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Impact of curative treatment on the physical fitness of patients with esophageal cancer: A systematic review and meta-analysis

Elja A.E. Reijneveld [a, *], Petra Bor [b], Jaap J. Dronkers [a], Núria Argudo [c], Jelle P. Ruurda [d], Cindy Veenhof [a, b]

[a] Expertise Center Healthy Urban Living, Research Group Innovation of Human Movement Care, HU University of Applied Sciences Utrecht, Utrecht, the Netherlands
[b] Department of Rehabilitation, Physiotherapy Science and Sport, University Medical Center Utrecht, Utrecht, the Netherlands
[c] Department of Surgery, Hospital del Mar, Hospital del Mar Medical Research Institute (IMIM), Universitat Pompeu Fabra, Spain
[d] Department of Surgery, University Medical Center Utrecht, Utrecht University, the Netherlands

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ABSTRACT

Background: Esophageal cancer and curative treatment have a significant impact on the physical fitness of patients. Knowledge about the course of physical fitness during neoadjuvant therapy and esophagectomy is helpful to determine the needs for interventions during and after curative treatment. This study aims to review the current evidence on the impact of curative treatment on the physical fitness of patients with esophageal cancer.
Methods: A systematic literature search of PubMed, Embase, Cinahl and the Cochrane Library was conducted up to March 29, 2021. We included observational studies investigating the change of physical fitness (including exercise capacity, muscle strength, physical activity and activities of daily living) from pre-to post-neoadjuvant therapy and/or from pre-to post-esophagectomy. Quality of the studies was assessed and a meta-analysis was performed using standardized mean differences.
Results: Twenty-seven articles were included. After neoadjuvant therapy, physical fitness decreased significantly. In the first three months after surgery, physical fitness was also significantly decreased compared to preoperative values. Subgroup analysis showed a restore in exercise capacity three months after surgery in patients who followed an exercise program. Six months after surgery, there was limited evidence that exercise capacity restored to preoperative values.
Conclusion: Curative treatment seems to result in a decrease of physical fitness in patients with esophageal cancer, up to three months postoperatively. Six months postoperatively, results were conflicting. In patients who followed a pre- or postoperative exercise program, the postoperative impact of curative treatment seems to be less.
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1. Introduction

Esophageal cancer is the ninth most common cancer and the sixth most common cause of cancer deaths worldwide [1]. The curative treatment for esophageal cancer increasingly involves a combination of treatments, most usually neoadjuvant chemotherapy or chemoradiotherapy, followed by surgical resection of the esophagus [2,3]. With this regimen a five year overall survival rate of almost 50% can be achieved [4]. However, esophageal cancer and curative treatment have a significant impact on the physical fitness of patients. At diagnosis many patients are already faced with a decline of their physical fitness due to the cancer itself [5,6], and each treatment intervention may lead to a further decline of the physical fitness [7–10] which frequently persists in the long term [11].

A decline in preoperative physical fitness seems to be negatively associated with the outcomes after surgery [12]. The presence of sarcopenia [13] and a decrease in muscle strength [14], exercise

* Corresponding author. HU University of Applied Sciences, Heidelberglaan 7, 3584, CS, Utrecht, the Netherlands.
E-mail address: elja.reijneveld@hu.nl (E.A.E. Reijneveld).

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capacity [15] and physical activity [16,17] in the preoperative phase have shown to be associated with a higher risk of postoperative complications and mortality in patients with esophageal cancer. In addition, a decline in physical fitness may have a negative impact on health related quality of life for cancer survivors [18,19].

Accordingly, to optimize patient outcomes, an important aim of esophageal cancer treatment is to preserve or restore the physical fitness of patients [20,21]. To achieve an optimal physical fitness, knowledge about the course of physical fitness during the treatment pathway is essential. The course of physical fitness may give insight into the separate influence of neoadjuvant therapy and surgery on the physical fitness of patients with esophageal cancer and into the ability of patients to recover to their physical fitness level prior to curative treatment. This knowledge will be helpful to determine the specific needs for interventions during and after curative treatment.

An earlier performed systematic review evaluated the impact of curative treatment on physical fitness in esophageal and gastric cancer patients and found a significant reduction of the exercise capacity after neoadjuvant therapy and surgery [12]. However, the impact on other physical fitness measures, including muscle strength and physical activity, remained unclear [12]. Furthermore, the impact of surgery was only described in studies with low numbers of participants, and there was little evidence about the long-term impact of surgery [12]. Because a considerable number of new studies have recently been published in this field, an update of this systematic review is warranted. Therefore, the aim of this systematic review and meta-analysis is to summarize the current evidence on the impact of neoadjuvant therapy and surgery on the physical fitness of patients with esophageal cancer.

2. Methods

This systematic review follows the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22]. Analytical methods and inclusion criteria were specified in advance and have not been changed post hoc.

2.1. Search strategy

The electronic databases PubMed, Embase, Cinahl and the Cochrane Library were searched for eligible articles up to March 29, 2021. The search strategy consisted of three components: (1) esophageal cancer, (2) neoadjuvant therapy or esophagectomy and (3) physical fitness. The complete search strategy can be found in online supplementary appendix A. Articles were included in this systematic review if: (1) study participants were patients with esophageal cancer receiving curative treatment consisting of neoadjuvant therapy and/or esophagectomy, (2) the change of physical fitness was measured from pre-to post-neoadjuvant therapy and/or from pre-to post-esophagectomy, (3) physical fitness was measured in terms of exercise capacity, physical activity, muscle strength or activities of daily living and (4) the study was a longitudinal, observational study published in full text in English, Dutch or German. Studies were excluded if both patients with esophageal and gastric cancer were included and no separate analyses for patients with esophageal cancer were available. Observational studies including other interventions (e.g. physiotherapeutic and/or dietetic interventions) as part of usual care treatment were not excluded, since the implementation of interventions aimed to improve or preserve physical fitness are more and more implemented in usual care treatment for patients with esophageal cancer [20,21].

2.2. Selection of studies

Two independent reviewers determined article eligibility for inclusion. Initially, articles were screened for eligibility on title and abstract. When titles and abstracts implied that an article was potentially eligible for inclusion, the full text article was retrieved. In addition, reference tracking was performed for all included articles.

2.3. Assessment of risk of bias

Risk of bias was assessed independently by two researchers, who were blinded to each other's quality assessment. All studies were assessed using the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool for before-after (pre- and post-intervention) studies [23]. The assessment tool includes 12 items. However, the twelfth quality item was not applicable for the studies in this review, because it assesses aspects concerning interventions that were conducted at group-level. The researchers evaluated the remaining 11 items as ‘yes’, ‘no’, ‘not applicable’, ‘cannot determine’, or ‘not reported’. This assessment was used to guide the overall rating for the quality of each study as ‘good’, ‘fair’, or ‘poor’ [23]. Following the guidelines from the assessment tool, no cut-off points were used. For any item assessed with ‘no’, the reviewer had to consider the potential risk of bias in the study [23]. Globally, a good study has low risk of bias and is considered valid. A fair study is prone to some bias but this is insufficient to invalidate its findings, varying in its strengths and weaknesses. Key items to downgrade the quality of a study were the inclusion of a selective sample of study participants, a high loss to follow-up and the lack of formal statistical tests. A poor study has high risk of bias and is considered invalid [23]. The percentage of agreement on the 11 items between the reviewers was calculated. In case of disagreement, consensus was reached through discussion, and when disagreement persisted by consulting a third researcher.

