)	· Mood symptoms · Physical QoL · Functioning · Hospital readmissions	Generic Mental QoL: Between-group difference: 3.2 (95% CI 0.5–6.0), *P = .02*	Telephone-delivered collaborative care for post-CABG depression can improve QoL, physical functioning, and mood symptoms at 8-month follow-up
Physiotherapy at the local treatment center	· Shoulder Pain (VAS) · ROM · Function (SRQ) · QoL (SF36)	n/a	· Shoulder Pain: 7 (95% CI 3–10) vs 2 (95% CI -1–5) *P = < 0.001* · Shoulder function: 41 (26-54) vs 11(3-22) P < .001	The telemedicine group improved significantly in terms of shoulder pain, mobility and function as well as in QoL
Standard postoperative teaching	· Symptom Distress (SDS) · Functional health (MOS-SF36)	Not specified	· Symptom distress: 1 week post-surgery F = 7.2, *P < 0.0001* · Functional Health: - Physical health scores F = 2.9, *P = 0.016* - Mental health scores F = 4.6, *P = 0.001*	Telephone calls during the immediate postoperative period resulted in improved patient outcomes
Usual care plus an in-hospital educational session with educational manual and videos	· Recruitment rate · Participant retention	QoL (EQ5D-5L)	· EQ-VAS 1.28 (95% CI -12.95 to 13.54)	This study highlights the feasibility of telephone coaching to improve adherence to mobility recovery goals

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Table 1. Continued

Study	Design	Objective	Participants			Intervention
			N (male/ female)	Characteristics	I: n [age (SD)] C: n [age (SD)]	Treatment
Latham 2014	RCT	Effectiveness of a telephone-based home exercise programme	232 (72/160)	Patients after hip fracture	I: 120 [77.2 (10.2)] C: 112 [78.9 (9.4)]	Home exercise programme with telephone calls
Moffet 2015	Multicenter non-inferiority randomized clinical trial	Effectiveness of in-home telerehabilitation	205(100/105)	Patients with primary total knee arthroplasty	I: 104 [65 (8)] C: 101 [67 (8)]	Physical therapy intervention with telerehabilitation.
Piqueras 2013	RCT	Effectiveness of interactive virtual telerehabilitation	181 (50/ 131)	Patients with primary total knee arthroplasty	I: 90 C: 91 I + C: 181 [73.3 (6.5)]	Interactive virtual telerehabilitation
Russell 2011	Non inferiority RCT	Efficacy of Internet-based telerehabilitation	65 (32/33)	Patients with primary total knee arthroplasty	I: 31 [66.2 (8.4)] C: 34 [69.6 (7.2)]	Internet-based telerehabilitation
Tousignant 2011	RCT	Efficacy of telerehabilitation at home	41[b]	Patients with primary total knee arthroplasty	I: 21 [66 (10)] C: 20 [66 (3)]	Telerehabilitation with videoconferencing

	Outcomes		Results[a]	Conclusion
Control	Primary	Secondary		
Nutrition education and telephone calls	Function (SPBB)	· Self-efficacy · Adverse events · Exercise adherence	· SPPB: score change from baseline at 6 months: 0.8 (95% CI 0.4 to 1.2), *P < .001*	The use of a home-based functionally oriented exercise programme resulted in modest improvement in physical function at 6 months after randomization
Physical therapy with Home Visits.	· Gain from baseline to follow-up (WOMAC)	· KOOS · Functional and strength tests · Knee range of motion	· WOMAC total score, adjusted for baseline: 22% (95% CI –6% to 2%)	Our results demonstrated the no inferiority of in-home telerehabilitation and support its use as an effective alternative to face-to-face service after hospital discharge
Standard clinical protocol of TKA rehabilitation	Active range of knee movement.	· Muscle strength · Walk speed · Pain · WOMAC	Change in baseline to 2 weeks: · Knee extension: 0.2 (SD 2.8) vs 0.9 (SD 3.7); *P = 0.045* · Knee flexion: 8.53 (SD 6.56) vs 7.71 (SD 6.89); *P = .298*	The use of interactive virtual telerehabilitation is equally as effective as conventional treatment
Rehabilitation in an outpatient physical therapy department	· WOMAC · Pain · Stiffness · Function	PSFS, TUG, pain intensity, knee flexion and extension, quadriceps muscle strength, limb girth measurement, gait	Change in Baseline to 6 weeks: · Global: 1.10 (95% CI 0.14 to 2.07), *P = 0.08* · Pain: 0.78 (95% CI –0.26 to 1.83), *P = .24* · Stiffness: 1.46 (SD 0.24 to 2.68), *P = .04* · Function: 1.07 (95% CI -0.01 to 2.14), *P = 0.18*	Telerehabilitation intervention achieved physical and functional outcomes at six weeks that were not inferior to face-to-face therapy
Usual home care services.	· WOMAC · QoL (SF36)	Not specified	· WOMAC: 8.1, (*P = .047* in favor of C) · SF36: Less Bodily pain C > I, *P = .013*, Better physical functioning C > I, *P = .019*	Home telerehabilitation is as effective as usual care in after two months of treatment

Table 1. Continued

Study	Design	Objective	Participants			Intervention
			N (male/ female)	Characteristics	I: n [age (SD)] C: n [age (SD)]	Treatment
ONCOLOGICAL SURGERY						
Van den Brink 2007	Prospective controlled trial	Effectiveness of telemedicine	163 (118/ 45)	Patients after surgery for head and neck cancer	I: 35 [59 (38-75)][c] C: 128 [61 (29-84)][c]	Electronic health information support
Coleman 2005	Multisite, two-group experimental study with repeated measures	Effectiveness of a telephone-based support intervention	106 (0/106)	Patients after breast cancer	I: 54 (age not specified) C: 52 (age not specified)	Telephone social support and education
Eakin 2011	RCT	Effectiveness of a telephone-based exercise intervention	143 (0/ 143)	Patients after breast cancer	I: 73 [51.7 (9.0)] C: 70 [54.1 (8.7)]	Telephone calls
Hawkes 2013	A two-armed prospective RCT	Effectiveness of a telephone-based intervention	410 (221/189)	Patients after colorectal cancer	I: 205 [64.9 (10.8)] C: 205 [67.8 (9.2)]	Telephone-delivered health care sessions

	Outcomes		Results[a]	Conclusion
Control	Primary	Secondary		
Standard care	QoL	Not specified	Change in Baseline to 6 weeks · State anxiety: -4.53 (SD 1.82), *P = .01* · Fear: -2.59 (SD 1.05), *P = .02* · Physical self-efficacy: 2.39 (SD 1.07), *P = .03* · General physical complaints: -1.27 (0.52), *P = .02*	The intervention improved some components of QoL more quickly than standard care, although they ultimately reached the same level of improvement
Telephone contact only	· Mood state (POMS) · Cancer related worry · Relationships · Loneliness · Symptom experience	Not specified	No statistically significant differences in outcomes were found at the end of any phase of the study	The mailed educational resource kit alone appeared to be as effective as the telephone social support in conjunction with the mailed resource kit
Participation in all study assessments but no intervention contacts	· QoL (FACT-B+4) · Fatigue (FACIT) · Anxiety (STAI) · Function (DASH)	Patient satisfaction	Change in baseline to 6 months: · QoL: 1.5 (95% CI −3.6 to 6.6), *P = .549* · Fatigue: 2.0 (95% CI −1.4 to 5.3), *P = .233* · Anxiety: −0.3 (95% CU −5.2 to 4.6), *P = .891* · Function: −0.21 (95% CI −3.7 to 3.3), *P = .902*	Results provide strong support for feasibility and modest support for efficacy of telephone-based interventions
Educational brochures	· Physical activities · QoL (SF36) · Cancer-related fatigue	· Weight management · Dietary intake	Change in baseline to 6 months: · MVPA: 11.5 (95% CI -18.8 to 41.9), *P = .457* · Physical component summary: 0.0 (95% CI -1.8 to 1.8), *P = .991* · Mental component summary: 0.7 (95% CI -1.1 to 2.5), *P = .455*	Telephone-delivered interventions are feasible and can improve some important health outcomes compared with usual care

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Table 1. Continued

Study	Design	Objective	Participants			Intervention
			N (male/ female)	Characteristics	I: n [age (SD)] C: n [age (SD)]	Treatment
Ligibel 2012	Multicenter pilot study, randomized 1:1 study	Feasibility of a telephone-based exercise intervention	121 (9/ 112)	Patients after breast, colon or rectal cancer	I: 61 [53.1 (10.8)] C: 60 [55.5 (10.6)]	Telephone-based intervention
Pinto 2013	RCT	Effectiveness of a telephone-based intervention	192 (0/192)	Patients after breast cancer	I: 106 [56.1 (9.9)] C: 86 [55.9 (9.9)]	Health care advice plus telephone-counselling
Pinto 2013	RCT	Effectiveness of a telephone-based intervention	46 (20/26)	Patients after colorectal cancer	I: 20 [59.5 (11.2)] C: 26 [55.6 (8.24)]	Telephone based physical Activity exercise
Vonk Noordegraaf 2014	RCT	Effectiveness of an eHealth intervention	215 (0/215)	Patients after hysterectomy and/or laparoscopic adnexal surgery	I: 110 [43.5 (7.8)] C: 105 [43.2 (8.5)]	eHealth programme

Abbreviations: CABG, coronary artery bypass graft; I, intervention; C, control; FU, follow up; MD, mean difference; HR, hazard ratio; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CR, cardiac rehabilitation; APN, advance practice nurse; QoL, quality of life; TKA, total knee arthroplasty; MVPA, moderate-to-vigorous-intensity physical activity; PA, physical activities; MOS, medical outcomes study; SF-36, short form health survey; BAI, Beck anxiety inventory; MSAS, Memorial symptom assessment Scale; VAS, Visual analogue scale; SRQ, shoulder rating questionnaire; SDS, symptom distress scale; SPBB, short physical performance battery; KOOS, knee injury and osteoarthritis outcome score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PSFS, patient specific functional Scale;

	Outcomes		Results[a]	Conclusion
Control	Primary	Secondary		
Routine care	Physical activity	· Fitness, · Physical functioning · Fatigue · Exercise self-efficacy	Change in Baseline to 16 weeks: · Physical activity: 54.5 (SD 142.0) vs 14.6 (SD 117.2), *P = .13*	A telephone-based exercise intervention has the ability to improve fitness and physical functioning
Health care advice plus telephone calls	Seven-Day Physical Activity Recall	· Motivational Readiness for PA · MOS SF36 · FACT-F	Change in baseline to 6 months: · 7-day PAR: 32.16 (95% CI 3.06 to 61.26) · SF36: -0.35 (95% CI -0.46 to -0.23) · FACT-F: 1.89 (95% CI -0.54 to 4.33)	Health care advice plus telephone-counselling improved PA among breast cancer patients at 3 and 6 months
Contact control to monitor problems	The effect on self-reported PA and fitness	· Motivational readiness for PA · Fatigue · Self-reported physical functioning · QoL (SF36)	Change in baseline to 6 months: · 7-day PAR: 1.18 (95% CI 0.81 to 0.149) · SF-36: 0.08 (95% CI 0.24 to 0.731)	A telephone-mediated home based intervention improved PA, motivational readiness and fitness levels
Access to a control website	Return to work	· QoL (SF36) · General recovery · Pain intensity	· Return to work: HR 1.43 (95% CI 1.003 to 2.040), *P = .048* · QoL: 1.43 (95% CI 1.003 to –2.040), *P = .048*	The use of eHealth resulted in a faster return to work, with a higher QoL

TUG, timed up and go; POMS, profile of mood states; STAI, state-trait anxiety inventory; DASH, disabilities of the arm, shoulder and hand; FACIT, functional assessment of chronic illness therapy; 7-day PAR, 7-day physical activity recall scale; FACT-B+4, functional assessment of cancer therapy-breast; FACT-F, functional assessment of cancer therapy scale-fatigue; n/a, not applicable

[a] Results are presented as Interventions versus control, unless otherwise stated

[b] This study did not specify the number of male/ female participants

[c] Results are presented as median (range)

Study characteristics

This review included 3424 patients in total. Overall, 56% (N = 1910) were female. The lowest mean age reported in any of the included studies was 43.2 [standard deviation (SD) 8.5] years and the highest reported mean age was 83.0 (SD 8.0) years.

Among the 23 included studies, seven studies reported on cardiac surgery (n = 1150)[24,26-29,42], eight studies reported on orthopedic surgery (n = 878) [8,30-35,43], and eight studies reported on oncological surgery in the abdominal, thoracic and cervical regions (n = 1396).[16,36-41,44]

A variety of inclusion and exclusion criteria have been reported. The majority of studies included patients who were discharged home or to short-term rehabilitation, who had a telephone or access to high-speed internet services, and had no communication disorders. Reported exclusion criteria were significant cognitive deficits and any concomitant medical conditions that influenced rehabilitation or precluded safe participation in exercises.

Type of interventions

The majority of studies implemented the intervention as a new care module for something that did not exist previously (n = 17)[8,24,26,27,29,30,32-38,40,42-44], and six studies implemented the intervention in addition to existing care. All interventions started after surgery, apart from the study by Vonk Noordegraaf et al.[40] that started 4 weeks before surgery. Interventions with telerehabilitation were aimed at physical exercise training (n = 10) or at education, information and support (n = 13).

Physiotherapists, exercise specialists, exercise physiologists or physicians provided all interventions aimed at physical exercise, while interventions aimed at education, information and support were predominantly provided by nurses. The type of telerehabilitation technology used was a telephone in 14 studies, videoconferencing in three studies, the internet in three studies, and a specific e-Health technology device in three studies. Considerable variation was seen in duration, type, frequency and intensity of the interventions. The duration ranged from 3 days to 13 months, with a mean of 3.71 (SD 2.97) months. The frequency of telerehabilitation sessions varied from once per day to once per month, with an intensity of 10 minute to 1 hour per session. All patients were measured at baseline before surgery and after the intervention, and many studies undertook one or two follow-up measurements to evaluate the intervention. Intervention details are shown in Table 2.

Types of outcome measures

The main findings from the included studies are described in Table 1.

Physical outcome measures

Physical outcome measures varied between studies and covered different domains of the ICF.[18] Outcome measures related to the ICF domain body functions and structures were related to the type of surgery: peak oxygen uptake[24], exercise capacity[45] and physical functioning[25,42], were frequently reported in cardiac surgery, whereas joint pain[34,43], range of motion[8,33,34] and stiffness were frequently reported in orthopaedic surgery. Outcome measures related to the ICF domain activities and participation were less dependent on type of surgery. Daily activity levels were often assessed with questionnaires such as the short physical performance battery[32], the 7-day physical activity recall scale[39] and motivational readiness for physical activities.[39,41]

Psychological outcome measures

Outcome measures of interventions aimed at education, information and support were mainly assessed using questionnaires, such as depression (Hamilton rating scale for depression)[29], illness-related fear and anxiety (Beck anxiety inventory)[46], social support, psychological functioning (medical outcomes study short form health survey)[25,30,47], symptom distress (Memorial symptom assessment scale)[28,30] and mood state (profile of mood state).[44]

Quality of life

QoL was investigated in 15 studies as a primary or secondary objective with the 36-item short form survey (SF36) [24,25,28-30,35,37,39-41,43], the EQ5D-5L questionnaire[31] and the functional assessment of cancer therapy-breast.[36] One study used a self-developed questionnaire for QoL[16], and the questionnaire was not specified in one study.[27]

Patient satisfaction

Patient satisfaction was investigated in the study by Eakin et al.[36] as a secondary objective. Patient satisfaction ratings were very high, although the exact numbers related to usual care were not reported.

