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ABSTRACT

Background
Physiotherapy in palliative oncology patients is less discussed in literature and needs to be thoroughly investigated.

Aim
The aim of this study was to gather and analyze the available evidence on the effect of physiotherapy in oncology patients who require palliative care.

Design
This review was conducted by including studies published in the last 23 years, using PubMed and Web of Science as databases. Out of 933 studies, only ten articles met the inclusion criteria. These studies were: (1) randomized Controlled Trials published after the year 2000; (2) written in English, Dutch or translated into one of these two languages; (3) primarily oncological, palliative patients; and (4) examining interventions within the scope of the physiotherapist's role.

Results
The 10 included studies were all of medium and low quality due to risk of bias. This can be explained by the small sample sizes and consequently power of the studies. Overall, the effect on muscle strength and peripheral neuropathy were proven to be significant by multiple studies (n=2). There was also an impact on psychological outcome measures, quality of life and other physical outcome measures, but these showed differences in significance between several studies.

Conclusions
The results reveal many benefits of physiotherapy in this setting. They highlight the need to provide these services to ensure a better quality of life. However, larger studies of higher methodological quality are needed to understand these effects, and to support the development of specific guidelines for treating palliative oncology patients.

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KEY WORDS

PHYSICAL THERAPY; TERMINALLY ILL; NEOPLASMS; PHYSICAL THERAPIST; PHYSICAL THERAPY MODALITIES

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KEY STATEMENTS

I. Exercise offers benefits for both cancer prevention and improving the prognosis of cancer survivors. But although the effects of exercise in oncology patients have been widely discussed and studied, palliative cancer patients were often excluded from these studies.

II. We examined the current evidence on the role of physiotherapists and physiotherapy interventions in palliative care for oncology patients and provided an overview of the effects already found in the heterogeneous studies.

III. This review highlights the potential benefits of physiotherapy interventions in improving physical outcomes for palliative care oncology patients. Future research should focus on conducting larger-scale RCTs with rigorous methodology to further explore the role of physiotherapists and physiotherapy in palliative care for oncology patients.

INTRODUCTION

Cancer is a widespread debilitating disease characterized by the uncontrolled growth and spread of abnormal cells in the body. When these cells form a mass, it is called a tumor. Malignant tumors have the ability to invade nearby tissues and organs and can spread to other parts of the body through the bloodstream or lymphatic system. This way, cancer can affect any part of the body and can cause a wide range of symptoms, depending on the location and stage of the disease [1].

Worldwide, an estimated 18.1 million people received a new cancer diagnosis in 2018, and 9.6 million patients died from cancer [2]. That year, 70,468 cancers were diagnosed in Belgium. More than 99% of those cancers were in adults (20 years and older) [3]. More men (37,649) than women (32,819) were diagnosed with cancer. About one in three men and one in four women are at risk of cancer before their 75th birthday [3].

The WHO definition of palliative care clearly states that the competence, attitudes and skills of palliative care should be integrated in health care, in general, and in cancer care, specifically: "Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life threatening illness, and is applicable early in the course of the illness, in conjunction with other therapies that are intended to prolong life". This systematic review builds on this definition. [4]

In 2015, more than half (53.4%) of patients with terminal cancer in Belgium received palliative care. This is an increase compared to 2008 (48.0%) [5]. In addition to these results 151,885 individuals died in 2019, of whom an estimated 109,461 persons, or 72%, were in need of palliative care. Among the latter, cancer was the leading cause of death [5]. Palliative care aims to improve the quality of life (QoL) of patients facing serious illnesses, by addressing their physical, psychological, and social needs. It avoids and relieves suffering through timely detection, careful assessment and treatment of pain and other problems [6].

The factors that contribute the most to the suffering in people who receive palliative care can vary depending on the individual and their specific condition and/or type of neoplasm. However, some common factors that may contribute to suffering in this population include [7-18]:

1. Physical symptoms: Pain [7, 8, 11, 12, 17], cancer-related fatigue (CRF) [7, 9-12, 17, 18], nausea [7, 11, 12], vomiting [11, 17], constipation [7, 11, 14, 17], dyspnea [7, 17] and chemotherapy induced peripheral neuropathy (CIPN) [7, 13].

2. Psychological distress: Anxiety [12], depression [12], fear [12], uncertainty about the future [8], social isolation [16], loneliness [16] and insomnia [7, 11].

3. Spiritual distress: Serious illness can raise questions about the meaning and purpose of life and may challenge patients' religious or spiritual beliefs [8].

Patients in palliative care suffer from a whole range of severe symptoms such as those above. Consequently, they progressively experience decreased physical functions, reduced mobility, and severe restrictions in their activities of daily living [14]. Additionally, the pain and other symptoms that these patients suffer from can become unbearable and markedly reduces their QoL [11]. The purpose of this systematic review is to examine what interventions, performed by a physiotherapist, can positively influence these symptoms, and thus provide relief [19, 20].