2.4. Data extraction

The following data were extracted from the included articles: (1) author, year and location; (2) sample size; (3) age of the participants; (4) type of neoadjuvant therapy; (5) outcome measures; (6) time-points of the measurements; (7) main results. If data were missing or further information was required, serious attempts were made to contact the first two authors of the article. If a study included patients with esophageal and gastric cancer, authors were contacted to request the separate data of patients with esophageal cancer.

2.5. Data analysis

A meta-analysis was performed if at least two studies reported the same outcome in the same time frame. The analyzed time frames included pre-to post-neoadjuvant therapy measurements (separated into $\leq$2 weeks and $\geq$4 weeks after completion of neoadjuvant therapy) and pre-to postoperative measurements (separated into <1 month, 1–3 months and $\geq$6 months postoperatively). Change scores between measurements with SDs were converted to a standardized mean difference (SMD) score, and the 95% CI was calculated. The analyses were performed with Review Manager 5.3 [24], using a random-effects model. Changes over time in physical fitness were considered small if the SMD was <0.2, moderate if the SMD was 0.2–0.8 or high if the SMD was $\geq$0.8 [25]. The I^2 was used to test heterogeneity between studies. The I^2 was considered to be low ($\leq$25%), moderate (26–75%) or high (>75%) [26]. In case of high heterogeneity, subgroup analyses were performed to assess whether differences in study characteristics influenced the effect size obtained. When a meta-analysis was not possible, results were described narratively.

3. Results

The process of study selection is presented in Fig. 1. The search strategy identified a total of 1414 articles, including 346 duplicate studies. 959 articles were excluded based on title and abstract and 82 articles based on full-text version. Finally, a total of 27 articles were included in the qualitative synthesis and 23 articles in the meta-analysis. The sample size of the included studies ranged from 12 to 155 participants. A summary of the characteristics and results of the included studies is displayed in Table 1. Outcome measures varied widely between the studies. Exercise capacity was measured using a cardiopulmonary exercise test (CPET) [10,27–30], 6-min walk test (6MWT) [9,30–38], incremental shuttle walk test (ISWT) [39], chester step test [40] steep ramp test [41] or 2-min walk test [42]. Muscle strength was measured in terms of hand grip strength (HGS) [9,30,31,33,35,41–46], knee extensor muscle strength [9,30,32,33,38,41], chair stand test [42,47], heel raising test [47], maximal inspiratory pressure (MIP) [30,42] or maximal expiratory pressure (MEP) [30]. Physical activity was measured using accelerometry [31,35], the international physical activity questionnaire (IPAQ) [32,48], the LASA physical activity questionnaire (LAPAQ) [42] or the physical activity level (PAL) score [49]. Activities of daily living (ADL) were assessed with the modified Katz scale [50], the modified Lawton and Brody Scale [50] or the Amsterdam linear disability score [51]. Gait speed was assessed with a 4-m walk test [44,45].

In several studies an exercise intervention was implemented in the pre- or postoperative phase as part of the usual care treatment (see Supplementary Table A.1). Four studies described a preoperative exercise intervention with the duration of at least one week [30,33,37,40]. In two studies patients were only advised to be physically active [41,48], and in two studies patients only received breathing exercises [34,38]. In the postoperative phase, elements of the enhanced recovery after surgery (ERAS) protocol were described in five studies, including early mobilization and airway clearance techniques during hospital admission [9,33,35,38,47,49]. In one study, patients followed a postoperative mobile health program after hospital admission [34].

3.1. Assessment of risk of bias

Results of the risk of bias assessment are described in Table 2. There was agreement between the two reviewers on 76% of the 297 methodological quality items. After a consensus meeting, disagreement persisted on 10 items, which was resolved by consulting a third reviewer. The items assessed with 'Yes' ranged from 5 to 10 items in the included studies. Four studies included a selective sample of study participants, and in only eight studies all eligible patients were included in the study. In three studies the curative treatment (intervention) was not clearly described, and outcome measures were not clearly defined in six studies. Loss to follow-up was more than 20% in 14 studies and not clearly reported in six studies. Five studies did not use formal statistical tests to assess changes in the outcome measures before and after curative treatment. In ten studies the outcome measures were measured multiple times before or after curative treatment. Fourteen studies were rated as 'good' [27–32,35,37,40–42,44,45,51], and thirteen studies were rated as 'fair'[9,10,33,34,36,38,39,43,46–50].

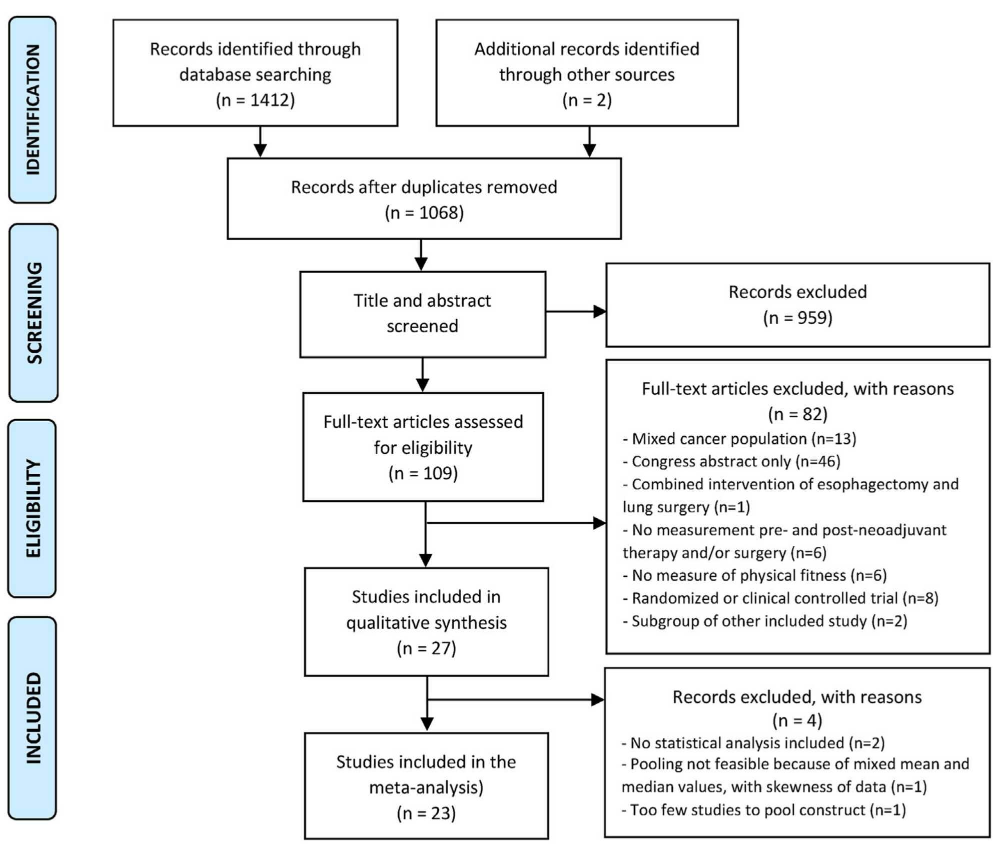

Fig. 1. Flow chart: search and screening of the included studies.