Table 2. Details of the interventions

Study reference	Type of technology	Pre-/ post-surgery	Care provider	Intervention
Arthur 2002	Telephone	Post	Exercise specialist	Exercise
Barnason 2006	Communication device	Post	Physician/ nurse content expert	Education/ information/ support
Coleman 2005	Telephone	Post	Oncology nurses	Education/ information/ support
Eakin 2011	Telephone	Post	Exercise physiologist	Exercise
Eriksson 2009	Videoconferencing	Post	Physiotherapist	Exercise
Hartford 2002	Telephone	Post	Nurse	Education/ information/ support
Hawkes 2013	Telephone	Post	Health coaches	Education/ information/ support
Jones 2011	Telephone	Post	Nurse	Education/ information/ support
Kortke 2006	Telemedical monitoring: not specified	Post	Physician	Exercise
Langford 2015	Telephone	Post	Physiotherapist	Education/ information/ support
Latham 2014	Telephone	Post	Physiotherapist	Exercise
Lee 2013	Telephone + wireless monitoring device	Post	Not specified	Exercise
Ligibel 2012	Telephone	Post	Behavioural counselors	Education/ information/ support
Moffet 2015	Internet	Post	Physiotherapist	Exercise
Pinto 2013	Telephone	Post	Oncologists and surgeons	Education/ information/ support
Pinto 2013	Telephone	Post	Research staff	Education/ information/ support
Piqueras 2013	IVT	Post	Physiotherapist	Exercise
Rollman 2009	Telephone	Post	Nurse care manager	Education/ information/ support/

Type	Duration	Frequency	Intensity	Outcome measurements
New care module	6 months	1 call p/2w	5 x p/w 1 hour	Baseline 3, 6 months FU
In addition to UC	12 weeks	1 x p/d	10 minutes	Baseline 6, 12 weeks FU
New care module	13 months	I:1 x p/w II: 1 x p/w III: 1 x p/2w IV: 1 x p/m	Not specified	Baseline 3,5,8 and 13 months FU
New care module	8 months	16 calls	15 to 30 minutes	Baseline 6, 12 months FU
New care module	8 weeks	2 to 3 x p/w	Not specified	Baseline 8 weeks FU
New care module	7 weeks	6 calls in total	20 to 60 minutes	Baseline Day 3, week 4, 8 FU
New care module	6 months	1 call p/2w	Not specified	Baseline 6, 12 months FU
New care module	72 hours	1 call p/d	Not specified	Baseline 72h, 1week FU
New care module	3 months	3 x p/w	30 minutes	Baseline 6, 12 months FU
In addition to UC	4 months	5 calls	Not specified	Baseline 4 months FU
New care module	6 months	3 x p/w	1 hour	Baseline 6, 9 months FU
New care module	12 weeks	1 call p/w	4 to 5 x p/w 50 minutes	Baseline 12 weeks FU
New care module	16 weeks	10 to 11 calls in total	30 to 45 minutes	Baseline 16 weeks FU
New care module	2 months	16	45 to 60 minutes	Baseline 2, 4 months FU
in addition to UC	12 weeks	2 to 5 x p/w	10 to 30 minutes	Baseline 3, 6, 12 months FU
in addition to UC	12 weeks	2 to 5 x p/w	10 to 30 minutes	Baseline 3, 6, 12 months FU
New care module	10 days	5 sessions in total	1 hour	Baseline 10 days, 3 months FU
New care module	8 months	Not specified	Not specified	2 weeks 2, 4, 8 months FU

Table 2. Details of the interventions

Study reference	Type of technology	Pre-/ post-surgery	Care provider	Intervention
Russell 2011	Videoconferencing	Post	Physiotherapist	Exercise
Tousignant 2011	Videoconferencing	Post	Physiotherapist	Exercise
Tranmer 2004	Telephone	Post	Nurse	Education/ information/ support
Van den Brink 2007	Internet	Post	Not specified	Education/ information/ support
Vonk Noordegraaf 2014	Internet	Pre and post	Not specified	Education/ information/ support

Abbreviations: FU, follow up; UC, usual care; IVT, interactive virtual telerehabilitation

Main outcomes

Evaluation of effects

Of all studies that investigated the effectiveness of physiotherapy with telerehabilitation on postoperative outcomes, 16 studies reported significant differences in favor of telerehabilitation for at least one functional outcome. Physical functioning measured with the medical outcomes study short form health survey increased significantly in the telerehabilitation group in the studies by Barnason et al.[25], Jones et al.[30] and Pinto et al.[41]

Physical activities measured with the 7-day physical activity recall scale increased significantly in the studies by Pinto et al.[39,41], while Ligibel et al.[38] and Hawkes et al.[37] were not able to find a difference.

Studies that investigated telerehabilitation in patients with orthopedic surgery reported a significant increase in knee extension in favor of telerehabilitation[8], while Eriksson et al.[43] found comparable improvements in shoulder function. Tousignant et al.[35] reported a significant decrease in pain in the telerehabilitation group, contrary to Russell et al.[34] who could not find a difference.

Mental health functions were positively affected by telerehabilitation in the studies by Barnason et al.[25] and Jones et al.[30], and Arthur et al.[24] reported a significant difference in social support.

Type	Duration	Frequency	Intensity	Outcome measurements
New care module	6 weeks	1 x p/w	45 minutes	Baseline 6 weeks FU
New care module	2 months	2 x p/w	Not specified	Baseline 2, 4 months FU
in addition to UC	5 weeks	6 calls in total	20 to 30 minutes	Baseline 5 weeks FU
In addition to UC	6 weeks	Not specified	Not specified	Baseline 6, 12 weeks FU
New care module	3 months	Not specified	Not specified	2, 6, 12 and 26 weeks

All studies came to the conclusion that exercise interventions with telerehabilitation had the ability to improve at least one of the functional outcome measures reported. Studies reported that telerehabilitation was feasible[26,36-38], not inferior to usual care[33,35] or equally as effective as usual care.[8,16,24,35,44]

QoL increased significantly in 10 studies[24,25,27,29,30,35,40-43] in favor of the intervention with telerehabilitation. Tranmer and Parry[28], van den Brink et al.[16] and Eakin et al.[36] did not find a difference in QoL between the intervention and control groups.

Meta-analysis

All included studies reported different types of interventions with telerehabilitation and different functional outcome measures, even after dividing the studies into three subgroups of patients (cardiac, orthopedic and oncological). Therefore, a meta-analysis on these outcomes was not appropriate. The authors were able to perform a meta-analysis on QoL because telerehabilitation is believed to have an effect on QoL in general.[16] Data from seven studies were sufficient to include for meta-analysis.[24,27,29-31,33,40] The overall pooled standardized mean difference for QoL for seven studies was 1.01 (95% confidence interval 0.18 to 1.84), indicating that QoL increased with telerehabilitation compared with usual care (Figure 2). The heterogeneity expressed with I^2 was high at 97%.

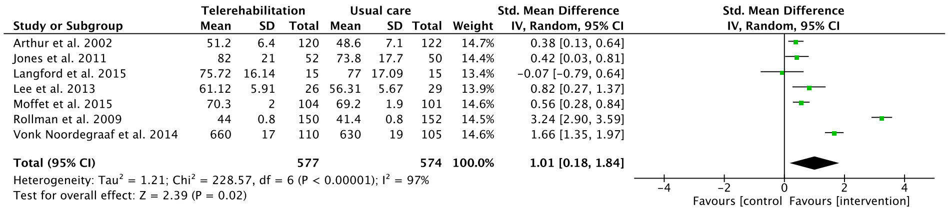

Figure 2. Forest plot of telerehabilitation interventions versus usual care with quality of life outcomes

Meta-analysis of standardized mean difference comparing QoL of participants receiving an intervention with telerehabilitation with control patients receiving usual care. The left side of the Forest plot indicates higher QoL levels in favor of the control intervention; the right side of the Forest plot indicates higher QoL levels in favor of the telerehabilitation intervention. Participants undergoing the telerehabilitation intervention demonstrated significantly higher levels in QoL compared with usual care.

Methodological quality of included studies

Standards of reporting varied considerably between studies. Random sequence generation was performed in 14 studies[8,24,25,28-30,32-37,40,44] and was lacking in two studies.[16,42] Allocation concealment appeared to be unclear in 10 studies[8,25-28,32,36,38,40,41], and selection bias could be present in three studies.[16,42,43] The majority of studies reported on blinding of outcome assessment, suggesting a low risk of detection bias. Incomplete outcome data were detected in seven studies[8,25,33,35,37,38,43] and were unclear in another seven studies[24,26,27,34,39,42,44], suggesting attrition bias. Selective reporting appeared to be present in four studies[16,35,37,44], which may have induced reporting bias. Other biases were not found between studies. A risk of bias summary and full details of individual studies can be found in Figures A and B (see online supplementary material).

DISCUSSION

This systematic review shows that physiotherapy with telerehabilitation is feasible and improves QoL in surgical populations, although the overall effectiveness on functional outcomes could not be determined.

The risk of bias assessment of the included studies was often high or unclear, which is a potential limitation of this review. Standards of reporting were not optimal across all included studies, with incomplete outcome reporting in seven studies. These methodological shortcomings are one of the reasons why a comparison of effectiveness between studies was not possible.

The majority of included studies (78%) investigated the effectiveness of telerehabilitation on more than one functional outcome measure, and reported a significant positive effect on at least one measure. However, none of the studies detected a significant positive effect on all outcome measures in favor of telerehabilitation. This is in line with the results of previously published systematic reviews focusing on the effectiveness of telerehabilitation in non-surgical populations. Kairy et al.[48] reported that most of the clinical outcomes in their included studies improved after telerehabilitation, but stated that there is still a need for more methodologically sound research to confirm its effectiveness. Wide variation was noted between the included studies in terms of type of intervention, duration, frequency and outcome measures. This heterogeneity made it inappropriate to pool data from different studies and investigate the overall pooled estimate of effect.[23]

The lack of overall significant evidence in favor of telerehabilitation could also be due to the fact that many studies used questionnaires to quantify outcome. In a review on the effectiveness of telerehabilitation in stroke patients, Laver et al.[10] stated that questionnaires often contain subscales with significant differences between the intervention and control groups, whereas the overall score does not differ.

This is the first systematic literature review to demonstrate that interventions with telerehabilitation have the potential to increase QoL in surgical populations. Van den Brink et al.[16] reported that despite the rarity of studies investigating telerehabilitation with QoL as an outcome measure, the results looked promising. Despite the high heterogeneity between studies leading to effects with large variation, a meta-analysis was still considered to be appropriate because QoL was measured with the same questionnaire in the different studies, and is not directly related to the type of patients or intervention provided.

Telerehabilitation has been shown to be a valuable tool in managing postoperative outcomes and functional progress in surgical patients.[32] Patients often deal with a temporary loss of mobility directly after surgery, and are confronted by integrated care from multiple health providers. Telerehabilitation allows patients to perform their exercises more frequently without extra face-to-face visits.[10,32,39,42,43] Therefore, these patients might benefit from a relief in burden of care and increased efficiency by providing them with telerehabilitation at home instead of conventional 'face-to-face' rehabilitation, leading to an increased perception of QoL. Kairy et al.[48] stated that telerehabilitation in patients with physical disabilities could lead to similar clinical outcomes compared with usual care, with possible positive effects on areas of healthcare utilization.

As restrictions in physical functioning of surgical patients are profound, physiotherapeutic interventions with telerehabilitation could be recommended to improve QoL after complex surgery.

On the basis of the secondary objective of this review, patient satisfaction was only reported in the feasibility study by Eakin et al.[36], where patient satisfaction ratings were high but exact numbers related to usual care were missing. This is in line with the significant outcomes of patient satisfaction with telerehabilitation illustrated in studies by Beaver et al.[11] and Cleeland et al.[49], where helpfulness in dealing with concerns at an appointment with telerehabilitation were reported as more helpful in meeting patient's needs. Although the populations in these studies were not exclusively surgical, and the interventions were not always exercise related, there is still sufficient indication for telerehabilitation interventions to be satisfactory in surgical patient groups, taking into account positive adherence and retention rates.[11,31,32,49]

Study limitations and strengths

The main strength of this review is its extended search and detailed assessment of articles according to the Cochrane Collaboration's tool for assessing risk of bias.[22] This revealed considerable variation in standards of reporting across studies, but contributed to the interpretation of results. A limitation of this study is the variety in contents of intervention and outcome measures that were used in studies. In order not to miss relevant articles, no restrictions were placed on these intervention and outcome parameters. However, this limits generalization to specific surgical groups, and restricted the performance of a meta-analysis on clinical outcome measures. However, despite this variety, QoL was measured with the same questionnaire in all studies, and was therefore eligible to be pooled by means of a random effects model.

Second, patients' pre-operative functional status was not taken into account as an inclusion criterion. As the telerehabilitation intervention could have less impact in patients with a higher functional status prior to surgery compared with patients with a lower functional status, the results on effectiveness could be skewed. This was also illustrated by Barnason et al.[25], who found that the degree of functional status in patients undergoing coronary artery bypass surgery was related to survival after surgery. This emphasized the importance of identifying and intervening in cases with poor functioning. Therefore, organizing patients by functional status before surgery can be an important factor to consider when applying a telerehabilitation intervention or investigating its effectiveness.

Finally, only one study reported patient satisfaction. It may have been possible to collect more data on patient satisfaction if non-randomized feasibility studies had been included.

Clinical implications and conclusions

This systematic review found that physiotherapy with telerehabilitation is feasible in surgical patients, and is at least equally effective compared with usual care. This systematic review with meta-analysis showed that QoL in surgical populations increased with telerehabilitation. As the effectiveness of telerehabilitation compared with usual care on physical outcomes is considered to be at least equal, this may be an important reason to choose physiotherapy with telerehabilitation instead of usual care for surgical populations. Despite methodological shortcomings within the included studies, this review illustrates the feasibility of telerehabilitation in surgical patients, but research relating to the (cost-) effectiveness and patient satisfaction of telerehabilitation requires further exploration. As telerehabilitation is developing continuously, and technology changes and improves at a high rate, it is recommended that alternative trials should be designed that allow iterations of new releases of technology.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.physio.2018.04.004.

Appendix A. Full electronic search strategy

Database	Search terms
MEDLINE	(“Physical Therapy Modalities”[Mesh] OR “Exercise Therapy”[Mesh] OR “Motor Activity”[Mesh] OR “Rehabilitation”[Mesh] OR “rehabilitation”[Subheading] OR physiotherap*[tiab] OR physical therap*[tiab] OR physical therap*[tiab] OR physical treatment[tiab] OR physio therap*[tiab] OR exercise*[tiab] OR rehabilitation[tiab] OR physical activit*[tiab] OR physical function*[tiab] OR recovery[tiab]) AND (“Telemedicine”[MAJR] OR “Telecommunications”[MAJR] OR “Remote Consultation”[MAJR] OR “Telephone”[MAJR] OR telemedicine[tw] OR telehealth[tw] OR ehealth[tw] OR tele-medicine[tw] OR tele-health[tw] OR e-health[tw] OR mobile health[tw] OR tele-rehabilitation[tw] OR telerehabilitation[tw] OR web-based[tw] OR remote consultation[tw] OR tele-consultation[tw] OR telephone consultation[tw]) AND (“Surgical Procedures, Operative”[MeSH] OR “Arthroplasty, Replacement”[Mesh] OR “Neoplasms”[Mesh] OR surgery[tw] OR abdominal[tw] OR thoracic[tw] OR orthopedic[tw] OR hip fracture*[tw]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR “clinical trial”[tw] OR random*[tw] OR research design [mh:noexp] OR comparative study [pt] OR Evaluation Studies[pt] OR follow-up studies [mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (“Animals”[Mesh] NOT “Humans”[Mesh])
EMBASE (Ovid)	(exp physiotherapy/ or exp kinesiotherapy/ or exp motor activity/ or exp rehabilitation/ or rh.fs. or (physiotherap* or physical therap* or physical treatment or physio therap* or exercise* or rehabilitation or physical activit* or physical function* or recovery).ti,ab.) AND (exp *telemedicine/ or exp *telecommunication/ or *teleconsultation/ or *telephone/ or (telemedicine OR telehealth OR ehealth OR tele-medicine OR tele-health OR e-health OR mobile health OR tele-rehabilitation OR telerehabilitation OR web-based OR remote consultation OR tele-consultation OR telephone consultation).ti,ab) AND (exp surgery/ or exp arthroplasty/ or exp neoplasm/ or (surgery or abdominal or thoracic or orthopedic or hip fracture*).ti,ab.) AND (randomized controlled trial/ or controlled clinical trial/ or randomization/ or double blind procedure/ or single blind procedure/ or clinical trial/ or comparative study/ or evaluation study/ or follow up/ or prospective study/ or crossover procedure/ or (clinical trial or random* or control* or prospectiv* or volunteer*).ti,ab.) NOT (animal/ NOT human/)