In 2018, the American College of Sports Medicine (ACSM) found strong evidence that regular physical activity significantly reduces the risk of several types of cancer [21]. Exercise offers benefits for both cancer prevention and improving the prognosis of cancer survivors. But although the effects of exercise in oncology patients have been widely discussed and studied, palliative cancer patients were often excluded from these studies [14].

The role of the physical therapist in the cancer journey is multifaceted. In addition to exercise therapy, education, behaviour modification, motivation, prevention, etc., are also an important part of physiotherapy interventions in patients with (a medical history of) cancer. These interventions can affect both quality of life and prognostic outcome measures of cancer and therefore deserve a prominent(er) role in the (after)care pathway of cancer patients/survivors [22]. Although this role in the curative oncology population has already been adequately evidenced, the specific role of physiotherapists in palliative oncology care remains unclear.

There is existing evidence regarding the possible analgesic effects, preservation of functions, improvement of functions, anabolic effect etc. [7-13, 18] in palliative oncology patients, but this evidence and research is scarce.

Physiotherapy in palliative oncological patients is a relevant but less discussed domain in the literature that needs to be thoroughly investigated so that we can, if proven effective, provide care and relief in this area as well [14].

By conducting rigorous studies and generating empirical evidence, the healthcare community can gain a deeper understanding of how physiotherapists can optimally contribute to palliative care. Therefore, this systematic review aims to synthesize the available evidence on the role of physiotherapists in the palliative care of cancer patients. By identifying the current gaps and challenges in the evidence base, this review will aim to inform the development of effective physiotherapy interventions that could optimize palliative care of oncology patients.

METHODS

Aim

This systematic review aims to examine the current evidence on the role of physiotherapists and physiotherapy interventions in palliative care for oncology patients. The aim is to research what they can contribute to the care of these patients. In this way, it is hoped that the effects already found in the heterogeneous protocols of the studies can be strengthened, provide an overview and if limitations are present, they can be incorporated into the future.

Research question

The research question reads as follows: 'The role of the physiotherapist in palliative care in oncology patients.' The question was composed of 2 letters of the PICO question formulation, namely as population (P) 'palliative oncology patients', and as outcome (O) 'the role of the physiotherapist'.

Eligibility criteria

Specifically, for the studies with blended populations, it was defined that of the overall group, at least 60% of them had to be both palliative and oncological. Only oncological patients, or only palliative patients were not adequate. No populations with children were included.
All interventions and topics that are part of the curriculum of rehabilitation sciences and physiotherapy, established and transmitted by the Free University of Brussels (VUB) were included as part of 'the role of the physiotherapist'.
To gather the highest quality of evidence, only randomized controlled studies (RCT's) were included.
Furthermore, only studies published from the year 2000 onwards were included, as a matter of including recent, relevant sources that are not outdated. Adding to this, only studies in English, Dutch or translated to English (or Dutch) were included. (Table 1)

INCLUSION CRITERIA	EXCLUSION CRITERIA

• *Population:*
  ○ Oncological, palliative patients (≥ 18 years)
  ○ Minimum 60% of total population
• *Outcome:*
  ○ Physiotherapist and physiotherapy (incl. massage, (gait) rehabilitation, exercise, physical applications, TENS)
• *Study design:*
  ○ RCT's
• *Publishing date:*
  ○ Studies published in and after the year 2000
• *Language:*
  ○ English, translated to English and Dutch
	• *Population:*
	  ○ Non-palliative oncological patients
	  ○ Palliative non-oncological patients
	• *Outcome:*
	  ○ Other therapies that are not within the scope of the physiotherapist's duties (e.g.: aromatherapy, music therapy, reflexology, yoga, dance therapy, tai-chi, …)
	• *Study design:*
	  ○ Other study designs than RCT's
	• *Publishing date:*
	  ○ Studies before the year 2000
	• *Language:*
	  ○ Other languages than English or Dutch

Table 1. Inclusion- and exclusion criteria

Search strategy, selection criteria and data extraction

Screening was conducted by 2 reviewers, who independently conducted the screening process. The screening program Rayyan was used, which was set to blind mode throughout the entire screening process.
The screening process went as follows: First, studies written before the year 2000 were excluded. Then, on reading the titles and abstracts, studies with the wrong study design and language were excluded. If it could already be deduced from the abstract and title that the study did not include the referring population or was about the wrong outcome (intervention not within the scope of the physiotherapist's responsibilities), these could also be excluded. Finally, the full text of the remaining studies was read, which were included or excluded based on population and outcome.
The search was conducted on 2 databases, Pubmed and Web of Science. (Table 1, Figure 1)
The last search was conducted on May. 15, 2023. The complete screening course can be found in the PRISMA diagram, found in Figure 1.