Table 1
Characteristics and main results of the included studies.

Author (year) and location	N	Age in years	nCT or nCRT	Time points	Outcome measures	Main results
Neoadjuvant therapy						
Argudo et al. (2020), Spain[30]	17	62.8 (11)	nCRT	- Before - 1 wk after - 6 wks after	- CPET workload (W) - CPET VO2peak (ml/kg/min) - 6MWT (m) - MIP (% of pred.) - MEP (% of pred.) - HGS (kg) - Quadriceps strength (kg)	↓ 113 (35) → 92 (33), p<.001 → 120 (41), p<.001 ↓ 19.4 (3.7) → 15.4 (3.6), p<.001 → 19.8 (4.8), p<.001 - 506 (67) → 482 (82), p=.234 → 532 (69), p=.004 - 83 (29) → 78 (27), p=.212 → 96 (31), p=.045 - 81 (28) → 76 (23), p=.402 → 92 (29), p=.063 - 32.4 (10.7) → 31.5 (11.6), p=.608 → 32.0 (9.9), p=.692 ↓ 46.0 (15.9) → 38.3 (13.6), p=.038 → 38.3 (10.5), p=.982
Bor et al.(2021), the Netherlands [41]	91	64 (9)	nCRT	- Before - 2 wks after	- HGS (kg) - Leg extension strength (Newton) - Max exercise capacity (Wpeak)	- 37 (12) → 36 (11), p=.156 - 398 (79) → 402 (90), p=.667 ↓ 245 (57) → 233 (65), p=.007
Ericson et al. (2020), Sweden[49]	20	66(32-77)[c]	nCRT	- Before - After	- Physical activity (PAL score)	- 1.4 (1.3-1.5) → 1.4 (1.3-1.5), p=.889
Guinan et al. (2018), Ireland [31]	28	62.9 (8.2)	nCT or nCRT	- Before - 6 wks after	- HGS (kg) - 6MWT (m) - Physical activity sed beh (% of waking hours) - Physical activity MVPA (min/day)	↓ 41.6 (10.3) → 37.3 (8.8), p<.01 No sign difference between nCT and nCRT group, p=.74 - 529.4 (66.8) → after 515.5 (84.2), p=.13 - 63.0 (11.1) → NR, p=NS - 23.3 (29.5) → NR, p=NS
Haj Mohammad et al.(2016), the Netherlands [51]	76	63 (9)	nCRT	- 2 wks before - 1 wk after	- ADL Amsterdam Linear Disability Score	↓ 90 (89-90)[d] → 88 (80-90), p<.01
Halliday et al. (2020), United Kingdom [40]	60	66 (9.7)	nCT	- Before - After - 4-6 wks after	- Chester Step Test (pred. VO_2 max in ml/kg/min)	- 24.3 (6.5) → 23.2 (6.3), p=.292 → 25.8 (6.1), p=.001
Liedman et al. (2001), Sweden [28]	29	63(45-78)[b]	nCRT	- Before - 4-6 wks after	- CPET working capacity (W)	↓ Decrease with 30W, p<.0001
Movahed et al.(2020), Iran [43]	71	66.3 (12)	nCRT	- Before - After - 4-6 wks after	- HGS (kg)	↓ 43.2 (19) → 36.1 (20), p<.001 → 36.4 (18), p=.01[a]
Tatematsu et al. (2013), Japan [32]	27	63.4 (6.8)	nCT	- Before - After	- Knee extensor muscle strength (Nm/kg) - 6MWT (m) - IPAQ (MET min/day)	- 2.5 (0.6) → 2.4 (0.5), p=NS - 574.9 (77.8) → 565.1 (75.3), p=NS - 119.1 (0-605.6)[c] → 99 (0-819), p=NS
Thomson et al. (2018), Australia [29]	38	66 (10.5)	nCT or nCRT	- Before - 4 wks after	- CPET work rate at AT (W) - CPET VO_2 at AT (mL/kg/min) - CPET Work rate at peak (W) - CPET VO_2 at peak (mL/kg/min)	↓ 69.3 (30.3) → 52.5 (20.9), p=.002 ↓ 12.4 (3.0) → 10.6 (2.0), p=.001 ↓ 101.6 (32.9) → 92.6 (31.4), p=.030 ↓ 16.6 (3.6) → 14.9 (3.7), p=.004 No sign difference between nCT and nCRT group, p=NR
Van Egmond et al. (2020), The Netherlands [42]	155	62.7 (8.8)	nCRT	- Before - 1 day preop	- HGS (% of pred.) - 30s CST (% of pred.) - MIP (% of pred.) - 2MWT (m) - LAPAQ (kcal/day)	- 111.0 (25.9) → 114.3 (21.7), p=.19 - 118.1 (28.9) → 117.0 (38.2), p=.91 - 119.7 (40.6) → 125.4 (38.5), p=.09 ↑ 193.6 (29.2) → 202.3 (35.6), p=.001 ↑ 475.4 (550.2)[d] → 864.5 (671.0), p<.001
Von Dobeln et al. (2016) Norway and Sweden [10]	65	63	nCT or nCRT	- Before - 4-6 wks after	- CPET (max exercise capacity in W)	↓ 150 (125-175)[d] → 125 (103-153), p<.001. No difference between nCT and nCRT group (p=.06).
Wang et al.(2020), China [44]	88	64.0 (7.2)	nCT	- Before - 1 day preop	- HGS (m) - Gait speed (m/s)	↓ 27.0 (24.1-30.2)[d] → 26.8 (23.8-28.8), p=.007 - 0.91 (0.83-1.00)[d] → 0.90 (0.82-0.99), p=.13
Whibley et al. (2018), United Kingdom [39]	24	62(49-74)[c]	nCT	- Before - After	- Incremental Shuttle Walk Test (m)	- 588.8 (162.2) → 590.4 (144.9), p=.91
Esophagectomy						
Akiyama et al. (2021), Japan [33]	48	65.7 (8.1)	NA	- 1 wk preop (only for the prehab group) - 1 day preop	- 6MWT (m) - HGS right (kg)	↓ Prehab group: 448.8 (81.5) → 492.9 (79.7)→ 431.5 (80), p<.000 ↓ Control group: 418.9 (71.8) → 378.0 (68.7), p<.05 - Prehab group: 31.0 (9.3) → 31.6 (9.8) → 29.3 (10.5), p=NR - Control group: 32.6 (9.9) → 32.1 (8.8), p=NR

Table 1 (*continued*)