Appendix A. Continued

Database	Search terms
CINAHL	(MH "Physical Therapy+" OR MH "Physical Therapy+" OR MH "Therapeutic Exercise+" OR MH "Motor Activity+" OR MH "Rehabilitation+" OR SU Rehabilitation OR TI physiotherap* OR TI physical therap* OR TI physical treatment OR TI physio therap* OR TI exercise* OR TI rehabilitation OR TI physical activit* OR TI physical function* OR TI recovery OR AB physiotherap* OR AB physical therap* OR AB physical treatment OR AB physio therap* OR AB exercise* OR AB rehabilitation OR AB physical activit* OR AB physical function* OR AB recovery) AND (MM "Telemedicine" OR MM "Telehealth" OR MM "Telecommunications" OR MM "Remote Consultation" OR MM "Telephone" OR TI telemedicine OR TI telehealth OR TI ehealth OR TI tele-medicine OR TI tele-health OR TI e-health OR TI mobile health OR TI tele-rehabilitation OR TI telerehabilitation OR TI web-based OR TI remote consultation OR TI tele-consultation OR TI telephone consultation OR AB telemedicine OR AB telehealth OR AB ehealth OR AB tele-medicine OR AB tele-health OR e-health OR AB mobile health OR AB tele-rehabilitation OR AB telerehabilitation OR AB web-based OR AB remote consultation OR AB tele-consultation OR AB telephone consultation) AND (MH "Surgery, Operative+" OR MH "Arthroplasty, Replacement+" OR MH "Neoplasms+" OR TI surgery OR TI abdominal OR TI thoracic OR TI orthopedic OR TI hip fracture* OR AB surgery OR AB abdominal OR AB thoracic OR AB orthopedic OR AB hip fracture*) AND (MH "Randomized Controlled Trials" OR MH "Single-Blind Studies" OR MH "Clinical Trials+" OR MH "Double-Blind Studies" OR MH "Random Assignment" OR PT clinical trial OR PT randomized controlled trial OR MH "Study Design" OR PT comparative study OR MH "Comparative Studies" OR MH "Evaluation Research" OR MH "Prospective Studies" OR MH "Crossover Design" OR TI random* OR AB random* OR TI control* OR prospectiv* OR volunteer* OR AB control* OR prospectiv* OR volunteer*)
Cochrane	#1 MeSH descriptor: [Physical Therapy Modalities] explode all trees #2 MeSH descriptor: [Exercise Therapy] explode all trees #3 MeSH descriptor: [Motor Activity] explode all trees #4 MeSH descriptor: [Rehabilitation] explode all trees #5 physiotherap* or physical therap* or physical therap* or physical treatment or physio therap* or exercise* or rehabilitation or physical activit* or physical function* or recovery:ti,ab,kw (Word variations have been searched) #6 #1 or #2 or #3 or #4 or #5 #7 MeSH descriptor: [Telemedicine] explode all trees #8 MeSH descriptor: [Telecommunications] explode all trees #9 MeSH descriptor: [Remote Consultation] explode all trees #10 MeSH descriptor: [Telephone] explode all trees #11 telemedicine or telehealth or ehealth or tele-medicine or tele-health or e-health or mobile health or tele-rehabilitation or telerehabilitation or web-based or remote consultation or tele-consultation or telephone consultation:ti,ab,kw (Word variations have been searched) #12 #7 or #8 or #9 or #10 or #11 #13 MeSH descriptor: [Surgical Procedures, Operative] explode all trees

Appendix A. Continued

Database	Search terms
Cochrane (Continued)	#14 MeSH descriptor: [Arthroplasty, Replacement] explode all trees
	#15 MeSH descriptor: [Neoplasms] explode all trees
	#16 surgery or abdominal or thoracic or orthopedic or hip fracture*:ti,ab,kw (Word variations have been searched)
	#17 #13 or #14 or #15 or #16
	#18 #6 and #12 and #17 in Trials
ICTRP	Telemedicine AND surgery
PEDro	Telerehabiliation AND surgery

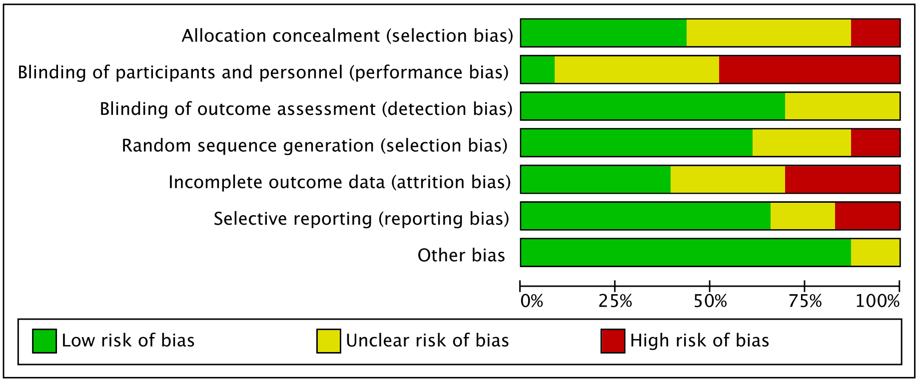

Figure A. Risk of bias assessment: summary

	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Random sequence generation (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arthur et al. 2002	+	−	+	+	?	?	+
Barnason et al. 2006	?	?	+	+	−	+	?
Coleman et al. 2005	+	+	+	+	?	−	+
Eakin et al. 2011	?	?	?	+	+	+	+
Eriksson et al. 2009	−	−	?	−	−	+	+
Hartford et al. 2002	?	?	?	?	?	?	?
Hawkes et al. 2013	+	−	+	+	−	−	+
Jones et al. 2011	+	−	+	+	+	+	+
Koertke et al. 2006	−	−	?	−	?	+	+
Langford et al. 2015	+	−	+	?	+	+	+
Latham et al. 2014	?	?	+	+	+	+	+
Lee et al. 2013	?	?	?	?	?	+	+
Ligibel et al. 2012	?	?	+	?	−	+	+
Moffet et al. 2015	+	−	+	+	−	?	+
Pinto et al. 2013	+	−	+	?	?	+	+
Pinto et al 2013	?	?	+	?	+	?	+
Piqueras et al. 2013	?	−	+	+	−	+	+
Rollman et al. 2009	+	?	+	+	+	+	?
Russell et al. 2011	+	−	+	+	?	+	+
Tousignant et al. 2011	+	?	?	+	−	−	+
Tranmer et al. 2004	?	?	+	+	+	+	+
Van den Brink et al. 2007	−	+	?	−	+	−	+
Vonk Noordegraaf et al. 2014	?	−	+	+	+	+	+

Figure B. Risk of bias assessment: full details

Chapter 6

Physiotherapy with telerehabilitation in patients with complicated postoperative recovery after esophageal cancer surgery: feasibility study

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ABSTRACT

Background: Improvement of functional status with physiotherapy is an important goal for patients suffering from postoperative complications and with an increased length of hospital stay (LoS) after esophagectomy. Supervised physiotherapy with telerehabilitation instead of conventional face-to-face care could be an alternative to treat these patients in their home environment after hospital discharge (T0), but its feasibility has not yet been investigated in detail.

Objective: The aim of this study was to investigate the feasibility of a 12-week postoperative supervised physiotherapy intervention with telerehabilitation for patients with esophageal cancer treated with esophagectomy and suffering from postoperative complications or with an increased LoS. The secondary objective was to investigate the preliminary effectiveness of telerehabilitation on functional recovery compared with usual care.

Methods: A prospective feasibility study with a matched historical comparison group was performed. Feasibility outcomes included willingness and adherence to participate, refusal rate, treatment duration, occurrence of adverse events, and patient satisfaction. Secondary outcome measures were measurements of musculoskeletal and cardiovascular functions and activities according to the domains of the International Classification of Functioning, disability and health.

Results: A total of 22 patients with esophageal cancer treated with esophagectomy and suffering from postoperative complications or with an increased LoS were included. Mean age at surgery was 64.55 (SD 6.72) years, and 17/22 (77%) patients were male. Moreover, 15 patients completed the intervention. Patient adherence was 99.8% in the first 6 weeks and dropped to 75.6% in the second period of 6 weeks, with a mean difference of −24.3% (95% CI 1.3 to 47.2; $P = .04$). Three months postoperatively, no differences in functional status were found between the intervention group and the matched historical comparison group.

Conclusions: This study showed that a postoperative physiotherapeutic intervention with telerehabilitation is feasible for patients with postoperative complications or an increased LoS after esophageal cancer surgery up to 6 weeks after T0.

INTRODUCTION

Background

Surgical resection of the esophagus is the primary curative treatment for patients with esophageal cancer and is associated with a high risk of postoperative complications, varying from 25 to 60%.[1,2] This leads to an increased length of hospital stay (LoS) and a delayed postoperative recovery, with a significant decline in physical function in the first 3 months after surgery.[2,3]

It has been demonstrated in many surgical populations that improving preoperative functional status by exercise training had a positive effect on long-term postoperative outcomes. [4,5] However, recent studies have shown that preoperative functional status was not associated with postoperative complications in patients treated with esophagectomy, justifying the need to focus on treating these patients in the postoperative phase.[6,7]

Patients with postoperative complications after esophagectomy often suffer from fatigue, decreased exercise capacity, and disability such as impaired walking capacity and their recovery could take up to 1 year and beyond.[3,8] These symptoms are explained by altered cardiopulmonary function, generalized muscle weakness, and malnutrition, and physiotherapists play an important role in improving these aspects of physical functioning.[9]

Telerehabilitation as an alternative to face-to-face care

Instead of face-to-face care, postoperative physiotherapy can also be streamed by telerehabilitation. Telerehabilitation is a medium to provide physiotherapy with electronic health (eHealth), defined as '*the delivery of rehabilitation services to patients at a distance using information and communication technologies*'.[10] Telerehabilitation has shown to be a valuable tool in improving postoperative outcomes and functional recovery in surgical patients, where patients considered the reduced traveling barriers, flexible exercise hours, and the ability to directly integrate exercises in daily life as positive.[11,12]

Moreover, telerehabilitation interventions have been valuable to overcome discontinuities that may arise in communication between hospital and primary care, where physiotherapists may have a lack of knowledge about how to treat patients after a highly complex surgery.[13]

There is evidence showing positive effects of physiotherapy with telerehabilitation on clinical outcomes in cancer patients, cardiac patients, and patients with musculoskeletal disorders, but information on the feasibility of this intervention in the postoperative phase of patients with esophageal cancer treated with esophagectomy is lacking.[14,15]

Objectives

Therefore, the primary objective of this prospective feasibility study was to investigate the feasibility of a 12-week postoperative supervised telerehabilitation program for patients with esophageal cancer treated with esophagectomy and suffering from postoperative complications or with an increased LoS. The secondary objective was to investigate the preliminary effectiveness of telerehabilitation on functional recovery compared with a matched historical comparison group receiving usual care.

METHODS

Ethical approval

The Medical Ethics Committee (METC) of the Amsterdam University Medical Centers provided ethical approval for this study (NL58388.018.16). All patients provided written informed consent. As this was a feasibility study, sample size calculations have not been performed, and the initial sample size of 30 participants was pragmatically chosen. Patients could leave the study at any time for any reason if they wished to do so without any consequences.

Study design

A prospective feasibility study was performed in patients treated with esophagectomy. To assess preliminary effectiveness, the patients who underwent the complete treatment were matched with a historical comparison group of patients that underwent esophagectomy and suffered from postoperative complications receiving usual face-to-face care, between March 2012 and October 2014. We decided to match 1 case to 2 patients from a historical comparison group to optimize statistical power. Data collected from this historical comparison group were part of a previous study performed by the same research group, from which the METC waived the need for informed consent.[6] Patients were matched for gender, age, American Society of Anasthesiologists (ASA) - physical status score, comorbidities, body mass index, pulmonary function, surgical procedure, and severity of postoperative complications.

Participants

Patients were recruited from the surgical wards at the Gastrointestinal Oncologic Center Amsterdam of the Amsterdam University Medical Centers, location Academic Medical Center, just before discharge from the hospital by the supervising physiotherapist or the investigator. Patients who refused to participate were referred to face-to-face physiotherapy in primary care.

Inclusion criteria

Participants were included if they were aged 18 years or older and the primary reason of hospital stay was status after esophagectomy, they had internet access at home, and they signed the informed consent form. Moreover, participants were included if they suffered from a postoperative complication, grade 3a-4 according to the Clavien-Dindo classification. This 5-scale classification reports surgical complications based on the type of therapy required to treat this complication.[16] Participants were also included if the postoperative length of stay was longer than 9 days because they were physically too weak to be discharged earlier. There was an indication for face-to-face physiotherapy in primary care if a patient was not yet able to walk or transfer independently because of a loss of muscle strength, mobility, or balance at discharge.

Exclusion criteria

Patients were excluded if they were unable to complete self-reported questionnaires, insufficiently able to read or speak Dutch, had cognitive disorders, or had any other severe medical conditions that prevented the patient from doing unsupervised exercises at home.

Intervention

Participants received a 12-week supervised home-based telerehabilitation intervention after hospital discharge (T0) in their home environment. Before T0, a physiotherapist from the surgical ward instructed the patient on the telerehabilitation intervention.

The telerehabilitation intervention was provided with Physitrack (Physitrack Limited). Physitrack is an eHealth platform that enables physiotherapists to design home exercise programs and to track patient adherence. Patients were provided with a goal-oriented exercise program created by the physiotherapist that could be accessed by a tablet, mobile phone, or computer (Figure 1). The physiotherapist accurately monitored the progress of the patient by weekly telephone, email, or video sessions, and exercises were adapted via the eHealth platform if needed. Physitrack had provided their services for this research project free of charge, and they will use the outcomes of this study to improve their services. They were not involved in the design, execution, analysis, and conclusions of this research. Physitrack will only have access to the published paper with its results, with no access to raw data.

The postoperative physiotherapeutic intervention with telerehabilitation was aimed at improving functional status. The intervention took 12 weeks of at least two sessions per week depending on if the treatment goals were achieved. The exercises were tailored to the patients' specific condition and needs, which were determined 1 day before T0. The physiotherapy goals were determined by using the patient-specific complaint list.[17] The exercises were aimed at improving the functional activity level of the patient, by increasing muscle strength, coordination, range of joint motion, and stamina. Intensity and frequency of the functional exercises were determined according to the guidelines of the American College of Sports Medicine.[18] Cardiorespiratory exercises to improve stamina were performed on a moderate-to-vigorous intensity level, measured with the Borg rating of perceived exertion scale (scores 6-20), for at least two sessions per week. Rating of perceived exertion with the Borg scale is a generally used and reliable scale to monitor and evaluate exercise intensity. A score from 13 to 16 relates to the moderate-to-vigorous intensity level, and this allowed us to monitor and adapt the appropriate intensity.[19] Exercises to improve muscle strength were performed 2-3 days per week on 60-70% of the 1 repetition maximum (moderate-to-hard intensity). We used the Holten curve that relates the percentage of the 1 repetition maximum to the estimated repetitions of that intensity. That allowed us to adapt the exercises without using a fitness equipment to measure the 1 repetition maximum directly.[18,20]

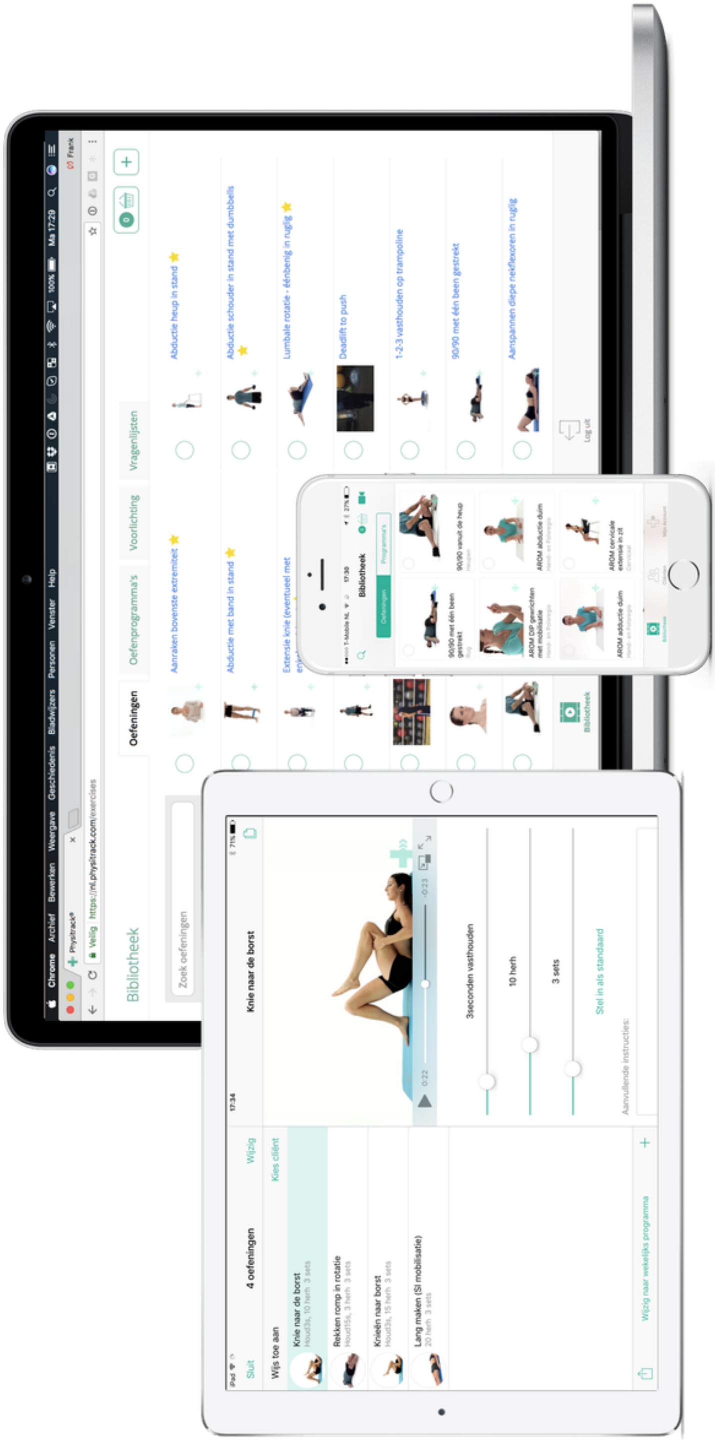

Figure 1. Exercise program by Physitrack®
Reproduced with permission from Physitrack®.