Author (year) and location	N	Age in years	nCT or nCRT	Time points	Outcome measures	Main results
				- Postop (before hospital discharge)	- HGS left (kg) - Knee extensor muscle strength right (Nm/kg) - Knee extensor muscle strength left (Nm/kg)	- Prehab group: 29.2 (9.4) → 30.6 (9.8) → 28.2 (9.3), p=NR - Control group: 32.3 (9.7) → 32.2 (9.0), p=NR - Prehab group: 1.7 (0.6) →1.8 (0.6) →1.7 (0.6), p=NR - Control group: 1.7 (0.6) → 1.6 (0.6), p=NR - Prehab group: 1.8 (0.6) → 1.8 (0.5) → 1.6 (0.5), p=NR - Control group: 1.6 (0.6) → 1.6 (0.7), p=NR Sign differences in absolute pre- and postoperative 6MWT scores between groups (p<.001). No sign differences in change scores or other outcomes measures.
Cheng et al. (2020), China [34]	20	62.2 (7.1)	NA	- 1 wk preop - 1 mo postop - 3 mo postop	- 6MWT (m)	- 506 (330-558)[d] → 469 (276-612), p=.22 → 486 (343-682), p=.52
Ericson et al. (2020), Sweden [49]	20	66(32-77)[c]	NA	- 4-6 wks preop - 3 mo postop - 6 mo postop	- Physical activity (PAL score)	- 1.4 (1.3-1.5) → 1.3 (1.2-1.4), p=.065 → 1.3 (1.2-1.4), p=.121[a]
Fagevik et al. (2005), Sweden [47]	12	63.3 (9.9)	NA	- Preop - 2 years postop	- 10x CST (s) - 10x heel raising (s)	↓ 23.4 (6.0) → 33.9 (17.1), p=.045 - 14.1 (3.7) → 18.4 (9.6), p=.113
Guinan et al. (2019), Ireland [35]	36	62.4 (8.8)	NA	- Preop - 1 mo postop - 6 mo postop	- 6MWT (m) - HGS (kg) - Physical activity sed beh (hrs/day) - Physical activity light int act (hrs/day) - Physical activity MVPA (min/day)	↓ 502.6 (76.7) → 463.5 (98.4) → 507.8 (87.8), p<.001 - 35.5 (9.9) → 33.9 (9.9) → 35.8 (10.9), p=.15 ↓ 7.2 (1.6) → 8.7 (1.7) → 8.5 (1.7), p=.002 ↓ 4.1 (1.5) → 2.3 (0.9) → 3.5 (1.4), p<.001 ↓ 11.5 (31.6) → 4.7 (12.9) → 12.5 (24.6), p<.001
Haj Mohammad et al.(2016), The Netherlands [51]	76	63 (9)	NA	- 1 wk after nCRT - 3 mo postop	- ADL Amsterdam Linear Disability Score	- 88 (80-90)[d] → 89 (82-90), p=.146
Inoue et al. (2016), Japan [15]	34	67.3 (8.1)	NA	- 1-10 days preop - 2 wks postop	- 6MWT (m) - knee extensor muscle strength right (kg) - knee extensor muscle strength left (kg) - HGS right (kg) - HGS left (kg)	↓ 496 (76) → 409 (108), p<.001 - 26.0(8.5) → 24.7(8.2), p=.08 ↓ 25.2 (9.4) → 22.9 (7.8), p=.02 ↓ 30.6 (9.1) → 28.7 (8.6), p=.01 ↓ 28.8 (8.6) → 27.5 (7.7), p=.01
Komatsu et al. (2018), Japan [48]	29	65.9(45-79)[c]	NA	- Preop - 2-4 wks* - 3 mo* - 6 mo* *after discharge	- IPAQ (MET min/week)	- 1382.5(0-16065)[c] → 1386.0(0-12558) → 1287.0(0-16.170) → 1386.0(0-31038), p=NR
Lidoriki et al. (2020), Greece [45]	50	60.8(10.2)	NA	- Preop - 6 mo postop	- HGS (kg) - Gait speed (m/s)	↓ McKeown group: 33.2 (8.0) → 30.0 (8.2), p=.018 ↓ Ivor Lewis group: 40.1 (8.0) → 35.2 (8.1), p<.001 ↓ McKeown group: 1.2 (0.2) → 0.9 (0.2), p=.004 ↓ Ivor Lewis group: 1.2 (0.2) → 1.1 (0.2), p=.029
Murphy et al. (2021), Ireland [46]	75	62.7(10.3)	NA	- Preop - 6 mo postop - 12 mo postop	- HGS (kg, median+range)	- 33.5 (18-52)[c] → 31.0 (18-56) → 31.5 (21-54), p=.210
Otani et al. (2020), Japan [36]	52	63(50-75)[c]	NA	- Preop - 3 mo postop - 6 mo postop - 12 mo postop - 24 mo postop - 60 mo postop	- 6MWT (m)	- OE group: 477(395-578)[c] → 460(276-590) → 450(331-609) → 449(344-629) → 460(350-600) → 452(390-612), p=NR - THE group: 431(380-568) → 486(339-552) → 492(383-604) → 500(390-604) → 450(354-594) → 473(432-570), p=NR - MIE group: 488 (348-586) → 456(328-550) → 496(436-590) → 507(428-592) → 530(486-584) → 490(320-548), p=NR Sign. differences between groups at 3, 6 and 12 mo postop, p<.05
Parameswaran et al. (2013), United Kingdom [50]	86	64(45-84)[c]	NA	- Within 3 wks preop - 6 wks postop - 3 mo postop - 6 mo postop	- ADL mod Katz Scale (% independent) - iADL mod Lawton and Brody Scale (% independent)	↓ OE group: 88 → 64 → 78 → 56, p=NR ↓ LAE group: 90 → 75 → 87 → 96, p=NR ↓ MIE group: 94 → 73 → 89 → 96, p=NR - OE group: 71 → 36 → 33 → 33, p=NR - LAE group: 81 → 50 → 61 → 75, p=NR - MIE group: 81 → 45 → 53 → 78, p=NR
Piraux et al. (2020), Belgium [37]	19	64.0 (8.3)	NA	- 2-4 wks preop (before prehabilitation) - 1 day preop - 4 wk postop - 12 wk postop	- 6MWT (m)	↓ 478 (115) → 516 (116), p=.249 → 438 (119), p=.006* → 553 (131), p=1.000* *p-values are compared to 1 day preop

(continued on next page)

Table 1 (*continued*)

Author (year) and location	N	Age in years	nCT or nCRT	Time points	Outcome measures	Main results
Taguchi et al. (2003), Japan [27]	51	61.7 (7.8)	NA	- Preop - 3 mo postop	- CPET VO2 AT (mL/min) - CPET VO2 max (mL/min)	↓ OE group: 885.0 (223.6) → 681.7 (157.6), p<.0001 ↓ VATS group: 817.1 (161.2) → 662.1 (153.5), p<.0001 No difference between groups, p=.222 ↓ OE group: 1185.6 (300.3) → 916.1 (238.6), p<.0001 ↓ VATS group: 1112.8 (220.2) → 835.6 (233.0), p<.0001 No differences between groups, p=.865
Tatematsu et al. (2013), Japan [38]	30	63.6 (7.1)	NA	- Preop - Postop (day of hospital discharge)	- Knee extensor muscle strength (Nm/kg) - 6MWT (m)	↓ 2.3 (0.6) → 2.1 (0.6), p<.001 ↓ 563.3 (73.2) → 485.3 (85.6), p<.001
Van Egmond et al. (2020), The Netherlands [42]	155	62.7 (8.8)	NA	- 1 day preop - 1 wk postop - 3 mo postop	- HGS (% of pred.) - 30s CST (% of pred.) - MIP (% of pred.) - 2MWT (m) - LAPAQ (kcal/day)	↓ 114.3 (21.7) → 108.2 (23.3), p=.015 → 104.8 (30.1), p=.001 - 117.0 (38.2) → 87.6 (34.0), p<.001 → 119.1 (38.1), p=.454 ↓ 125.4 (38.5) → 88.4 (33.6), p<.001 → 120.4 (38.1), p=.010 ↓ 202.3 (35.6) → 147.5 (37.2), p<.001 → 191.2 (34.4), p=<.001 ↓ 864.5 (671.0)[d] → NR → 453.0 (539.4), p<.001
Von Dobeln et al. (2016), Norway and Sweden [10]	15	63	nCT or nCRT	- Before nC(R)T - 1-2 years postop	- CPET (max exercise capacity in W)	↓ 128 (115-170)[d] → 107 (80-125), p=.001. No difference between nCT and nCRT group (p=.81).

Abbreviations: N: number of participants, nCT: neoadjuvant chemotherapy, nCRT: neoadjuvant chemoradiotherapy, NA: not applicable, mo: months, wk: week, HGS: Hand Grip Strength, 6MWT: Six-Minute Walk Test, sed beh: sedentary behavior, MVPA: moderate to vigorous physical activity, CPET: cardiopulmonary exercise testing, IPAQ: International Physical Activity Questionnaire, MET: Metabolic Equivalent of Task, AT: anaerobic threshold, VO2: oxygen uptake, CST: Chair Stand Test, light int act: light intensity activity, hrs: hours, ADL: activities of daily living, iADL: instrumental activities of daily living, pred: predicted, 30s CST: 30-second Chair Stand Test, MIP: maximal inspiratory pressure, 2 MWT: Two-minute walk test, LAPAQ: LASA physical activity questionnaire, NR: not reported, NS: not significant, OE: Open esophagectomy, THE: Transhiatal esophagectomy, MIE: Minimally invasive esophagectomy, LAE: laparoscopically assisted esophagectomy, VATS: video-assisted thoracoscopic esophagectomy, ↓: significant decrease in physical fitness, ↑: significant increase in physical fitness.

[a] P values are compared to baseline values.
[b] Mean + range.
[c] Median + range.
[d] Median + Interquartile range

Table 2
Methodological quality of before-after studies using the 'Quality Assessment Tool for Before–After (Pre-Post) Studies with No Control Group'.

Study	1	2	3	4	5	6	7	8	9	10	11	12	Overall quality rating
Akiyama, 2021 [33]	N	Y	Y	Y	Y	Y	Y	NR	NR	N	N	NA	Fair
Argudo, 2020 [30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Good
Bor, 2021 [41]	Y	Y	Y	Y	Y	Y	Y	NR	NR	Y	N	NA	Good
Cheng, 2020 [34]	N	Y	N	N	Y	Y	N	NR	Y	Y	Y	NA	Fair
Ericson, 2020 [49]	Y	Y	Y	N	N	Y	N	NA	N	Y	Y	NA	Fair
Fagevik, 2005 [47]	N	Y	Y	N	Y	Y	N	NR	N	Y	N	NA	Fair
Guinan, 2018 [31]	Y	Y	Y	NR	Y	Y	Y	NR	N	Y	N	NA	Good
Guinan, 2019 [35]	Y	Y	Y	N	Y	Y	Y	NR	N	Y	Y	NA	Good
Haj Mohammad, 2016 [51]	Y	Y	Y	N	Y	Y	Y	NR	N	Y	N	NA	Good
Halliday, 2020 [40]	Y	Y	Y	N	Y	N	Y	NR	Y	Y	N	NA	Good
Inoue, 2016 [15]	Y	Y	N	Y	Y	Y	Y	NR	N	Y	N	NA	Fair
Komatsu, 2018 [48]	Y	Y	Y	N	CD	Y	Y	NR	N	N	Y	NA	Fair
Lidoriki 2021 [45]	Y	Y	Y	N	Y	Y	Y	NR	NR	Y	N	NA	Good
Liedman, 2001 [28]	Y	Y	Y	Y	Y	Y	N	NR	NR	Y	N	NA	Good
Movahed, 2020 [43]	Y	Y	N	Y	Y	Y	Y	NR	N	Y	Y	NA	Fair
Murphy, 2021 [46]	N	Y	Y	Y	Y	Y	Y	NR	N	Y	Y	NA	Fair
Otani, 2020 [36]	Y	Y	Y	N	CD	Y	Y	NR	N	NA	Y	NA	Fair
Parameswaran, 2013 [50]	N	Y	Y	Y	CD	Y	Y	NR	N	N	Y	NA	Fair
Piraux, 2020 [37]	Y	Y	Y	N	Y	Y	Y	NR	N	Y	Y	NA	Good
Taguchi, 2003 [27]	Y	Y	Y	Y	Y	Y	N	NR	NR	Y	N	NA	Good
Tatematsu, 2013 [32]	Y	Y	Y	N	Y	Y	Y	NR	NR	Y	N	NA	Good
Tatematsu, 2013 [38]	Y	Y	N	N	Y	Y	Y	NR	Y	Y	N	NA	Fair
Thomson, 2018 [29]	Y	Y	Y	N	Y	Y	Y	NR	Y	Y	N	NA	Good
Van Egmond, 2020 [42]	Y	Y	Y	CD	Y	N	Y	NR	N	Y	Y	NA	Good
Von Dobeln, 2016 [10]	Y	Y	Y	N	Y	Y	N	NR	N	Y	N	NA	Fair
Wang, 2020 [44]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	NA	Good
Whibley, 2018 [39]	Y	Y	Y	N	Y	N	Y	NR	CD	NR	N	NA	Fair

(1) Objective clearly stated; (2) eligibility criteria described; (3) representative patient population; (4) all eligible participants enrolled in study; (5) sufficient sample size; (6) intervention described; (7) outcome measures specified; (8) outcome assessors blinded; (9) loss to follow-up; (10) statistical analysis for pre-to-post changes; (11) interrupted time-series design; (12) individual data used for group-level effects.
Abbreviations: Y: yes; N: no; NA: not applicable; NR: not reported; CD: cannot determine. Overall quality rating: good, fair or poor.