Feasibility outcome measures

Feasibility outcome measures were calculated for the 15 patients that completed the 12-week supervised home-based telerehabilitation intervention. Feasibility outcomes included refusal rate; adherence to the telerehabilitation intervention operationalized in amount and duration of email, phone, and video calls conducted by patients and physiotherapists; treatment duration per session; adverse events; and patient satisfaction. Patient satisfaction was recorded with a modified telemedicine satisfaction and usefulness questionnaire (TSUQ), a 30-item Likert-type questionnaire including three subscales (usefulness, communication, and user friendliness) at 6 weeks postoperatively (T1) and at 3 months postoperatively (T2).[21] Scores range from 30 to 150, with high scores indicating a higher satisfaction.

The telerehabilitation intervention was considered as feasible if at least 80% adherence rate was achieved, if no adverse events took place, and if the average total patient satisfaction was higher than 75% (score >120).

Effectiveness outcome measures

Secondary outcome measures on preliminary effectiveness were musculoskeletal and cardiovascular functioning and level of activities according to the domains of the International Classification of Functioning, Disability and Health.[22]

Handgrip strength was measured with the Jamar grip strength dynamometer (Lafayette Instrument Company) as a measure of generalized muscle strength. [23,24] Maximal inspiratory pressure was measured as an indicator of inspiratory muscle strength, with a Micro Respiratory Pressure Meter.[2,4] Functional lower extremity muscle function was measured with the 30-second chair stand test (30CST). This test measures extremity strength in relation to demanding functional daily activities such as stair climbing and getting out of a chair.[25] Walking capacity was measured with the 2-minute walk test (2MWT).[26]

Fatigue was measured with the Multidimensional Fatigue Inventory.[27]

Self-reported activities were measured with the Longitudinal Ageing Study Amsterdam (LASA) physical activity Questionnaire (LAPAQ), in which patients reported the type, frequency, and duration of daily activities in the past 14 days. Health-related quality of life (HRQL) was measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, version 3.0. [28]

Effectiveness of outcome measures were recorded before the start of the intervention (T0), and T1 and T2.

Standardized operating procedures of all measurements were used to guarantee uniformity and accuracy in operationalization. Trained and experienced physiotherapists performed the standardized measurements.

Statistical analysis

Data were analysed in the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 25.0. IBM Corp, Armonk, New York). Statistical tests were analysed two sided and considered significant with an alpha ≤.05.

Baseline characteristics were summarized with descriptive statistics, where discrete variables were expressed as counts with percentages, ordinal variables as median and interquartile ranges (P25-75), and continuous variables as mean and standard deviation, and in case of a skewed distribution, they were expressed as median and interquartile range. Differences in outcomes before and after the intervention were determined by using a paired samples T-test or a Wilcoxon matched-pairs signed rank test for skewed data. Differences between the intervention group and the historical comparison group were tested with a linear mixed model analysis to account for the dependency between observations.

RESULTS

Baseline characteristics

From January 2017 to October 2018, 22 patients with esophageal cancer that underwent esophagectomy were included in the study after having obtained informed consent. The study was terminated after inclusion of the 22nd patient because there was a point achieved in data collection after which no new or relevant information emerged with respect to answering the primary research question.

Mean age at surgery was 64.6 (SD 6.7) years, and 17/22 (77%) patients were male. All patients received neoadjuvant chemoradiation therapy. At enrollment, mean pulmonary function expressed as a percent score of predicted pulmonary function value was 116.1 (SD 18.7) for forced vital capacity, 109.0 (SD 19.3) for forced expiratory volume in 1 second and 109.2 (SD 30.1) for inspiratory vital capacity. Except for 2, all patients were surgically treated with a minimally invasive transthoracic esophagectomy. In addition, 8/22 (36%) patients had a hospital stay of more than 9 days. Moreover, 20/22 (91%) patients suffered from postoperative complications, of which 14/22 (70%) required a surgical, endoscopic, or radiological intervention. Patient characteristics are presented in Table 1.

Feasibility

A total of 15/22 (68%) patients completed the 12-week program. From the 7 patients that did not complete the study, 1 was discharged to a nursing home after inclusion, 2 quitted the study intervention after 3 and 4 weeks because they preferred face-to-face physiotherapy, and 4 patients were withdrawn by the investigator because postoperative treatment required a multidisciplinary approach (n = 3) or because of the presence of metastases (n = 1). These patients did not systematically differ in baseline characteristics from the patients who completed the program.

The average duration of the treatment program was 11.1 (SD 5.2) weeks. From all exercises provided to patients, 1337/4671 (28.62%) was aimed at lower extremity muscle strength, 996/4671 (21.32%) at respiration, and 1150/4671 (24.62%) at walking.

The patient adherence, operationalized in performance rate of exercises to the telerehabilitation intervention, was 99.8% in the first 6 weeks and dropped to 75.6% in the second period of 6 weeks, with a mean difference of −24.3% (95% CI 1.3 to 47.2; P = .04). The accomplishment of treatment goals was the main reason reported for being less or not adherent to the program anymore.

Table 1. Patient characteristics

Patient characteristics	Study population (N = 22)
Gender (male), n (%)	17 (77)
ASA[a] classification, n (%)	
I[b]	5 (22)
II[c]	10 (45)
III[d]	7 (31)
Age (years), mean (SD)	64.6 (6.7)
BMI[e], mean (SD)	26.5 (4.4)
Comorbidities, n (%)	
Cardiovascular	7 (31)
COPD[f]	0 (0)
DM II[g]	2 (9)
Cigarette smoking	2 (9)
Pulmonary function (percent predicted), mean (SD)	
FVC[h]	116.1 (18.7)
FEV_1[i]	109.0 (19.3)
IVC[j]	109.2 (30.1)
Surgical procedure, n (%)	
Transhiatal open	0 (0)
Transhiatal minimally invasive	1 (5)
Transthoracal open	0 (0)
Transthoracal minimally invasive	20 (91)
Esophageal resection with colon interposition	1 (5)
Clavien-Dindo postoperative complications, n (%)	
No complications	2 (9)
Grade 1	2 (9)
Grade 2	4 (18)
Grade 3a	3 (14)
Grade 3b	4 (18)
Grade 4a	7 (32)
Grade 4b	0 (0)
Grade 5	0 (0)

Table 1. Continued

[a]ASA: American Society of Anesthesiologists.
[b]I: healthy person.
[c]II: mild systemic disease.
[d]III: severe systemic disease.
[e]BMI: body mass index is calculated as weight in kilograms divided by height in meters squared.
[f]COPD: chronic obstructive pulmonary disease.
[g]DM II: diabetes mellitus type 2.
[h]FVC: functional vital capacity.
[i]FEV1: forced expiratory volume in the first second of expiration.
[j]IVC: inspiratory vital capacity.

The physiotherapist and patients contacted each other 204 times in 243 weeks, with a minimum of 1 and a maximum of three times a week for coaching, for regular follow-ups, and for adjusting the treatment program, dependent on the patient's needs. Of these 204 direct patient contacts, 1 (0.5%) took place with a video connection, 26 (12.7%) with email, 122 (59.8%) with telephone, and 55 (27.0%) with live contact via home visits.

Total average patient satisfaction (range 30-150) measured at T1 was 135.0 (SD 19.5), with sub scores on usefulness (range 10-50) = 44.66 (SD 7.4), communication (range 11-55) = 48.3 (SD 8.1), and user friendliness (range 9-45) = 42.8 (SD 3.2). Patients appreciated weekly follow-ups by telephone or email and especially appreciated the flexibility they had to perform the exercises at home. They rated the telerehabilitation app as user friendly, and they did not miss the physical presence of the physiotherapist to follow the exercise program. No adverse events took place during measurements or exercise sessions. Total average patient satisfaction at T2 was 139.6 (SD 15.4). Textbox 1 provides a selection of quotes, addressed by participants more than once about experiences with the program.

Textbox 1. Patient experiences

Quotes
"It gave a lot of confidence to work at home on my recovery with supervision of a PT " *Mrs. S., 70y*
"I could do the exercises whenever I wanted, that was very convenient" *Mr. W., 54y*
"Without this program I would never have been that far" *Mr. J., 66y*
"I should not have thought about going to the physiotherapist twice a week" *Mrs. B., 60y*
"By practicing at home, I knew what I was doing it for. That was very motivating" *Mr. B., 62y*
"I missed incentives in the program" *Mr. B.,49y*
"I did not miss the physical presence of the physiotherapist, I felt that I could always reach him through the app" *Mrs. B, 64y*
"Along the way, I found the exercise program less relevant, I could already do my daily activities again" *Mr. S., 62y*

Effectiveness

A total of 15 patients that completed the telerehabilitation program were matched with 30 patients from a historical comparison group matched on both pre- and postoperative characteristics (gender, age, preoperative pulmonary function, type of surgery, and postoperative complications classified according to Clavien-Dindo). Table 2 provides details about the matching characteristics.

At T0, patients in the intervention group had significantly lower functional capacity measures compared with reference values than patients in the matched historical comparison group (Table 3).

Table 2. Patient characteristics of the intervention group matched with a historical comparison group

Patient characteristics	Intervention (N = 15)	Matched controls (N = 30)
Gender (male), n (%)	11 (73)	22 (73)
ASA[a] classification, n (%)		
I[b]	3 (20)	5 (16)
II[c]	8 (53)	15 (50)
III[d]	4 (26)	10 (33)
Age (years), mean (SD)	62.8 (6.9)	60.3 (7)
BMI[e], mean (SD)	26.1 (3.5)	25.2 (4)
Comorbidities, n (%)		
Cardiovascular	6 (40)	5 (16)
COPD[f]	0 (0)	3 (10)
DM II[g]	1 (7)	1 (3)
Cigarette smoking	1 (7)	7 (23)
Pulmonary function (percent predicted), mean (SD)		
FVC[h]	115.0 (20.1)	116.3 (16.2)
FEV_1[i]	105.4 (20.1)	110.2 (20.7)
IVC[j]	114.1 (21.9)	112.0 (16.7)
Surgical procedure, n (%)		
Transhiatal open	0 (0)	0 (0)
Transhiatal minimally invasive	0 (0)	2 (7)
Transthoracal open	0 (0)	1 (3)
Transthoracal minimally invasive	14 (93)	27 (90)
Esophageal resection with colon interposition	1 (7)	0 (0)

Table 2. Continued

Clavien-Dindo postoperative complications, n (%)		
No complications	2 (13)	11 (37)
Grade 1	2 (13)	4 (13)
Grade 2	2 (13)	7 (23)
Grade 3a	3 (20)	4 (13)
Grade 3b	2 (13)	1 (3)
Grade 4a	4 (27)	2 (7)
Grade 4b	0 (0)	1 (3)
Grade 5	0 (0)	0 (0)

[a]ASA: American Society of Anesthesiologists.

[b]I: healthy person.

[c]II: mild systemic disease.

[d]III: severe systemic disease.

[e]BMI: BMI is calculated as weight in kilograms divided by height in meters squared.

[f]COPD: chronic obstructive pulmonary disease.

[g]DM II: diabetes mellitus type 2.

[h]FVC: functional vital capacity.

[i]FEV1: forced expiratory volume in the first second of expiration.

[j]IVC: inspiratory vital capacity.

Table 3. Functional status capacity outcome measures at hospital discharge (T0). Beta values represent the differences in functional status between the historical control group and the intervention group at T0

Functional status outcome	Intervention	Control	Beta	95% CI	*P*-value
RHGS[a] (percent predicted), mean (SD)	92.4 (19.7)	107.9 (23.2)	−15.5	−31.9 to 0.79	.04[b]
LHGS[c] (percent predicted), mean (SD)	97.1 (20.8)	106.2 (22.4)	−11.9	−26.6 to 2.9	.11[b]
30CST[d] (percent predicted), mean (SD)	50.8 (31.6)	89.0 (34.4)	−33.2	−53.8 to −12.7	.003[b]
2MWT[e] (meters), mean (SD)	117.4 (50.6)	154.4 (32.3)	−22.6	−42.7 to −2.5	.03[b]

[a]RHGS: right-handgrip strength.
[b]*P* ≤. 05 is considered significant.
[c]LHGS: left-handgrip strength.
[d]30CST: 30-second chair stand test.
[e]2MWT: 2-min walk test.

Three months postoperatively, no differences in functional status measures were found between the intervention group and the matched control group (Table 4).

Within the intervention group, 30CST, 2MWT, fatigue, and HRQL improved significantly between T0 and T1 and between T1 and T2, whereas activities of daily life (ADL) decreased significantly between T0 and T1 and improved again between T1 and T2 (Table 5).

Table 4. Within group differences between hospital discharge (T0) and 3 months postoperatively (T2) and between group differences at T2 in measures of functional status. Within group differences represent the differences in functional status between T0 and T2. Beta values represent the differences in functional status between the historical control group and the intervention group T2

Functional status outcome	Within group differences (T0-T2)[a,b]		
	Intervention (N = 15)		Historical control (N = 30)
	Mean (95% CI)	*P*-value	Mean (95% CI)
LHGS[c]	10.4 (0.1 to 20.8)	.048[d]	−4.1 (−8.7 to 0.5)
RHGS[e]	12.3 (0.9 to 23.7)	.04[d]	−3.2 (−8.9 to 2.4)
MIP[f,g]	—[h]	—	—
30CST[i]	69.7 (51.6 to 87.8)	<.001[d]	29.8 (18.7 to 40.9)
2MWT[j]	82.4 (53.4 to 111.3)	.001[d]	41.2 (27.3 to 55.1)
ADL[g,k]	—	—	—
Fatigue[g]	—	—	—
HRQL[l]	—	—	—

[a]T0: hospital discharge.
[b]T2: 3 months postoperatively.
[c]LHGS: left-handgrip strength.
[d]*P* < .05 is considered significant.
[e]RHGS: right-handgrip strength.
[f]MIP: maximal inspiratory pressure.

	Between group differences at T2	
	Beta	
P-value	Mean (95% CI)	*P*-value
.08	0.8 (14.2 to −12.7)	.91
.25	−1.0 (−15.3 to 13.3)	.89
—	13.7 (−14.0 to 41.4)	.32
<.001[d]	5.9 (−15.3 to 27.0)	.58
<.001[d]	16.8 (−7.6 to 41.2)	.17
—	−444.3 (−1417.0 to 528.3)	.36
—	−3.6 (−16.0 to 8.8)	.55
—	3.5 (−9.0 to 16.11)	.57

[g]These measurements were not performed at T0 and, therefore, were excluded from this analysis.

[h]Missing data.

[i]30CST: 30-second chair stand test.

[j]2MWT: 2-minute walk test.

[k]ADL: activities of daily life.

[l]HRQL: health-related quality of life.

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Table 5. Mean differences in functional status outcomes between hospital discharge and 6 weeks postoperatively (T1) and between T1 and 3 months postoperatively of the intervention group (N = 15)

Measurements	Δ[a]T0-T1[b,c] (95% CI)	*P*-value	ΔT1-T2[d] (95% CI)	*P*-value
RHGS[e]	7.4 (−5.1 to 19.8)	.22	5.1 (−1.5 to 11.6)	.12
LHGS[f]	9.6 (−0.6 to 19.8)	.06	1.0 (−5.0 to 6.9)	.74
MIP[g,h]	—[i]	—	9.6 (−1.1 to 20.3)	.07
30CST[j]	53.0 (38.5 to 67.5)	<.001[k]	19.0 (10.2 to 27.9)	.001[k]
2 MWT (m)[l]	51.0 (21.9 to 80.2)	.002[k]	30.3 (15.5 to 445.0)	.001[k]
MFI[m] fatigue	−10.2 (−16.8 to −3.6)	.007[k]	−16.8 (−24.6 to −9.0)	.001[k]
EORTC QLQ C30[n], (Score)	25.6 (14.6 to 36.5)	<.001[k]	14.6 (6.4 to 22.8)	.002[k]
LAPAQ[o] (Kcal/day)	−514.7 (−866.7 to 160.7)	.008[k]	173.6 (9.5 to 337.7)	.04[k]

[a]Δ: mean difference.
[b]T0: hospital discharge.
[c]T1: 6 weeks postoperatively.
[d]T2: 3 months postoperatively
[e]RHGS: right-handgrip strength.
[f]LHGS: left-handgrip strength.
[g]MIP: maximal inspiratory pressure.
[h]These measurements were not performed at T0 and, therefore, were excluded from this analysis.
[i]Missing data.
[j]30CST: 30-second chair stand test.
[k]$P < .05$ is considered significant.
[l]2MWT: 2-minute walk test.
[m]MFI: Multidimensional fatigue inventory; scores range from 20 to 100, with a higher score representing more fatigue and reduced activity/motivation.
[n]EORTC QLQ C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; scores range from 0 to 100, with high scores indicating a better quality of life.
[o]LAPAQ: Longitudinal Ageing Study Amsterdam physical activity questionnaire; total amount of activities in kilocalories per day.

DISCUSSION

Principal findings

To our knowledge, this is the first study demonstrating that postoperative physiotherapy with telerehabilitation is feasible in patients suffering from postoperative complications after esophagectomy, primarily in the first 6 weeks after T0. This is in line with a study by Latham et al.[11], who stated that telerehabilitation is a valuable tool to manage postoperative outcomes and functional progress directly after T0 in a patient's home environment.