3.2. Impact of neoadjuvant therapy

Fourteen studies were identified investigating the change of physical fitness during neoadjuvant therapy [10,28–32,39–44,49,51]. In seven studies patients received chemoradiotherapy [28,30,41–43,49,51] and in four studies patients received only chemotherapy [38–40,44]. In three studies patients received chemoradiotherapy or chemotherapy [10,29,31]. Forest plots for the

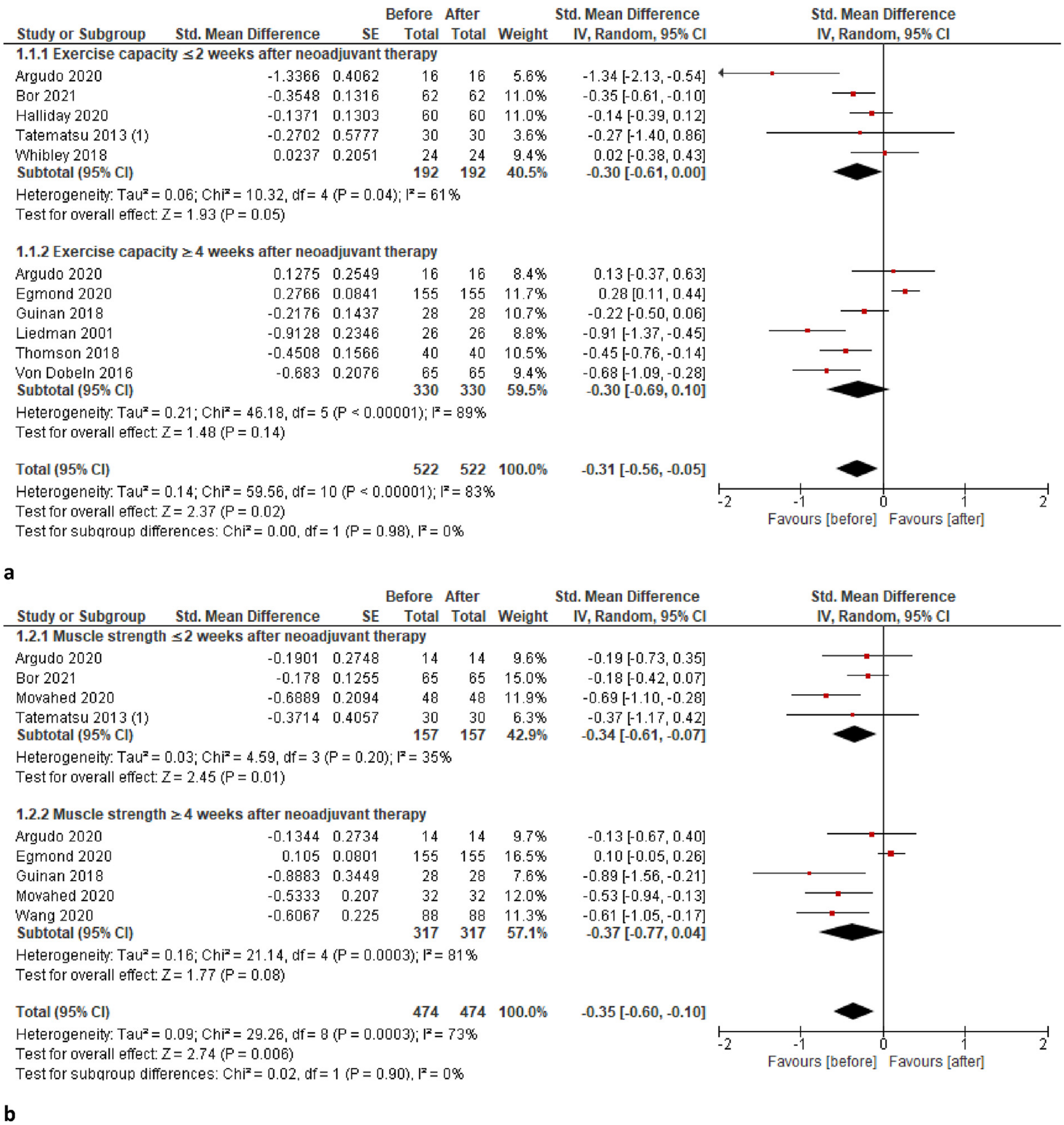

Fig. 2. Forest plots of the change in physical fitness from before to after neoadjuvant therapy: **(a)** change in exercise capacity at ≤2 weeks, ≥4 weeks and overall **(b)** change in muscle strength at ≤2 weeks, ≥4 weeks and overall.

change of exercise capacity and muscle strength during neoadjuvant therapy can be found in Fig. 2. Overall, the results showed a moderate and significant decrease in exercise capacity (SMD -0.31 (−0.56; −0.05), p = .02, I^2 = 83%) and muscle strength (SMD -0.35 (−0.60; −0.10), p < .01, I^2 = 73%) after neoadjuvant therapy, respectively with high and moderate heterogeneity. Within two weeks after neoadjuvant therapy, the decline in exercise capacity (SMD -0.30 (−0.61; 0.00), p = .05, I^2 = 61%) and muscle strength (SMD -0.34 (−0.61; −0.07), p = .01, I^2 = 35%) was moderate and significant, both with moderate heterogeneity. At four weeks or more after neoadjuvant therapy, the decreases in exercise capacity (SMD -0.30 (−0.69; 0.10), p = .14, I^2 = 89%) and muscle strength (SMD -0.37 (−0.77; 0.04), p = .08, I^2 = 81%) were not significant with high heterogeneity.

The results for the change of exercise capacity showed high heterogeneity. In this analysis, two studies included a preoperative exercise program in the curative treatment pathway [30,40], and therefore, a subgroup analysis was performed on studies with and without a preoperative exercise intervention. In studies with an exercise intervention [30,40], exercise capacity restored after neoadjuvant therapy (SMD -0.08 (−0.31; 0.15, p = .48, I^2 = 0%), and in studies without an exercise intervention [10,28–32,39,41,42] exercise capacity decreased after neoadjuvant therapy (SMD -0.39 (−0.70; −0.07, p < .01, I^2 = 86%). The difference between subgroups was not significant (p = .12). No subgroup analyses were performed on the results within the different time frames, since only one study in these analyses included an exercise intervention.