The adherence rates were significantly higher in the first 6 weeks after T0 than in the second period of 6 weeks, where patients reported that they were generally more able to perform their ADL and were less dependent on the telerehabilitation intervention, which might explain the lower adherence rates despite a further incline in functional status. From a functional perspective, these lower adherence rates should be interpreted as a desired outcome, because it illustrates the patient's gradual independence of physiotherapeutic care.

The consistently high patient satisfaction rates of the telerehabilitation intervention in our study are confirmed in a systematic review by Mair et al.[29], who stated that the greatest advantages experienced by patients were increased accessibility of specialist expertise, increased flexibility, less travel required, and reduced waiting times. This is also in agreement with the study by Moffet et al.[30], who investigated patient satisfaction with in-home telerehabilitation after total knee arthroplasty and found similar results, concluding that patient satisfaction was at least equal to conventional health care delivery.

In this study, we compared patients who underwent the telerehabilitation program with a historical comparison group of patients receiving usual care and found equal functional status outcome measures at T2. This is in line with studies that found telerehabilitation interventions to be equally effective as usual care on at least one outcome measure; however, overall significant evidence in favor of telerehabilitation was still lacking.[31,32]

Despite the similar functional outcomes T2, it has to be noted that most of the functional status outcome measures of our intervention group at T0 were significantly lower than those of the matched historical comparison group. It could be argued that the intervention group gained more progress on functional status because of the physiotherapeutic treatment with telerehabilitation, in comparison with the matched historical comparison group, ultimately resulting in equal outcomes T2.

Within the intervention group, most of the functional outcome measures significantly improved between T0-T1 and T1-T2, apart from ADL that significantly decreased during the first 6 weeks of the intervention and restored in the second period of 6 weeks. A possible explanation could be that after T0, patients mostly stayed at home because they felt too weak to keep up with their ADL. Moreover, in the first 6 weeks, the telerehabilitation intervention primarily focused on increasing muscle strength of the lower extremities. After 6 weeks, the shift was gradually made toward implementing the exercises in daily life, finally resulting in a significant increase in ADL in the second period of 6 weeks.

Limitations

This study has intrinsic limitations. First, only 22 patients were included in this study, of which 15 patients completed the study. This might limit the generalizability of our findings. However, despite the small sample size, the included participants represented the population of interest in terms of baseline characteristics and postoperative complications. Moreover, inclusion was terminated after the inclusion of the 22nd participant, because no new findings were to be expected with adding new participants to the study.

Second, this study was not a pilot feasibility trial, where patients were randomly assigned either to the intervention group or a control group to determine effectiveness of the investigational treatment. Instead, we compared the intervention group with a matched historical comparison group. Therefore, bias could not be ruled out completely.

We were not able to compare functional status outcome measures half way through the telerehabilitation intervention because the historical controls were not measured T1.

Third, patient satisfaction was measured with a modified TSUQ that had not been validated in this specific population. Kairy et al.[33] concluded in their systematic review investigating clinical outcomes, clinical process, health care utilization, and costs associated with telerehabilitation that patient satisfaction ratings were generally high, irrespective of the population. However, they also stated that operationalization and standardization of satisfaction were frequently lacking and too much focus was on the technology part instead of aspects of service delivery. The satisfaction questionnaire we used addressed both aspects, and therefore, we are confident that the satisfaction ratings were representative of the telerehabilitation intervention provided.

CONCLUSIONS

This study shows that patients are able to improve their functional status by doing functional exercises in their own meaningful environment supported by telerehabilitation and tablet use with distant guidance from an experienced physiotherapist. The feasibility of the physiotherapeutic intervention with telerehabilitation for this specific patient category has implications for (re) organizing postoperative physiotherapeutic care in the patient's home environment. Telerehabilitation cannot replace face-to-face physiotherapy as physical examination remains necessary, but taking into account positive adherence rates and satisfaction, we strongly suggest considering this way of treatment delivery for patients with esophageal cancer treated with surgery and suffering from postoperative complications, especially in the first 6 weeks after T0. We also recommend to investigate the potential cost-effectiveness of telerehabilitation compared with usual care. Although we found equal functional status outcomes in both the intervention group and the historical comparison group T2, we suggest performing a randomized controlled trial to draw firm conclusions on its effectiveness.

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ETHICAL APPROVAL

The Medical Ethics Committee of the Amsterdam University Medical Centers provided ethical approval for this study (NL58388.018.16).

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CONFLICTS OF INTEREST

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Chapter 7

General discussion

GENERAL DISCUSSION

Physiotherapists play an important role in improving pre-and postoperative physical functioning of patients undergoing elective surgery to enhance recovery and to reduce the risk of postoperative complications and the length of hospital stay.[1] There is increasing evidence that a patient's preoperative physical functioning is associated with the incidence of postoperative complications and functional recovery.[2-4] Despite the high incidence of postoperative complications in patients with esophageal cancer undergoing esophagectomy, it is currently unknown how preoperative physical functioning relates to the occurrence of postoperative complications and to the recovery of postoperative physical functioning.

Therefore, this thesis aimed to investigate the pre-and postoperative course of physical functioning in patients undergoing surgery for esophageal cancer.

Main findings

Preoperative physical functioning is not associated with postoperative complications in patients with esophageal cancer

There is a wealth of evidence describing the association between preoperative physical functioning and postoperative outcome in high-risk surgical populations.[2,4] For example, in patients undergoing coronary artery bypass graft surgery, a strong association was found between preoperative inspiratory muscle strength and postoperative pulmonary complications.[5] Subsequently, the risk of postoperative pulmonary complications significantly decreased by improving patients' preoperative inspiratory muscle strength. In older patients scheduled for elective abdominal oncological surgery it was shown that preoperatively achieved levels of physical functioning sustained postoperatively.[6] This was further confirmed in a systematic review and meta-analysis of Moran et al.[3] who concluded that improved preoperative physical functioning has the ability to decrease the incidence of postoperative complications.

However, we did not find an association between preoperative physical functioning and postoperative complications in patients with esophageal cancer undergoing elective surgery in the Amsterdam University Medical Centers, location Academic Medical Center. We did not find significant differences in preoperative physical functioning, even after comparing the proportion of patients suffering from postoperative complications and those without **(Chapter 2)**. Although this seemed to be surprising at a first glance, our population differed systematically from comparable high-risk surgical populations in baseline characteristics.

There may be two reasons for this.
First, the incidence of postoperative pulmonary complications was low. This could be explained by the minimally invasive surgical approach being performed in the vast majority of patients. **(Chapter 2,3**). It is known that minimally invasive procedures lead to a lower risk of postoperative pulmonary complications.[7] At the same time, there was a relatively high incidence of gastrointestinal complications such as esophago-enteric leak from anastomosis and atrial dysrhythmia, from which it's arguable that its risk is unrelated to preoperative physical functioning **(Chapter 2)**.

Second, the patients included in our study showed higher pulmonary function and preoperative physical functioning than comparable high-risk surgical populations **(Chapter 2,3)**. This was contrary to a study of Feeney et al.[8] where preoperative pulmonary function and inspiratory muscle strength in patients with esophageal cancer undergoing surgery, were lower than predicted. In general, the risk of postoperative pulmonary complications is significantly associated with preoperative pulmonary function and inspiratory muscle strength.[8] Therefore, the high preoperative pulmonary function in our study cohort combined with being treated with a minimally invasive surgical approach, may explain the low incidence of postoperative pulmonary complications.[7]

Patients with esophageal cancer recover to baseline preoperative physical functioning three months after surgery, irrespective of postoperative complications
Until recently, the development of physical functioning over time was not known for patients undergoing esophageal cancer surgery.

We found that preoperative physical functioning was higher than predicted based on reference values. Moreover, physical functioning significantly improved in the preoperative phase (3 months until 1 day before surgery) **(Chapter 3)**. This was despite the neoadjuvant chemoradiation therapy that all patients received, from which it is known that this leads to cardiopulmonary toxicity and decreased aerobic capacity.[3,9]

Of note, all aspects of physical functioning returned to baseline levels in our population three months postoperatively, except from fatigue and handgrip strength. This was also confirmed in a study of Lawrence et al.[10], who found a significant postoperative decline in handgrip strength in older patients undergoing major abdominal surgery, while all other aspects of physical functioning restored to baseline levels. This could be explained by the nutritional impairments patients may suffer from after esophageal cancer surgery, where handgrip strength not only reflects whole body muscle strength, but also nutritional status.[11]

Another important finding was that the course of physical functioning over time was not different for patients with and without postoperative complications **(Chapter 3).** This further contributes to the findings in our previous study, where we did not find an association between preoperative physical functioning and postoperative complications **(Chapter 2).** This is in line with a study of Minnella et al.[12], who did not find significant differences in the incidence of postoperative complications, length of hospital stays and readmission rates between patients with better preoperative physical functioning than a control group.

Muscle strength is highly associated with muscle mass in patients with esophageal cancer
Esophageal cancer surgery is associated with significant weight loss due to malnutrition and a loss of muscle mass and muscle strength.[12] This may lead to sarcopenia, a progressive and generalized muscle disorder, that leads to increased morbidity and mortality.[13] Probable sarcopenia is identified by low muscle strength, confirmed by low muscle mass and considered severe in case of low physical performance.[14] Therefore, both muscle strength and muscle mass need to be assessed.[13] However, technologies to measure muscle mass, such as dual x-ray absorptiometry (DXA) and computed tomography (CT) are very expensive or lead to radiation exposure.[14,15] There is a need for clinical methods to easily and rapidly assess muscle mass with minimal patient burden to identify patients with decreased muscle mass. Measurements of muscle mass such as bioelectrical impedance analysis (BIA) and more recently ultrasound assessment are affordable, reliable and valid, but not yet widely available.[16]

Therefore, we assessed the association between muscle mass and muscle strength in surgical patients with esophageal cancer prior to CRT. We found an independent association of handgrip strength, respiratory muscle strength and functional lower extremity strength with muscle mass in patients with esophageal cancer awaiting surgery **(Chapter 4)**.These results could be used to predict muscle mass based on muscle strength in preoperative patients with esophageal cancer.

Postoperative physiotherapy at home through eHealth is a feasible alternative to face-to-face care
Despite high preoperative physical functioning, the incidence of postoperative complications remained high in patients treated with esophagectomy **(Chapter 2)**. Patients with postoperative complications after esophagectomy often suffer from fatigue, decreased exercise capacity and disability, which justifies an indication for postoperative physiotherapy. Once discharged from the hospital, patients will face many challenges to manage their own postoperative functional recovery outside of the hospital setting. Although patients are prepared in the hospital for a smooth and seamless transition by providing the appropriate knowledge, education and referral information, the continuation of care in the home situation is not always successful.[15] Especially in vulnerable populations, impediments in social support, challenges with transportation and lack of self-efficacy might prevent them from receiving the appropriate care that contributes to an optimal postoperative functional recovery.[15]

Therefore, treating patients in their home situation with eHealth, directly after discharge from the hospital is a promising alternative in terms of managing a patient's postoperative functional recovery from a distance.[16]

In our systematic review of intervention studies in surgical patients, we already concluded that physiotherapy through eHealth is feasible and at least equally effective compared to usual care **(Chapter 5).** Moreover, based on a meta-analysis, we concluded that physiotherapy through eHealth has the potential to enhance quality of life.

As a result, we performed a study to investigate the feasibility of postoperative physiotherapy through eHealth in patients with postoperative complications after an esophagectomy. We confirmed its feasibility, predominantly in the first six weeks after discharge **(Chapter 6)**. Patients were more able to self-manage their health condition and to integrate this into their physical functioning by performing functional exercises under supervision of a physiotherapist through eHealth.

Moreover, patient satisfaction rates on the physiotherapy intervention through eHealth in our study were consistently high. This was also confirmed in other studies, where the main contributors to patients' satisfaction were the reduced travel times, increased access to specialist care and increased flexibility in performing exercises.[17,18] This was further confirmed in the high adherence rates up to almost hundred percent, mainly in the first 6 weeks after discharge from the hospital.

We also investigated the effectiveness of the eHealth intervention by comparing the intervention group with a matched historical control group receiving usual care. We concluded that there were no significant differences in outcomes of physical functioning after three months, which is in agreement with the conclusions of our systematic review **(Chapter 5)** and similar to previous studies that found eHealth interventions to be equally effective as usual care on at least one functional outcome measure.[19,20]

However, most of the functional status outcome measures of our intervention group at baseline were significantly lower than those of the matched control group. It could therefore be hypothesized that the intervention group gained more progress on physical functioning than the matched controls, finally resulting in equal outcomes 3 months postoperatively.

Methodological considerations

Study population

The patients included in our studies showed on average high preoperative pulmonary function and physical functioning compared to reference values **(Chapter 3).** Moreover, few patients with chronic obstructive pulmonary disease, diabetes mellitus type 2 and cardiovascular comorbidities were present. In that respect, our study population systematically differed from other patients with esophageal cancer undergoing surgery. Klevebro et al.[21] reported in their European multicenter cohort study of 1590 included patients that cardiorespiratory comorbidity and impaired pulmonary function were associated with postoperative complications after esophageal cancer surgery. These findings confirm the relatively healthy population included in our study and could be an explanation why no association was found between preoperative physical functioning and postoperative complications **(Chapter 2).**

For the study described in **Chapter 3** only one-third of the patients were assessed at both postoperative measurements. Loss to follow-up was mainly caused by the inability to test due to weakness or no-show. It could be argued that predominantly patients with postoperative complications or low physical fitness levels were among these patients. A detailed analysis however revealed that the patients lost to follow-up did not systematically differ in baseline characteristics and physical functioning at baseline.

Despite the reported prevalence of sarcopenia of at least 57% in surgical patients with esophageal cancer, only two of the included patients **(chapter 4)** were detected with sarcopenia based on CT scanning.[13] The low prevalence of sarcopenia in our study population may be explained by a selection of relatively healthy patients that consented to participate in the study. However, additional analysis of patients not included in our study to rule out this potential selection bias, did not reveal additional cases. In several studies it has been proposed that there is still a lack of consensus on the best techniques to measure muscle mass and reference standards to confirm sarcopenia.[22,23] Therefore, the absence of a clear definition of sarcopenia and its diagnostic criteria may have caused an underestimation of sarcopenia in our study cohort.[14]

Study design

In **Chapter 3** we prospectively investigated our study population from 3 months before surgery to 3 months after surgery. Measurements on physical functioning were performed 3 months and 1 day before surgery and 1 week and 3 months after surgery. All patients received neoadjuvant chemoradiation therapy in the preoperative phase of which the negative effects on physical functioning and physiological capacity are well known.[11,24] Unfortunately, we have not been able to measure our patients directly after neoadjuvant chemoradiation therapy to objectify the effects on physical functioning. However, we did not find differences in physical functioning between 3 months and 1 day before surgery, suggesting that patients were able to recover to baseline physical functioning if they would have suffered from negative effects due to chemoradiation therapy.

In our feasibility study described in **Chapter 6** we investigated the effectiveness of the eHealth intervention with usual care. Although a randomized controlled trial is considered as the golden standard to investigate the effectiveness of an intervention, we compared the intervention group with a matched historical control group. We performed statistical matching on multiple relevant patient characteristics, but there were still few imbalances present. Therefore, a systematic bias could not completely be ruled out.

Outcome measures

In the studies described in **Chapter 2,3, 4 and 6** we measured physical functioning. Physical functioning as part of functional status contains more aspects than we investigated, but we only selected indicators with good clinical applicability and clinical relevance, that have been shown to have an association with postoperative complications in other surgical populations.[25] This approach allows for assessing patients on relevant physical parameters, and guides tailored physiotherapeutic intervention.

In addition, several determinants of physical functioning were compared to currently available reference values, matched for age and gender presented in the peer-reviewed literature. Within physiotherapy, there is a lack of consistency in interpreting these reference values because they have either been based on the means and standard deviations of comparable normative samples or on values from regression equations.[26] This might have led to an incorrect interpretation of high versus low physical functioning although these reference values are widely used in physiotherapy practice to indicate physical functioning.

For our systematic review described in **Chapter 5**, we decided to include all studies providing surgical patients with an intervention through eHealth in order not to miss any relevant articles**.** Because of the heterogeneity in intervention- and outcome measures we were not able to compare them on effectiveness in a meta-analysis.

Implications for clinical practice

Risk stratification

The importance of a patient's physiological and physical functioning to successfully recover from surgery has been emphasized in literature.[2,27] Optimizing preoperative physical functioning may not only improve postoperative outcome, but also enhance quality of life and reduce hospital costs.[3]

Preoperative risk stratification typically allows for determining who may benefit from preoperative improvement of physical functioning. A recent European multicenter cohort study of Klevebro et al.[21] stated that cardiorespiratory comorbidity and impaired pulmonary function are associated with postoperative complications. Therefore, current clinical guidelines even suggest that every high-risk surgical patient should be provided with preoperative physiotherapy to improve physical functioning.[28] This is however debatable, to say the least.

There are two different perspectives on the definition of 'risk'. The first refers to the patient's individual risk profile of an adverse outcome, such as postoperative pulmonary complications, poor postoperative recovery and mortality, related to the general population.[29] This risk is determined by patient-specific characteristics, such as age, comorbidities and physical functioning before surgical intervention. In that respect, our study population could be considered as 'lower risk', since they showed few cardiovascular comorbidities, high pulmonary function and high preoperative physical functioning **(Chapter 2)**. The second perspective refers to the risks of the specific surgical procedure on adverse outcomes related to all surgical procedures.[29] This second perspective seems to be more applicable to our study population, where more than half of the patients suffered from a postoperative complication *despite* few cardiovascular comorbidities, high pulmonary function and high preoperative levels of physical functioning.

Therefore, knowledge about a patients' risk not only refers to the individual factors, such as age, comorbidities and physical functioning, but also to factors associated with the type of surgery.[29]

Our study clearly showed that the incidence of postoperative complications was high, despite high levels of preoperative physical functioning. Therefore, the question is justified if preoperative improvement of physiological and physical functioning is beneficial for all patients with an indication for esophagectomy. Little improvement in physiological and physical functioning is to be expected if these levels are already high. Moreover, there seemed to be no relationship between preoperative functional status and postoperative complications in our study cohort **(Chapter 2)**.

This illustrates the necessity of a systematic evaluation of both the pre- and postoperative course of physical functioning as well as knowledge about specific patient-, disease- and surgical characteristics, before deciding on whether and when improvement of physical functioning by tailored physiotherapy is indicated, either pre- or postoperatively. This preoperative risk stratification should be performed in every patient with esophageal cancer, based on known individual risk factors and relevant aspects of physical functioning.

Physical exercise and nutrition

The individual risk for poor postoperative outcome in patients diagnosed with esophageal cancer is further determined by a patient's nutritional status.[1,30] Malnutrition is a combination of inadequate intake and increased protein requirements, hypermetabolism and hypercatabolism that alter nutrient utilization with as a consequence cachexia, manifested in a poor physical functioning and low metabolic reserve.[24,31] This may ultimately result in sarcopenia, a phenotypic feature of cachexia, leading to a reduced overall survival compared to non-sarcopenic patients.[24] Therefore, the risk of sarcopenia should be identified as early as possible after being diagnosed with esophageal cancer.[24] Patients with a high risk of malnutrition are highly recommended to follow a multimodal treatment containing exercise resistance training with nutritional therapy to avoid sarcopenia.[12,31] Although our study population hardly contained sarcopenic cases, it still remains important to identify individuals at risk before surgery from a preventative perspective, taking in to consideration the prevalence of sarcopenia up to 35% one year post-esophagectomy.[11]

Our study showed an association between muscle strength and muscle mass, which facilitates the early identification of individuals with probable sarcopenia and the functional consequences in patients with esophageal cancer, as suggested by the European Working Group on Sarcopenia in Older People (EWGSOP).[14,32,33]

Bridging the gap between hospital and primary care

In **Chapter 6** we showed that postoperative recovery of patients with esophageal cancer suffering from postoperative complications after hospital discharge could be managed with physiotherapy through eHealth in a patient's home situation.[34] Physiotherapy with eHealth allows patients to perform their exercises at home flexibly and more frequently with reduced traveling time and costs and without extra face-to-face visits.[34-36] Moreover, physiotherapy through eHealth could be a valuable tool to overcome discontinuities that may arise in communication between hospital and primary care physiotherapy just after hospital discharge.[20] It allows for a smooth transition of knowledge about disease specific issues as well as expertise required to provide physiotherapy at home.[15] In addition, eHealth applications allow for improving interdisciplinary coordination and integration of care in complex patients.[37]

Therefore, as restrictions in physical functioning may be profound in patients with postoperative complications after complex surgery, physiotherapeutic interventions through eHealth should be strongly considered to improve physical functioning in a patient's home situation, especially in the first period after discharge.

Suggestions for further research

Our study population generally contained individuals with few known risk factors for postoperative complications and poor postoperative outcomes. Yet, recent literature has confirmed the association between preoperative risk factors and postoperative outcomes in patient undergoing esophageal cancer surgery, although this association was not found in our population.[21] Therefore, we highly recommend to perform a large observational cohort study consisting of a heterogenous population of patients with esophageal cancer. This would allow for investigating a prediction model of physical functioning and other conventional risk factors to determine whether patients indicated for esophagectomy are at high risk for a delayed postoperative recovery.[38]

This model may then be applied for clinical use to differentiate which patients should be referred to a physiotherapist to obtain tailored care to improve pre- and postoperative physical functioning and thereby enhancing postoperative recovery.

The predictive value of muscle strength and muscle quantity to determine sarcopenia and its functional consequences should be further investigated in a cohort of both sarcopenic and non-sarcopenic patients. Once physiotherapists are able to identify patients who are at risk for sarcopenia, it will allow them to provide these patients with a physiotherapeutic intervention to increase muscle mass and muscle strength, which might subsequently improve postoperative recovery and functional outcome.[9,24]

Finally, the applicability of a postoperative eHealth intervention involves more than feasibility and positive satisfaction. Although we found equal physical functioning outcomes between the intervention and historical control group three months after surgery, we suggest performing a randomized controlled trial for only these patients at high risk for poor postoperative functional recovery, to draw firm conclusions on its effectiveness.

General conclusion

This thesis was aimed at investigating the pre- and postoperative course of physical functioning in patients with esophageal cancer undergoing elective surgery and to identify factors associated with poor postoperative physical recovery. Contrary to the course of physical functioning of many comparable high-risk surgical populations, our studies illustrated that preoperative physical functioning was higher than predicted, returned to baseline values three months postoperatively and that the course of physical functioning did not systematically differ between patients with and without postoperative complications.

The selection of relatively healthy patients included in our studies could be explained by the fact that patients were excluded for surgery if their physical functioning was too low, because of the associated risks for postoperative morbidity and mortality.[7] If we would be able to identify patients with poor preoperative physical functioning and to provide them with tailored preoperative physiotherapeutic treatment to improve their physical functioning, these patients may still be eligible for surgical treatment.

Therefore, our findings emphasize the urge of stratifying risks preoperatively on poor postoperative outcomes based on individual risk factors, to decide who needs preoperative physiotherapeutic treatment.

The majority of our study population did not show these individual risk factors and would not have benefited from preoperative training, yet still more than half of them suffered from postoperative complications. These postoperative complications in their turn, may hamper postoperative functional recovery and therefore postoperative physiotherapy with eHealth in the patient's home situation should be strongly considered for patients at risk, to promote them being functionally independent again after high-risk surgery.

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APPENDIX

Summary

PHYSICAL FUNCTIONING IN SURGICAL PATIENTS WITH ESOPHAGEAL CANCER:
from risk stratification to targeted physiotherapy

A large proportion of patients with esophageal cancer develops a postoperative complication. Impairments in preoperative physical functioning are an important prognostic factor for the development of postoperative complications and a delayed functional recovery. There is significant evidence for the relationship between preoperative physical functioning and postoperative functional recovery, but this evidence is lacking for patients with esophageal cancer.

To determine which patients are at risk for postoperative complications and a delayed functional recovery, the course of pre- and postoperative physical functioning over time has been systematically investigated in this thesis. Based on this, patients can be identified who may benefit from tailor-made pre- or postoperative physiotherapy treatment to enhance postoperative recovery.

Chapter 1 explains the consequences of major abdominal and/ or thoracic surgery on physical functioning and what contribution the physical therapist can make in both the pre- and postoperative trajectory. The main objective of this thesis is to evaluate the pre- and postoperative course of physical functioning in patients with esophageal cancer who undergo surgery. In addition, the objectives per study have been described.

Chapter 2 describes whether there is a relationship between preoperative functioning and the occurrence of postoperative complications in patients with esophageal cancer who have undergone surgery. A prospective cohort study was conducted for this purpose between March 2012 and October 2014, in which 94 patients with esophageal cancer were examined for determinants of physical functioning one day before the operation. This involved inspiratory muscle strength, handgrip strength, physical activities and quality of life. Postoperative complications were registered according to the Clavien-Dindo classification. Of the 94 patients enrolled in this study, 90 patients underwent esophageal resection with gastric tube reconstruction. Of these, 55 patients developed one or more postoperative complications. After performing univariate and multivariate regression analyzes, there appeared to be no relationship between preoperative physical functioning and the occurrence of postoperative complications. In contrast to other comparable populations undergoing thoracic surgery, preoperative physical functioning in patients with esophageal cancer appears not to be associated with postoperative complications.

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In **Chapter 3**, the pre- and postoperative course of physical functioning was investigated in patients with esophageal cancer who undergo surgery, in order to better determine whether a physiotherapy intervention is indicated, when it should take place and who might benefit from this intervention. For this purpose, 155 patients with esophageal cancer were examined between March 2012 and June 2016, twice preoperatively (3 months and 1 day before surgery) and twice postoperatively (5 days and 3 months after surgery) for physical functioning and quality of life. Changes in physical functioning over time have been analyzed with longitudinal regression techniques. In 60 of the 155 patients who underwent surgery, all measurements were performed. Three months postoperatively, physical functioning returned to the level of 3 months preoperatively, with the exception of handgrip strength and fatigue. Moreover, no difference was found in the course of physical functioning over time between the group of patients with and without postoperative complications. This study has shown that, on average, patients with esophageal cancer had a good preoperative condition related to reference values. In addition, all patients appeared to return to the old level of physical functioning 3 months after the operation, regardless of the occurrence of postoperative complications. This study shows that the level of preoperative physical functioning is not necessarily an indicator of postoperative recovery for every patient. It is therefore important to first evaluate the pre- and postoperative functioning of high-risk surgical populations before determining whether physiotherapy treatment is necessary.

In **Chapter 4** we investigated whether there is an association between preoperative muscle strength and muscle mass in patients with esophageal cancer indicated for surgery, because previous research has shown that these aspects are independent predictors of delayed postoperative recovery. One hundred twenty-five patients were eligible for this cross-sectional study, of which the CT scans of 93 patients were suitable for analyzing muscle mass at the level of the third lumbar vertebra (L3). The measured muscle mass from the CT scans was then compared with handgrip strength, in- and expiratory muscle strength of the respiratory muscles and functional leg muscle strength. The associations were determined using linear regression techniques. The results show that gender, weight, handgrip strength and inspiratory muscle strength were independently associated with muscle mass measured at L3. All of these variables together explain 66% of the variability in muscle mass measured at L3. This study shows that there is a clear association between muscle strength and muscle mass in patients with esophageal cancer who undergo surgery and that enables physiotherapists to make an estimation about the amount of muscle mass and the functional consequences, by assessing muscle strength.

Chapter 5 concerns a systematic literature review with meta-analysis, in which an overview is provided of scientific literature on the effectiveness of physiotherapy through tele-rehabilitation on postoperative functional outcomes and quality of life in surgical populations. For this, randomized controlled studies, clinically controlled studies, quasi-randomized and quasi-experimental studies with similar control groups were eligible without restriction on language or publication date. The methodological quality was investigated with the Cochrane Risk of Bias tool. Twenty-three studies were eligible for qualitative analysis and 7 studies for meta-analysis. Despite the variation in treatment and outcome measures, this literature review shows that physiotherapy with telerehabilitation has the potential to improve quality of life in patients who have undergone surgery. In addition, physiotherapy with telerehabilitation proved to be feasible and at least as effective as conventional physiotherapy. These may be sufficient reasons to consider physiotherapy with telerehabilitation, even though the overall effectiveness on physical outcome measures remains unclear.

In **Chapter 6** a feasibility study was conducted on a postoperative physiotherapy intervention with telerehabilitation in patients who have undergone esophageal resection with a postoperatively complicated recovery. In addition, the effectiveness of this intervention on functional recovery was investigated by comparing the intervention group with a historical cohort of comparable patients who did not undergo this intervention. Finally, 15 out of 22 patients underwent a 12-week physiotherapy treatment in their own home situation directly after discharge from the hospital, where exercise therapy and support were offered via an eHealth application. Patient adherence, patient satisfaction and duration of treatment was investigated. In addition, the effect of this intervention on physical functioning was investigated. Patient adherence was particularly high in the first 6 weeks of the intervention and then declined. No difference was found in physical functioning after the treatment between the intervention group and the historical control group. Because of the high patient satisfaction and adherence, this study shows that physiotherapy in the home situation with eHealth should be considered in patients with esophageal cancer who have undergone complicated surgery, especially in the first 6 weeks after discharge.

In **Chapter 7** the most important findings, methodological considerations and clinical implications are discussed. In addition, recommendations are made for future follow-up research into the physiotherapy assessment and treatment process for patients who undergo high-risk surgery. This thesis demonstrates the importance of systematically evaluating pre- and postoperative physical functioning, before determining which patients are at risk of a delayed postoperative recovery. Based on this, patients can be identified who may benefit from tailor-made pre- or postoperative physiotherapy treatment to enhance postoperative recovery.

APPENDIX

Samenvatting

FYSIEK FUNCTIONEREN BIJ CHIRURGISCHE PATIËNTEN MET SLOKDARMKANKER:
van risicostratificatie naar doelgerichte fysiotherapie

Een groot deel van de patiënten met slokdarmkanker ontwikkelt een postoperatieve complicatie. Stoornissen in het preoperatief fysiek functioneren zijn een belangrijke prognostische factor voor het ontwikkelen van postoperatieve complicaties en een vertraagd functioneel herstel. Er bestaat significant bewijs voor de relatie tussen preoperatief fysiek functioneren en postoperatief functioneel herstel, maar dit bewijs ontbreekt voor patiënten met slokdarmkanker.

Om te bepalen welke patiënten risico lopen op postoperatieve complicaties en een vertraagd functioneel herstel, is in dit proefschrift het beloop in pre- en postoperatief fysiek functioneren in de tijd systematisch onderzocht. Op basis daarvan kunnen patiënten geïdentificeerd worden die mogelijk baat hebben bij een op maat gesneden pre- of postoperatieve fysiotherapeutische behandeling om het postoperatieve herstel te bespoedigen.

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In **Hoofdstuk 1** wordt uiteengezet wat de gevolgen van een grote operatie in de buik en/ of borstholte kunnen zijn op het fysiek functioneren en welke bijdrage de fysiotherapeut in zowel het pre- als postoperatieve traject kan hebben. De voornaamste doelstelling van dit proefschrift is het evalueren van het pre- en postoperatieve beloop van fysiek functioneren bij patiënten met slokdarmkanker die een operatie ondergaan. Daarnaast worden de doelstellingen per studie beschreven.

In **Hoofdstuk 2** wordt beschreven of er een relatie bestaat tussen het preoperatief functioneren en het optreden van postoperatieve complicaties bij patiënten met slokdarmkanker die een operatie hebben ondergaan. Hiervoor is tussen maart 2012 en oktober 2014 een prospectieve cohortstudie uitgevoerd, waarbij 94 patiënten met slokdarmkanker een dag voor de operatie onderzocht zijn op determinanten van fysiek functioneren. Het ging hierbij om inspiratoire spierkracht, handknijpkracht, fysieke activiteiten en kwaliteit van leven. Postoperatieve complicaties werden geregistreerd volgens de Clavien-Dindo classificatie. Van de 94 patiënten die voor dit onderzoek zijn geïncludeerd, hebben uiteindelijk 90 patiënten een slokdarmresectie met buismaagreconstructie ondergaan. Daarvan hebben uiteindelijk 55 patiënten een of meerdere postoperatieve complicaties ontwikkeld. Na het uitvoeren van uni- en multivariate regressieanalyses, bleek er uiteindelijk geen relatie te zijn tussen preoperatief fysiek functioneren en het optreden van postoperatieve complicaties. In tegenstelling tot andere vergelijkbare populaties die een thoracale chirurgische ingreep ondergaan, blijkt bij patiënten met slokdarmkanker die een operatie ondergaan het preoperatief fysiek functioneren niet geassocieerd te zijn met postoperatieve complicaties.

In **Hoofdstuk 3** is het pre- en postoperatieve beloop in fysiek functioneren onderzocht bij patiënten met slokdarmkanker die een operatie ondergaan, om beter te kunnen bepalen of er een fysiotherapeutische interventie geïndiceerd is, wanneer deze zou moeten plaatsvinden en wie mogelijk baat zou hebben bij deze interventie. Hiervoor zijn 155 patiënten met slokdarmkanker tussen maart 2012 en juni 2016 tweemaal preoperatief (3 maanden en 1 dag voor de operatie) en tweemaal postoperatief (5 dagen en 3 maanden na de operatie) onderzocht op fysiek functioneren en kwaliteit van leven. Met behulp van longitudinale regressietechnieken zijn de veranderingen in fysiek functioneren over de tijd geanalyseerd. Van de 155 patiënten die de operatie hebben ondergaan, zijn uiteindelijk bij 60 patiënten alle metingen uitgevoerd. Drie maanden postoperatief bleek het fysiek functioneren weer op het niveau te zijn van 3 maanden preoperatief, met uitzondering van handknijpkracht en vermoeidheid. Bovendien werd er geen verschil gevonden in het beloop van fysiek functioneren over de tijd tussen de groep patiënten met en zonder postoperatieve complicaties. Deze studie heeft aangetoond dat patiënten met slokdarmkanker gemiddeld genomen een goede preoperatieve conditie hadden, gerelateerd aan referentiewaarden. Daarnaast bleken alle patiënten 3 maanden na de operatie gemiddeld genomen weer op het oude niveau van fysiek functioneren uitgekomen te zijn, ongeacht het optreden van postoperatieve complicaties. Deze studie toont daarmee aan dat het niveau van preoperatief fysiek functioneren niet voor iedere patiënt per se een indicator is voor het postoperatieve herstel. Daarom is het van belang om eerst het pre- en postoperatieve functioneren van risicovolle chirurgische populaties te evalueren alvorens te bepalen of een fysiotherapeutische behandeling noodzakelijk is.