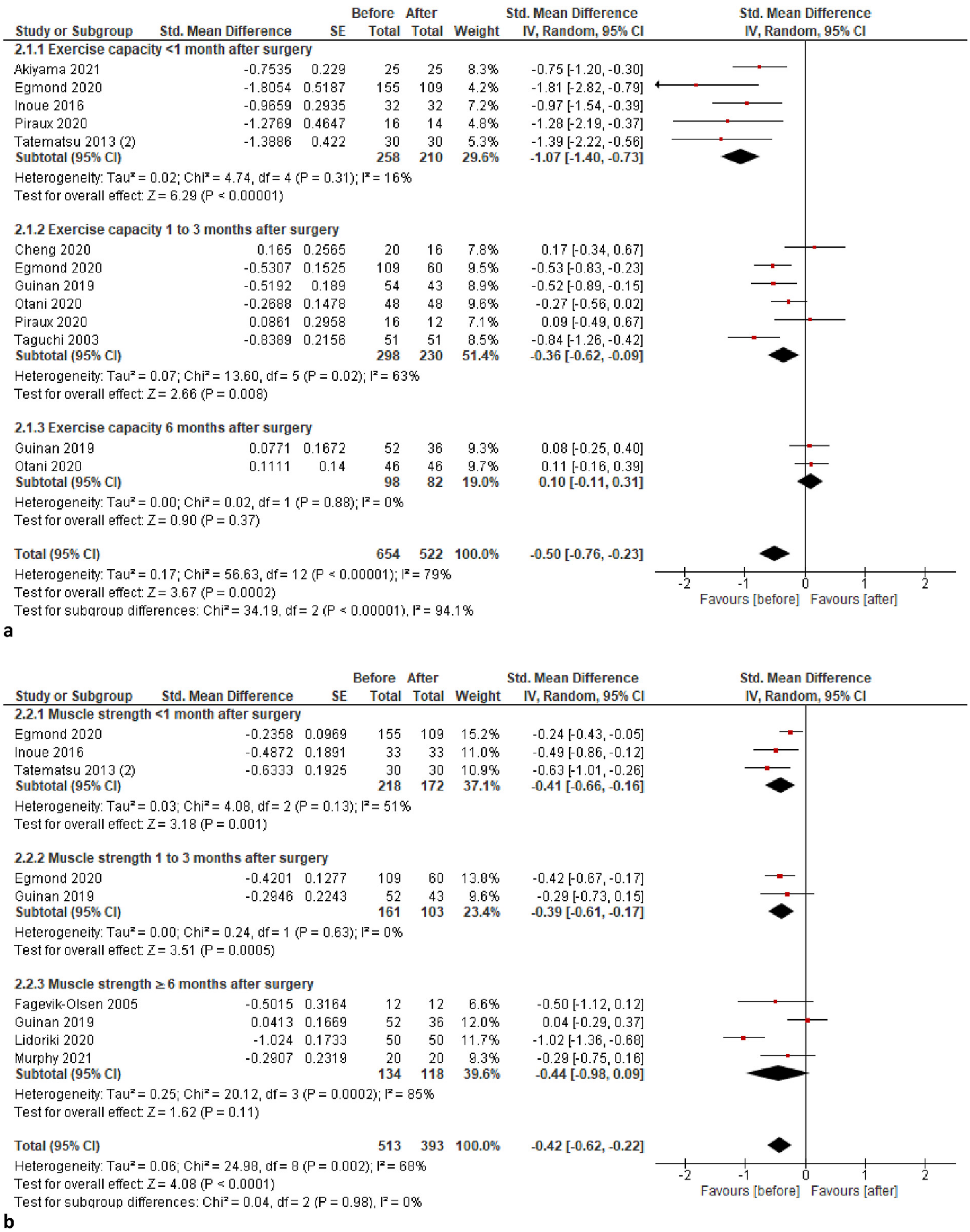

Fig. 3. Forest plots of the change in physical fitness from before to after esophagectomy: (**a**) change in exercise capacity at < 1 month, 1–3 months, 6 months after surgery and overall (**b**) change in muscle strength at < 1 month, 1–3 months, ≥ 6 months after surgery and overall.

Physical activity was measured in four studies [31,32,42,49]. However, studies reported different forms of physical activity and in three studies median values were reported because of skewness in physical activity data. Therefore, physical activity data could not be pooled. ADL and gait speed were assessed in one study and were also not included in the meta-analysis [44,51]. Within two weeks after neoadjuvant therapy, two studies described no significant change in physical activity compared to values before neoadjuvant therapy [32,49] and one study found a significant decrease in ADL [51]. At four weeks or more after neoadjuvant therapy, physical activity did not significantly change in one study [31], and significantly increased in another study [42]. One study described a non-significant decrease in gait speed [44]. In addition, two studies assessed whether the impact of neoadjuvant therapy on physical fitness differed between patients treated with chemoradiotherapy and patients treated with chemotherapy only [10,31]. In both studies, no significant differences were found in the impact of those treatment regimens on physical fitness.

3.3. Impact of esophagectomy

Seventeen studies described the impact of esophagectomy on physical fitness [9,10,27,33–38,42,45–51]. Forest plots for the change of exercise capacity and muscle strength after esophagectomy compared to preoperative values can be found in Fig. 3. Overall, the results showed a moderate and significant decline in exercise capacity (SMD -0.50 (−0.76; −0.23), $p < .01$, $I^2 = 79\%$) and muscle strength (SMD -0.42 (−0.62; −0.22), $p < .01$, $I^2 = 68\%$) after surgery, respectively with high and moderate heterogeneity. In the first month after surgery, exercise capacity showed a high and significant decrease with low heterogeneity (SMD -1.07 (−1.40; −0.73), $p < .01$, $I^2 = 16\%$) and muscle strength showed a moderate and significant decrease with moderate heterogeneity (SMD -0.41 (−0.66; −0.16), $p < .01$, $I^2 = 51\%$). Between one and three months after surgery, there was a moderate and significant decrease in exercise capacity with moderate heterogeneity (SMD -0.36 (−0.62; −0.09), $p < .01$, $I^2 = 63\%$). Muscle strength also showed a moderate and significant decrease with low heterogeneity (SMD -0.39 (−0.61; −0.17), $p < .01$, $I^2 = 0\%$). At six months after surgery, exercise capacity was restored to preoperative values with low heterogeneity (SMD 0.10 (−0.11; 0.31), $p = .37$, $I^2 = 0\%$). Muscle strength showed a non-significant decrease, with high heterogeneity (SMD -0.44 (−0.98; 0.09), $p = .11$, $I^2 = 85\%$).

The results for the change of exercise capacity showed high heterogeneity. In the analyses within one month after surgery and between one and three months after surgery, two studies included a preoperative exercise intervention [33,37], and one study included a postoperative exercise intervention [34]. To explore whether the impact of esophagectomy differed between studies with and without a pre- or postoperative exercise program, therefore, a subgroup analysis was performed. In the first month after surgery, subgroup analyses showed no significant difference ($p = .22$) in the impact of esophagectomy on exercise capacity between studies with an exercise intervention (SMD -0.86 (−1.27; −0.45) [33,37], $p < .01$, $I^2 = 2\%$), and studies without an exercise intervention (SMD -1.24 (−1.70; −0.79), $p < .01$, $I^2 = 8\%$) [9,38,42]. Between one and three months after surgery.

Studies with an exercise intervention showed a restore in exercise capacity (SMD 0.13 (−0.25; 0.51), $p = .50$, $I^2 = 0\%$) [34,37], and studies without an exercise intervention showed a decrease in exercise capacity (SMD -0.51 (−0.73; −0.29), $p < .01$, $I^2 = 39\%$) [27,35,36,42]. The difference between subgroups was significant ($p < .01$). No subgroup analyses were performed for the analysis at six months after surgery since no studies with exercise interventions were included in this analysis.

Physical activity was measured in four studies [35,42,48,49]. Because of the reporting of different constructs of physical activity, mixed mean and median values, and the lack of statistical analyses in one study, physical activity data could not be pooled. ADL was measured in two studies [50,51]. In one study no statistical analyses were performed, and therefore, ADL data was not included in the meta-analysis. Gait speed was measured in one study [45], and could also not be pooled. In the first month after surgery one study reported a physical activity level comparable to baseline values [48]. Between one and three months after surgery, physical activity was decreased in all four studies, which was significant in two studies [35,42]. Two studies described a decrease in ADL and instrumental ADL between one and three months after surgery [50,51]. At six months after surgery, two studies showed a reduced physical activity level, which was significant in one study [35,49]. One study described physical activity values similar to baseline [48]. ADL was still decreased at six months after surgery in patients who underwent an open 'esophagectomy', but restored in patients who underwent a 'laparoscopically assisted' or 'minimal invasive' esophagectomy. Instrumental ADL was still decreased in all patients [50]. Gait speed was also decreased at six months after surgery [45].