In **Hoofdstuk 4** is onderzocht of er een associatie bestaat tussen preoperatieve spierkracht en spiermassa bij patiënten met slokdarmkanker die een indicatie voor een operatie hebben, omdat uit eerder onderzoek bekend is dat deze aspecten onafhankelijke voorspellers zijn voor een vertraagd postoperatief herstel. Voor deze cross-sectionele studie kwamen 125 patiënten in aanmerking, waarvan uiteindelijk de CT-scans van 93 patiënten geschikt waren om de spiermassa te analyseren op het niveau van de derde lumbale wervel (L3). De gemeten spiermassa uit de CT-scans is vervolgens vergeleken met handknijpkracht, in- en expiratoire spierkracht van de ademhalingsmusculatuur en functionele beenspierkracht. Vervolgens zijn met lineaire regressietechnieken de associaties bepaald. De resultaten laten zien dat geslacht, gewicht, handknijpkracht en inspiratoire spierkracht onafhankelijk geassocieerd waren met spiermassa gemeten op L3. Al deze variabelen gezamenlijk verklaren 66% van de variabiliteit in spiermassa gemeten op L3. Deze studie toont aan dat er een duidelijke associatie is tussen spierkracht en spiermassa bij patiënten met slokdarmkanker die een operatie ondergaan en dat stelt fysiotherapeuten in staat om door middel van spierkracht te testen, een uitspaak te doen over de hoeveelheid spiermassa en de functionele consequenties.

Hoofdstuk 5 betreft een systematische literatuurstudie met meta-analyze, waarbij een overzicht wordt gegeven van wetenschappelijke literatuur naar de effectiviteit van fysiotherapie door middel van telerevalidatie op postoperatieve functionele uitkomsten en kwaliteit van leven in chirurgische populaties. Hiervoor kwamen gerandomiseerde gecontroleerde studies, klinisch gecontroleerde studies, quasi-gerandomiseerde en quasi-experimentele studies met vergelijkbare controlegroepen in aanmerking zonder restrictie op taal of publicatiedatum. De methodologische kwaliteit werd onderzocht met de Cochrane Risk of Bias tool. Uiteindelijk kwamen 23 studies in aanmerking voor kwalitatieve analyse en 7 studies voor een meta-analyse. Ondanks de variatie in behandeling en uitkomstmaten, blijkt uit deze literatuurstudie dat fysiotherapie met telerevalidatie de potentie heeft om kwaliteit van leven te verbeteren bij patiënten die een operatie hebben ondergaan. Daarnaast bleek fysiotherapie met telerevalidatie haalbaar en minstens even effectief te zijn als gangbare fysiotherapie. Dit kunnen voldoende redenen zijn om fysiotherapie met telerevalidatie te overwegen, ondanks dat de algehele effectiviteit op fysieke uitkomstmaten nog onduidelijk blijft.

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In **Hoofdstuk 6** is een haalbaarheidsstudie uitgevoerd naar een postoperatieve fysiotherapeutische interventie met telerevalidatie bij patiënten die een slokdarmresectie hebben ondergaan en daarbij een postoperatief gecompliceerd herstel hebben doorgemaakt. Daarnaast is onderzocht wat de effectiviteit van deze interventie was op functioneel herstel door de interventiegroep te vergelijken met een historisch cohort van vergelijkbare patiënten die deze interventie niet hebben ondergaan. Uiteindelijk hebben 15 van de in totaal 22 patiënten na ontslag uit het ziekenhuis een 12 weken durende fysiotherapeutische behandeling ondergaan in de eigen thuissituatie waarbij de oefentherapie en de begeleiding werden aangeboden via een eHealth-applicatie. Hierbij werd onderzocht wat de therapietrouw, patiënttevredenheid en behandelduur was. Daarnaast werd onderzocht wat het effect van deze interventie op het fysiek functioneren was. De therapietrouw was met name in de eerste 6 weken van de interventie hoog en daalde daarna. Er werd geen verschil gevonden in fysiek functioneren na afloop van de behandeling tussen de interventiegroep en de historische controlegroep. Vanwege de hoge patiënttevredenheid en therapietrouw toont deze studie aan dat vooral in de eerste 6 weken na ontslag fysiotherapie in de thuissituatie met eHealth overwogen moet worden bij patiënten met slokdarmkanker die een gecompliceerde operatie hebben ondergaan.

In **Hoofdstuk 7** komen de belangrijkste bevindingen, methodologische overwegingen en klinische implicaties aan bod. Daarnaast worden aanbevelingen gedaan voor toekomstig vervolgonderzoek naar het fysiotherapeutische onderzoek en behandeltraject bij patiënten die een hoog-risicovolle operatie ondergaan. Dit proefschrift toont het belang aan van het systematisch in kaart brengen van het pre- en postoperatief fysiek functioneren, alvorens te bepalen welke patiënten risico lopen op een vertraagd postoperatief herstel. Op basis daarvan kunnen patiënten geïdentificeerd worden die mogelijk baat hebben bij een op maat gesneden pre- of postoperatieve fysiotherapeutische behandeling om het postoperatieve herstel te bespoedigen.

APPENDIX

Portfolio

PORTFOLIO

Name PhD student:	Maarten Alexander van Egmond
PhD period:	2014-2020
Name PhD supervisor:	Prof. Dr. R.H.H. Engelbert and Prof. Dr. J.H.G. Klinkenbijl
Name Co-supervisors:	Dr. M. van der Schaaf and Prof. Dr. M.I. van Berge Henegouwen

PhD training	Year	Workload ECTS
General courses		
Scientific writing in English for publication. Graduate School for medical sciences, UvA, Amsterdam	2014	1.5
Systematic reviews. Graduate School for medical sciences, UvA, Amsterdam	2015	0.7
Clinical data management. Graduate School for medical Sciences, UvA, Amsterdam	2016	0.32
Basic course legislation and organization (BROK). Graduate school for medical sciences, UvA, Amsterdam	2016	1
Project management. Graduate school for medical sciences, UvA, Amsterdam	2016	0.6
Practical biostatistics. Graduate school for medical sciences, UvA, Amsterdam	2017	1
Longitudinal data analysis. EpidM, Amsterdam University Medical Centers, VUMC, Amsterdam	2017	3
Cambridge English Language Assessment. Amsterdam	2016	0.2
Seminars, workshops and master classes		
Interpretation cardiopulmonary exercise testing. The Physiology Academy, Amsterdam	2015	0.2
Studiedag voeding, bewegen en kanker. Mark Two Academy, Utrecht	2020	0.2
Presentations		
Fysiotherapeutische risicostratificatie bij chirurgische slokdarmkankerpatienten. Oral presentation, PhD symposium: 'De eerste stap'. AMC, Amsterdam	2014	0.5

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PhD training	Year	Workload ECTS
Fysiotherapeutische risicostratificatie bij chirurgische slokdarmkankerpatienten; de eerste stappen naar voorspoedig herstel. Oral presentation, Dag van de Fysiotherapeut, KNGF. Utrecht	2014	0.5
The association of preoperative functional status with postoperative complications in esophageal cancer patients. Oral presentation, Research meeting GIOCA. AMC, Amsterdam	2014	0.5
Het gebruik van normwaarden in wetenschappelijk onderzoek: wat is normaal? Oral presentation, Research meeting. Amsterdam University of Applied Sciences, Amsterdam	2014	0.5
Fysiotherapeutische screening en behandeling bij chirurgische slokdarmkankerpatienten. Poster presentation, National Esophageal Cancer Day. AMC, Amsterdam.	2014	0.5
Physiotherapeutic risk stratification and tailored intervention in esophageal cancer patients undergoing elective surgery. Oral presentation, Board of Directors. Amsterdam University of Applied Sciences, Amsterdam	2015	0.5
Preliminary results physiotherapeutic risk stratification for gastro intestinal cancer patients undergoing elective surgery. Oral presentation, Research meeting Rehabilitation Department. AMC, Amsterdam	2015	0.5
Preoperative functional status is not associated with postoperative surgical complications in low risk patients undergoing esophagectomy. Oral presentation, Research Meeting GIOCA. AMC, Amsterdam	2015	0.5
Postoperative Telerehabilitation to improve functional recovery in patients after esophagectomy: a feasibility-study. Oral presentation, Research meeting Rehabilitation Department. AMC, Amsterdam	2016	0.5
Fysiotherapie bij patiënten met slokdarmkanker: actief naar voorspoedig herstel. Oral presentation, National Esophageal Cancer Day. AMC, Amsterdam	2016	0.5
Functional muscle strength is associated with muscle mass in patients with esophageal cancer awaiting surgery. Poster presentation, 10th international conference on cachexia, sarcopenia & muscle wasting. Rome, Italy.	2017	0.5

PhD training	**Year**	**Workload ECTS**
Preoperative functional status is not associated with postoperative surgical complications in low risk patients undergoing esophagectomy. Poster presentation, World Confederation for Physical Therapy Congress. Cape Town, South-Africa	2017	0.5
Kwaliteit van leven na een operatie: optimale voeding en beweging. Oral presentation, National Pancreatic Cancer Day. AMC, Amsterdam	2017	0.5
Does Better in lead to Better out? Research results and practical implications. Oral presentation, Refereeravond Revalidatiegeneeskunde. AMC, Amsterdam	2017	0.5
Hoe word ik weer fit na een operatie? Het belang van actief bewegen na ontslag. Oral presentation, National Esophageal Cancer Day. AMC, Amsterdam.	2018	0.5
The pre- and postoperative course of functional status of patients with esophageal cancer undergoing esophagectomy: a prospective longitudinal study. Poster presentation, Dag van de Fysiotherapeut, KNGF. ‘s Hertogenbosch.	2018	0.5
Ver van huis na het ziekenhuis: minisymposium. Oral presentation, Dag van de Fysiotherapeut, KNGF. ’s Hertogenbosch.	2019	0.5
The pre- and postoperative course of functional status of patients with esophageal cancer undergoing esophagectomy: a prospective longitudinal study. Oral presentation rapid five session, World Confederation for Physical Therapy Congress. Geneva, Switserland.	2019	0.5
Postoperative physiotherapy with eHealth after esophageal cancer surgery is feasible. Oral presentation, Physitrack. Amsterdam	2019	0.5
Fysiek functioneren bij chirurgische patiënten met slokdarmkanker. Oral presentation , Studiedag Voeding, Bewegen en Kanker. Mark Two Academy, Utrecht	2020	0.5

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PhD training	Year	Workload ECTS
(Inter)national conferences		
Annual Congress Royal Dutch Society of Physiotherapy, KNGF. Barneveld	2017	0.5
World Confederation for Physical Therapy Congress. Cape Town, South Africa	2017	1
World Confederation for Physical Therapy Congress. Geneva, Switserland	2019	1
Annual Congress Royal Dutch Society of Physiotherapy, KNGF. ‘s Hertogenbosch	2019	1

Teaching	Year	Workload ECTS
Lecturing		
Training Standardized Operating Procedures: Physiotherapeutic risk stratification for gastro intestinal cancer patients undergoing elective surgery. Workshop. OLVG, Amsterdam	2012	1
Clinical Reasoning, Evidence Based Practice, Scientific Writing. Amsterdam University of Applied Sciences, European School of Physiotherapy, Amsterdam	2014-2020	4
Physiotherapeutic risk stratification and tailored intervention in esophageal cancer patients undergoing elective surgery. Minor Rehabilitation. Amsterdam University of Applied Sciences, Amsterdam	2017-2020	1
Mentoring		
Student thesis: The effectiveness of telehealth on postoperative outcomes within high-risk surgical patients: A systematic review (Leyon & Muliar 2014)	2014	1
Student thesis: Muscle Strength in oesophageal cancer patients undergoing esophagectomy (Stender et al. 2016)	2016	1
Student thesis: Activity tracker for hospitalized patients (Benabbes & Kolomvounis 2016)	2016	1
Student thesis: A systematic review to find the most effective intervention for post-thoracic surgery patients (Delmas Benito & Thacker 2017)	2017	1

Grants	Year
Doctoral grant for teachers from the Dutch Research Council (NWO	2014

Publications	Year
Peer reviewed	
van Egmond MA, van der Schaaf M, Klinkenbijl JH, Engelbert RH, van Berge Henegouwen, MI. Preoperative functional status is not associated with postoperative surgical complications in low risk patients undergoing esophagectomy. *Dis Esophagus.* 2017 Jan 1;30(1):1-7.	2017
van Egmond MA, van der Schaaf M, Vredeveld T, Vollenbroek-Hutten MMR, van Berge Henegouwen MI, Klinkenbijl JH, Engelbert RHH. Effectiveness of physiotherapy with telerehabilitation in surgical patients: a systematic review and meta-analysis. *Physiotherapy.* 2018 Sep;104(3):277-298.	2018
van Egmond MA, van der Schaaf M, Hagens ERC, van Laarhoven HWM, van Berge Henegouwen MI, Haverkort EB, Engelbert RHH, Gisbertz SS. Muscle Strength Is Associated With Muscle Mass in Patients With Esophageal Cancer Awaiting Surgery. *J Geriatr Phys Ther.* 2020;43(2):82-88.	2020
van Egmond MA, van der Schaaf M, Klinkenbijl JHG, Twisk JWR, Engelbert RHH, van Berge Henegouwen MI. The pre- and postoperative course of functional status in patients undergoing esophageal cancer surgery. *Eur J Surg Oncol*. 2020;46(1):173–179.	2020
Hagens ER, Feenstra ML, **van Egmond MA**, van Laarhoven HW, Hulshof, MC, Boshier PR, Low DE, van Berge Henegouwen MI, Gisbertz SS. Influence of body composition and muscle strength on outcomes after multimodal oesophageal cancer treatment. *Cachexia Sarcopenia Muscle*. 2020;11(3):756-767.	2020
van Egmond MA, Engelbert RH, Klinkenbijl JH, van Berge Henegouwen MI, van der Schaaf M. Physiotherapy With Telerehabilitation in Patients With Complicated Postoperative Recovery After Esophageal Cancer Surgery: Feasibility Study. *J Med Internet Res.* 2020;22(6):e16056.	2020

Other	
van Egmond MA, van der Schaaf M, Engelbert RHH. Slokdarmresectie bij slokdarmkanker; Preoperatieve functionele status niet geassocieerd met postoperatieve complicaties. *Fysiopraxis.* 2017; jul-aug:32-35.	2017

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APPENDIX

Contributions of authors

CONTRIBUTIONS OF AUTHORS

Chapter 2: van Egmond MA, van der Schaaf M, Klinkenbijl JH, Engelbert RH, van Berge Henegouwen, MI. Preoperative functional status is not associated with postoperative surgical complications in low risk patients undergoing esophagectomy. *Dis Esophagus.* 2017 Jan 1;30(1):1-7.

MAvE, MvdS and MIvBH were responsible for study conception and study design. MAvE was responsible for acquisition of data, analysis and interpretation, drafting of the manuscript and critical revision of the manuscript. MvdS and MIvBH contributed to acquisition of data, analysis and interpretation, drafting of the manuscript and critical revision of the manuscript. RHE contributed to the study conception, study design, analysis and interpretation, drafting of the manuscript and critical revision of the manuscript. JHK contributed to study conception, study design, acquisition of data, analysis and interpretation, drafting of the manuscript and critical revision of the manuscript.

Chapter 3: van Egmond MA, van der Schaaf M, Klinkenbijl JHG, Twisk JWR, Engelbert RHH, van Berge Henegouwen MI. The pre- and postoperative course of functional status in patients undergoing esophageal cancer surgery. *Eur J Surg Oncol*. 2020;46(1):173–179.

MAvE, MvdS and MIvBH were responsible for study concepts and study design. MAvE was responsible for data acquisition, quality control of data and algorithms, data analysis and interpretation, statistical analysis, manuscript preparation, editing and review. MvdS contributed to quality control of data and algorithms, data analysis and interpretation, editing and review. RHE contributed to study concepts, study design, quality control of data and algorithms, data analysis and interpretation, editing and review.

JHK contributed to study concepts, study design, data analysis and interpretation, manuscript editing and review. MIvBH contributed to data analysis and interpretation, manuscript editing and review. JT contributed to study concepts, study design, quality control of data and algorithms ,data analysis and interpretation, statistical analysis and manuscript review.