4. Discussion

This systematic review and meta-analysis summarizes the recent literature on the physical fitness of patients with esophageal cancer during the curative treatment pathway consisting of neoadjuvant therapy and esophagectomy. The results showed a moderate and significant decrease in muscle strength and exercise capacity in the first two weeks after neoadjuvant therapy compared to values before neoadjuvant therapy. At least four weeks after the completion of neoadjuvant therapy, exercise capacity and muscle strength were still decreased, but the results were not significant. After surgery, exercise capacity and muscle strength decreased significantly in the first three months compared to preoperative values. At six months after surgery, there is limited evidence that exercise capacity restored to preoperative values and muscle strength showed a non-significant decrease. The results from the current study are in line with the results of the earlier published systematic review evaluating the physical fitness in patients with esophago-gastric cancer [12]. This study also concluded that exercise capacity was significantly reduced after neoadjuvant therapy and in the first three months after esophagectomy, and that the long-term impact was unclear. In our review, more studies were included and a meta-analysis was performed, which strengthens their conclusions.

After neoadjuvant therapy, the majority of the studies showed a decrease in physical fitness. Remarkable is the high heterogeneity in the results at four weeks or more after the completion of neoadjuvant therapy. In the subgroup analysis on studies with and without a preoperative exercise intervention, there was a trend that neoadjuvant therapy had less impact on exercise capacity in patients who followed a preoperative exercise program, which partly explains the high heterogeneity between studies. However, in the subgroup of studies without a preoperative exercise program, the heterogeneity between studies remained high. This heterogeneity is mainly caused by the results from one study, showing an improvement in exercise capacity after neoadjuvant therapy [42]. In this study, the authors described that the included patients had higher physical fitness levels compared to normative values [42]. Previous research suggests that patients with higher physical fitness levels have a better adaptive capacity and resiliency to stressors like neoadjuvant therapy [52]. Therefore, the high physical fitness levels of patients in this study may have resulted in the maintenance or a more rapid restore of the physical fitness during and after neoadjuvant therapy, in contrast to other included studies.

In the first three months after esophagectomy, patients were faced with a significant decline of their exercise capacity compared to preoperative values. At six months postoperatively, exercise capacity restored to preoperative values. However, this conclusion have to be drawn with some caution. Only two studies were included in this analysis, both using a 6MWT to measure functional exercise capacity [35,36]. The 6MWT seems to be a valid measure to assess functional exercise capacity in patients with cancer [53]. Nevertheless, the 6MWT is a sub-maximal exercise test and poorly correlates with maximal exercise capacity, as measured by a CPET [54]. Furthermore, ceiling effects were described in previous literature [55,56]. Therefore, it may be questioned whether exercise capacity is really restored at six months after surgery.

In addition to the postoperative course of exercise capacity, our study showed a non-significant decrease in muscle strength at six months after surgery and conflicting results for physical activity and ADL. Muscle strength, and especially hand grip strength, is shown to be related to the nutritional status in patients with cancer [57]. Six months after esophagectomy, a significant weight loss and reduced nutritional intake were frequently described in patients with esophageal cancer [58], and therefore, the postoperative decrease in muscle strength may be explained by a diminished nutritional status. Accordingly, to achieve a recovery of muscle strength after esophagectomy, also the nutritional status of patients has to be taken into account in clinical practice. Similar to the results on muscle strength, physical activity level and ADL were not restored in alle studies. However, the measurement methods and results varied between studies, and a meta-analysis on physical activity level and ADL was not possible. Therefore, no clear conclusions can be drawn about the impact of curative treatment on physical activity level and ADL. In contrast to exercise capacity and muscle strength tests, physical activity and ADL provide insight into the activities that a patient actually performs. Therefore, structural and more standardized methods to measure physical activity and ADL during the curative treatment pathway are recommended for future studies.

Several studies in this review described the implementation and feasibility of an exercise intervention in the usual care treatment for patients with esophageal cancer, which may have influenced the impact of curative treatment on the level of physical fitness [30,34,37,40]. Therefore, we performed subgroup analyses on studies with and without exercise interventions. In the preoperative phase, there was a trend that neoadjuvant therapy had less impact on exercise capacity in patients who followed a preoperative exercise program. However, the difference between subgroups was not significant, and there were only two studies with exercise interventions in the subgroup analysis. Therefore, more research is needed to investigate whether a preoperative exercise program is effective to improve the preoperative physical fitness. Postoperatively, the impact of esophagectomy seems to be less in patients who followed a pre- or postoperative exercise intervention, with a significant difference between subgroups at three months after surgery. It is noteworthy that both a pre- and a postoperative exercise program seem to be beneficial to improve the postoperative exercise capacity [34,37]. These findings are in line with previous randomized controlled trials in patients with esophageal cancer, showing an improved postoperative exercise capacity in patients who followed a preoperative [59] or a postoperative exercise program [60,61], compared to the control group. Accordingly, based on the current evidence, both a preoperative and a postoperative exercise program may be beneficial to improve physical fitness in the first months after surgery.

This review describes the course of physical fitness during the whole curative treatment pathway in patients with esophageal cancer, and gives a complete overview of the available literature. There are also some limitations. First, there was a wide variety between studies in the outcome measures and time points of the measurements. Although we performed separate analyses on different time frames in the meta-analysis, the time points of the measurements within the used time frames were not identical, which may have caused some bias. Second, in several studies an exercise intervention was implemented in addition to curative (medical) treatment, which may have influenced the impact of curative treatment on physical fitness in these studies. The performed subgroup analyses on studies with and without an exercise intervention give insight into the influence from the exercise interventions on the course of physical fitness during curative treatment. However, there was only a low number of studies with exercise interventions, and therefore no firm conclusions can be drawn about the differences between the subgroups.

For clinical practice, monitoring of physical fitness in patients with esophageal cancer during curative treatment is important to have insight into the recovery of patients, and to assess whether patients are able to restore to their physical fitness level prior to curative treatment. Preoperatively, patients often show a decrease in their physical fitness level, which has been shown to be a risk factor for postoperative pulmonal complications [41]. To identify patients at risk for postoperative complications, it is therefore recommended to monitor the preoperative physical fitness level at multiple time points. Postoperatively, curative treatment had a substantial impact on physical fitness in the first three months, but seems to be less in studies where patients followed a pre- or postoperative exercise program. Based on our findings and previous literature on the effectiveness of exercise interventions in patients with esophageal cancer [59–61], both pre- and postoperative exercise programs seem to be beneficial to improve physical fitness in the first months after esophagectomy. On the longer term, the impact of esophagectomy on physical fitness was unclear, and therefore, more knowledge is needed about the long-term impact of curative treatment on physical fitness in patients with esophageal cancer.

In summary, neoadjuvant therapy and esophagectomy result in a decreased physical fitness level in patients with esophageal cancer, up to three months postoperatively. The long-term impact of curative treatment remained unclear. Based on the decline in physical fitness, the implementation of a pre- or postoperative exercise intervention seems to be beneficial to improve the postoperative physical fitness in patients with esophageal cancer.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data sharing

Data are available on request. Study data (means, SDs, and patient numbers) per outcome can be requested by e-mailing the corresponding author.

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Supplementary data

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