Chapter 4 van Egmond MA, van der Schaaf M, Hagens ERC, van Laarhoven HWM, van Berge Henegouwen MI, Haverkort EB, Engelbert RHH, Gisbertz SS. Muscle Strength Is Associated With Muscle Mass in Patients With Esophageal Cancer Awaiting Surgery. *J Geriatr Phys Ther.* 2020;43(2):82-88.

MAvE, MvdS and SSG were responsible for study conception and study design. MAvE was responsible for acquisition of data, analysis and interpretation, drafting of the manuscript and critical revision of the manuscript. MvdS and SSG contributed to acquisition of data, analysis and interpretation, drafting of the manuscript and critical revision of the manuscript. ERH contributed to study design, acquisition of data, analysis and interpretation drafting of the manuscript and critical revision of the manuscript. HWvL, MIvBH, EBH and RHE contributed to study design, analysis and interpretation, drafting of the manuscript and critical revision of the manuscript.

Chapter 5 van Egmond MA, van der Schaaf M, Vredeveld T, Vollenbroek-Hutten MMR, van Berge Henegouwen MI, Klinkenbijl JH, Engelbert RHH. Effectiveness of physiotherapy with telerehabilitation in surgical patients: a systematic review and meta-analysis. *Physiotherapy.* 2018 Sep;104(3):277-298.

MAvE, MvdS and RHE were responsible for study conception and study design, data analysis and interpretation. MAvE, MvdS and TV were responsible for study selection, data extraction and synthesis. MAvE was responsible for drafting of the manuscript and critical revision of the manuscript. RHE contributed to drafting of the manuscript and critical revision of the manuscript. MvdS, TV, MMV, MIvBH, and JHG contributed to study design, data analysis and interpretation, drafting of the manuscript and critical revision of the manuscript.

Chapter 6: van Egmond MA, Engelbert RH, Klinkenbijl JH, van Berge Henegouwen MI, van der Schaaf M. Physiotherapy With Telerehabilitation in Patients With Complicated Postoperative Recovery After Esophageal Cancer Surgery: Feasibility Study. *J Med Internet Res* 2020;22(6):e16056. MAvE, RHE and MvdS were responsible for study conception and study design. MAvE was responsible for acquisition of data, analysis and interpretation, drafting of the manuscript and critical revision of the manuscript. MIvBH contributed to acquisition of data. RHE and MvdS contributed to analysis and interpretation of data. RHE, JHG, MIvBH and MvdS contributed to drafting of the manuscript and critical revision of the manuscript.

APPENDIX

Dankwoord

DANKWOORD

Het is klaar! Ruim zes jaar geleden begon ik aan dit avontuur, primair gedreven om de fysiotherapeutische zorg voor mensen met slokdarmkanker te verbeteren. Ik heb mij gedurende deze intensieve, maar vooral inspirerende periode, omringd geweten door een groot aantal lieve en bijzondere mensen, zonder wie dit proefschrift er niet was gekomen. Uit de grond van mijn hart: Dank jullie wel! Een aantal van jullie wil ik in het bijzonder noemen.

Allereerst wil ik alle patiënten bedanken die ik tijdens mijn promotiestudie heb mogen begeleiden. Van jullie heb ik veruit het meeste geleerd.

Ik heb van de zijlijn meegemaakt hoe ontwrichtend het is als je van het een op het andere moment geconfronteerd wordt met de diagnose slokdarmkanker, hoe je leven op de schop gaat, veel zekerheden verworden tot onzekerheden en je niet weet hoe de dag van morgen eruit gaat zien. Nassim Nicholas Taleb noemt dit in zijn boek *The Black Swan: the impact of the highly improbable* een ‘Zwarte Zwaan’: een toevallige gebeurtenis, die zich onverwacht voordoet, niet te voorspellen en totaal ontwrichtend is. De diagnose slokdarmkanker is zo’n ‘Zwarte Zwaan’. Tegelijk heb ik met bewondering kunnen zien hoe jullie vol goede moed en positiviteit de draad weer probeerden op te pakken, de zeilen weer hesen en op koers probeerden te komen, ondanks alles stormen die zich wel of niet zouden aandienen, onzeker over wat zich achter de horizon zou bevinden. Het is als varen in een zeilboot: je komt op plekken, waar je nooit eerder geweest bent, maar ook op plekken waar je nooit had willen zijn. Je ziet de mooiste vergezichten, je ontdekt hoe prachtig de natuur kan zijn, maar tegelijkertijd ook hoe meedogenloos.

Ik heb geprobeerd jullie een beetje bij te schijnen om jullie reis misschien wat te vergemakkelijken.

Dat is het verhaal dat de kaft van mijn proefschrift vertelt, prachtig uitgebeeld door Evelien Jagtman.

Ik wil twee mensen in het bijzonder bedanken, Ger en Carolina.
Ger, wie had kunnen denken dat ik ooit van collega in Reade je fysiotherapeut zou worden? Ik heb met bewondering aanschouwd hoe vastberaden je was om te herstellen. Je energie en toewijding zullen me altijd bijblijven. Het feit dat je tijdens je herstel alweer bezig was om op basis van je eigen ervaringen het voedingsplan in Reade te veranderen, tekent je betrokkenheid. Daarnaast was je bereid om je ervaringen te delen met studenten fysiotherapie. Je hebt op hen een onuitwisbare indruk achtergelaten, net zoals op mij.

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Mijn promotietraject liet zich vergelijken met een zeiltocht, waarbij het soms voor de wind ging, maar waar soms toch ook hier en daar een storm opstak. Gelukkig had ik een promotieteam aan boord die mij zo goed als mogelijk hielp op koers te blijven. Bedankt voor al jullie inspanningen om de haven zonder schipbreuk binnen te lopen.

Mijn promotor Prof. Dr. R.H.H. Engelbert. Beste Raoul, het is je gelukt om me aan mijn plafond te laten krabbelen. Ik wil je bedanken voor je vertrouwen en je enthousiasme. Ik realiseer me wat een klus het voor jou moet zijn om al jouw promovendi, met allemaal verschillende persoonlijkheden, begeleiding op maat te bieden. Ik heb het je niet altijd makkelijk gemaakt. Ik kan je nu zeggen, Raoul, ik ben trots op mezelf, echt waar!

Mijn promotor Prof. Dr. J.H.G. Klinkenbijl. Beste Jean, vlak nadat mijn promotie startte, vertrok je uit het AMC om in het Gelre Ziekenhuis te gaan werken. Desondanks was je altijd zeer betrokken bij de voortgang van mijn promotie en dacht je altijd mee in oplossingen. Dank je wel voor je begeleiding en steun.

Mijn copromotor Dr. M. van der Schaaf. Beste Marike, eigenlijk heb jij me geleerd hoe je een goede wetenschappelijke studie moet opzetten en beschrijven. Je hebt de gave om op zodanige manier feedback te geven, dat je het antwoord niet direct weggeeft, maar iemand wel de goede richting op wijst. Daar heb ik heel veel van geleerd en daar wil ik je voor bedanken.

Mijn copromotor Prof. Dr. M.I. van Berge Henegouwen. Beste Mark, ik waardeer jouw enorme passie voor het vak. De patiënten staan bij jou altijd op nummer één, iets dat me zeer aanspreekt. Ik wil je bedanken voor je gedrevenheid en je constructieve feedback, om mijn studies uit te voeren en af te ronden.

De overige leden van de promotiecommissie, Prof. dr. O.R.C. Busch, Prof. dr. F. Nollet, Prof. dr. C.R.N. Rasch, Prof. dr. N.L.U. van Meeteren, Prof. dr. C. Veenhof en Dr. B.P.L. Wijnhoven. Ik wil jullie hartelijk danken voor het lezen en beoordelen van mijn proefschrift en jullie bereidheid zitting te nemen in de promotiecommissie.

Alle medeauteurs, Jos Twisk, Eliza Hagens, Hanneke van Laarhoven, Liesbeth Haverkort, Suzanne Gisbertz, Tom Vredeveld en Miriam Vollenbroek-Hutten. Dank jullie wel voor het delen van jullie kennis en waardevolle input op de beschreven studies in dit proefschrift.

Collega's fysiotherapie van het Amsterdam UMC, locatie AMC, administratie revalidatie en GIOCA. Ik had dit promotietraject nooit succesvol kunnen afleggen zonder jullie steun. Jullie zorgden ervoor dat patiënten doorverwezen en ingepland werden voor fysiotherapeutische screening en jullie zorgden ervoor dat patiënten tijdens ziekenhuisopname werden gemeten. Dank daarvoor. Eén iemand wil ik daarbij in het bijzonder noemen.

Sander Steenhuizen. Beste Sander, jij bent een van de belangrijkste pijlers van mijn promotietraject geweest. In het ziekenhuis voerde jij de meeste metingen uit op de afdeling. Je zorgde ervoor dat alle data netjes gerapporteerd werd, deed extra inspanningen om mensen te includeren voor de haalbaarheidsstudie, boven op de drukke werkzaamheden die je al had en in de tussentijd dacht je kritisch en constructief mee met de bevindingen uit de studies. Ik overdrijf niet, je was van onschatbare waarde. Dank je wel.

Dear (former) colleagues from Team ESP, you have been extremely important during my PhD study over the past 6 years. Although at times I was more focused on research than on teaching, I have always felt supported by you. The enthusiasm with which you welcomed new publications and every step closer to graduation over the years, was heartwarming.

A special word of thank to Marleen Koolen. Dear Marleen, thank you for all your support. You have experienced how busy I was and how the balance between education, research and personal life was sometimes lost. You always thought constructively in finding the best solution for me as a person and I am very grateful for that.

Dear (former) ESP students, thank you for your support during my PhD study. Some of you have experienced what it is like to be part of my research either as part of your final thesis or as a research assistant. Special thanks to Karlijn Musch, Whitney Corning and Heather Moore for collecting data, assessing patients and providing them with challenging exercises.

Voormalig studenten van de Nederlandse opleiding fysiotherapie aan de HvA, Joyce Buitenhuis, Denise Wieferink en Charlotte de Kreek. Dank jullie wel voor jullie enthousiaste inzet en hulp bij het uitvoeren van metingen, het controleren van de Case Report Forms en het invoeren van data.

Kiek van der Putte. Beste Kiek, het is mede dankzij jou dat ik hier sta. Twaalf jaar geleden nam je me als toenmalig teammanager aan als docent op de opleiding Fysiotherapie en heb je ervoor gezorgd dat ik de Master Evidence Based Practice kon doen. Dat bleek uiteindelijk het startsein voor deze promotiestudie. Ik ben dankbaar dat jij en de HvA mij toen maximaal gefaciliteerd hebben om mij verder te kunnen ontwikkelen.

Beste promovendi, medeonderzoekers en lectoren van de HvA, dank voor jullie support. Het gezamenlijk bespreken van onderwerpen of dilemma's in ons onderzoeksoverleg heeft me veel opgeleverd. Ik vind het een mooie gedachte dat we in de toekomst nog veel promotiefeestjes gaan vieren en nieuwe projecten gaan opzetten.

Beste (oud) collega's van Polifysiek, Ferdinand de Haan, Nanda van de Linde, Albertina Poelgeest en Michel Terbraak, dank jullie wel voor het uitvoeren van de metingen bij patiënten in Polifysiek en het vormgeven van de eerste stappen van een kwaliteitssysteem voor mijn onderzoek.

Mijn paranimfen, Jo Thewessem en Jesse Aarden.

Jo, je hebt voor mij een cruciale rol gespeeld in het voortzetten van mijn promotietraject op het moment dat ik dacht dat het beter zou zijn om te stoppen. Dankzij jouw vragen, leerde ik mezelf te bevragen en vond ik uiteindelijk het plezier terug om mijn promotietraject af te ronden. Ik zou alle promovendi jou toewensen in hun begeleidingsteam. Ik hoop dat je inmiddels bekomen bent van de schrik om mijn paranimf te zijn. Het voelt geruststellend je aan mijn zijde te hebben.

Jesse, knabbel (of was het babbel?), partner in crime, wat fijn om samen met jou op te trekken in onze promotiestudies. Je enthousiasme voor de gezondheidzorg en het onderzoek inspireren me enorm en je feedback op mijn proefschrift heeft me echt een stap verder geholpen. Ik heb het idee dat we aan een half woord genoeg hebben. Ik kijk er naar uit om in de toekomst nog meer mooie projecten met je op te zetten.

En dan een woord van dank aan al mijn naaste vrienden en familie, want jullie zijn degenen waar het uiteindelijk in het leven echt om draait. Veel dank voor jullie interesse en betrokkenheid.

Een aantal van jullie wil ik in het bijzonder bedanken.

Heeren! Bart Brouwer, Hugo Helmes, Jo Thewessem, Young Fokker, Jeroen van Egmond, een mooie club zijn we; zes totaal verschillende persoonlijkheden met ontzettend veel raakvlakken, en met ons hart op de tong. Dank jullie wel voor jullie steun. Ik kijk altijd weer uit naar onze gezamenlijke borrels met Nattes, Zattes, Eiwit, kaas, worst en pinda's. Wat een feest.

Anna-Eva Prick en Gijs Roeloffzen. Beste Anna-Eva, jij bent mij een paar jaar geleden voorgegaan in het promotietraject. Toen we nog buren waren, heb ik van dichtbij meegemaakt welke hobbels er allemaal te nemen waren. Bedankt voor al je tips, ze hebben me geholpen. We did it! Beste Gijs, eindelijk heb ik tijd om samen onze bierbrouwerij weer nieuw leven in te blazen. Wanneer zullen we beginnen?

Maurice Ploem. Beste Maurice, concertmaatje. Met jou een mooi klassiek concert bezoeken was voor mij de ultieme vorm van ontspanning in tijden van onderzoekstress. De ontmoetingen die we samen hebben zijn voor mij altijd heel speciaal. Helaas is het daar de laatste jaren niet zo vaak meer van gekomen, maar ik weet ook dat we dat samen zo weer oppakken. Ik verheug me erop.

Marco Knijn. Beste Marco, ik ken je al zo lang en we hebben veel meegemaakt samen. Ik vond het heel bijzonder om met jou de master EBP te doen, het startpunt van mijn promotietraject waar je getuige van bent geweest. De biertjes na afloop van onze avondcolleges bij onze grote vriend “Noneck” waren legendarisch. We hebben elkaar weinig gezien gedurende de laatste fase van mijn promotietraject, des te meer kijk ik uit naar de toekomst.

Jerry Caffin. Beste Jerry, je oprechte interesse en loyaliteit betekenen veel voor mij in onze bijzondere vriendschap. De goede gesprekken die we hebben over van alles en nog wat, doen me altijd goed. Samen voetbal kijken, met name naar ons aller Ajax, leverde de afgelopen jaren altijd de nodige (ont)spanning op. Onze Champions League uitjes (dankzij Jesse) waren onvergetelijk. We gaan samen nog mooie avonturen beleven, ik kijk er naar uit!

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Ik ben klaar om te wenden.....Ree!

APPENDIX

About the author

ABOUT THE AUTHOR

Maarten van Egmond was born on December 3rd 1974 in Alkmaar, the Netherlands. In 1994 he graduated from secondary school at the Jan Arentsz College in Alkmaar. Between 1994 and 1998 he studied physiotherapy at the Amsterdam University of Applied Sciences. From 2000 until 2010 he worked as a physiotherapist in Rehabilitation Center Reade in Amsterdam where he treated patients with Spinal Cord Injuries, Amyotrophic Lateral Sclerosis, Multiple Sclerosis and Guillain-Barré syndrome. From 2008 to 2010 he combined this with a job as a lecturer at the Amsterdam University of Applied Sciences, School of Physiotherapy.

In 2010 Maarten left Reade and became involved in the development of Polifysiek, an outpatient clinic of the Amsterdam University Medical Centers, based within the Amsterdam University of Applied Sciences where a triad of education, research and patient care was created to further developing healthcare. At the same time, he became lecturer at the European School of Physiotherapy and started his University Master Evidence Based Practice in Health Care at the Faculty of Medicine of the University of Amsterdam and graduated in 2012. His master thesis entitled: 'Preoperative functional status in esophageal cancer patients undergoing elective surgery' was the starting point of this PhD study that effectively started in January 2014. He received a Doctoral Grant for Teachers by the Dutch Research Council (Nederlandse organisatie voor Wetenschappelijk Onderzoek) that allowed him to combine his PhD study with teaching at the European School of Physiotherapy.

In 2019 Maarten became Associate Professor Research at the school of physiotherapy of the Amsterdam University of Applied Sciences. He is responsible for embedding research and research skills in the physiotherapy curriculum, in cooperation with the management team, program coordinators, curriculum committee, lecturers and students. Besides teaching clinical reasoning, neurological rehabilitation and complex care and coordinating the final thesis at the European School of Physiotherapy, he also has been involved in developing a new university master at the Amsterdam University of Applied Sciences.

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In his spare time, Maarten enjoys running, cycling, sailing and playing guitar. He lives together with Ludwine in Monnickendam and together they are proud parents of Laura (2012) and Iris (2014).

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