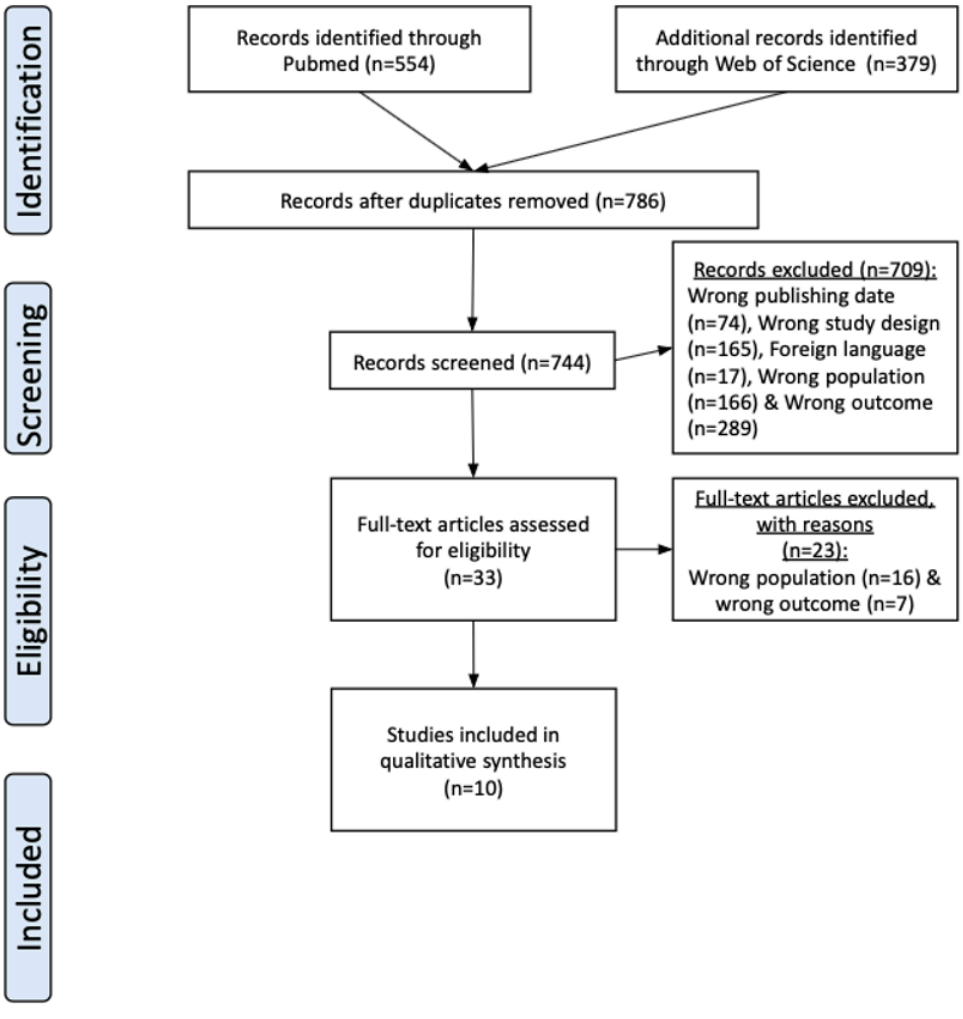

Figure 1.

To have as many hits as possible in our search strategy and hence be sure not to overlook any relevant articles, the advanced search builder was used, both on Pubmed and on Web of Science. Both the Mesh database, and the all-term database were used. The exact terms can be found in Table 2. The search strategy can be found in Table 3.

	P	I/E	C	O
MESH TERMS	[Neoplasms]	/	/	[Physical therapist]
	[Terminally Ill]			[Physical therapy modalities]
FREE TEXT	'Oncological patients in palliative care'	/	/	'Physiotherapy'
	'Cancer patients in palliative care'			'Physiotherapist'

Table 2. Search database - Mesh Terms & Free Text

	TERMEN	PUB MED	WEB OF SCIENCE
P	(("Neoplasms"[Mesh]) AND ("Terminally Ill"[Mesh])) OR (Oncological patients in palliative care) OR (Cancer patients in palliative care)	40 094	38 919
O	("Physical Therapists"[Mesh]) OR ("Physical Therapy Modalities"[Mesh]) OR (Physiotherapy) OR (physiotherapist)	238 722	109 288
PO	((("Neoplasms"[Mesh]) AND ("Terminally Ill"[Mesh])) OR (Oncological patients in palliative care) OR (Cancer patients in palliative care)) AND (("Physical Therapists"[Mesh]) OR ("Physical Therapy Modalities"[Mesh]) OR (Physiotherapy) OR (physiotherapist))	**554**	**379**

Table 3. Search history PubMed & Web of Science

Quality assessment and methodological rating

Since only RCTs were included, the ROB2 screening tool was merely used to assess the risk of bias of the studies. Figure 2 contains the risk of bias figure. The risk of bias assessment was again evaluated independently by 2 reviewers. After the full run through, another collaborative consultation was scheduled, after which a unified consensus regarding the risk of bias assessment was formed.

The distribution in terms of overall risk of bias can be seen in the table.

A summary of the other results can be found in Figure 3.

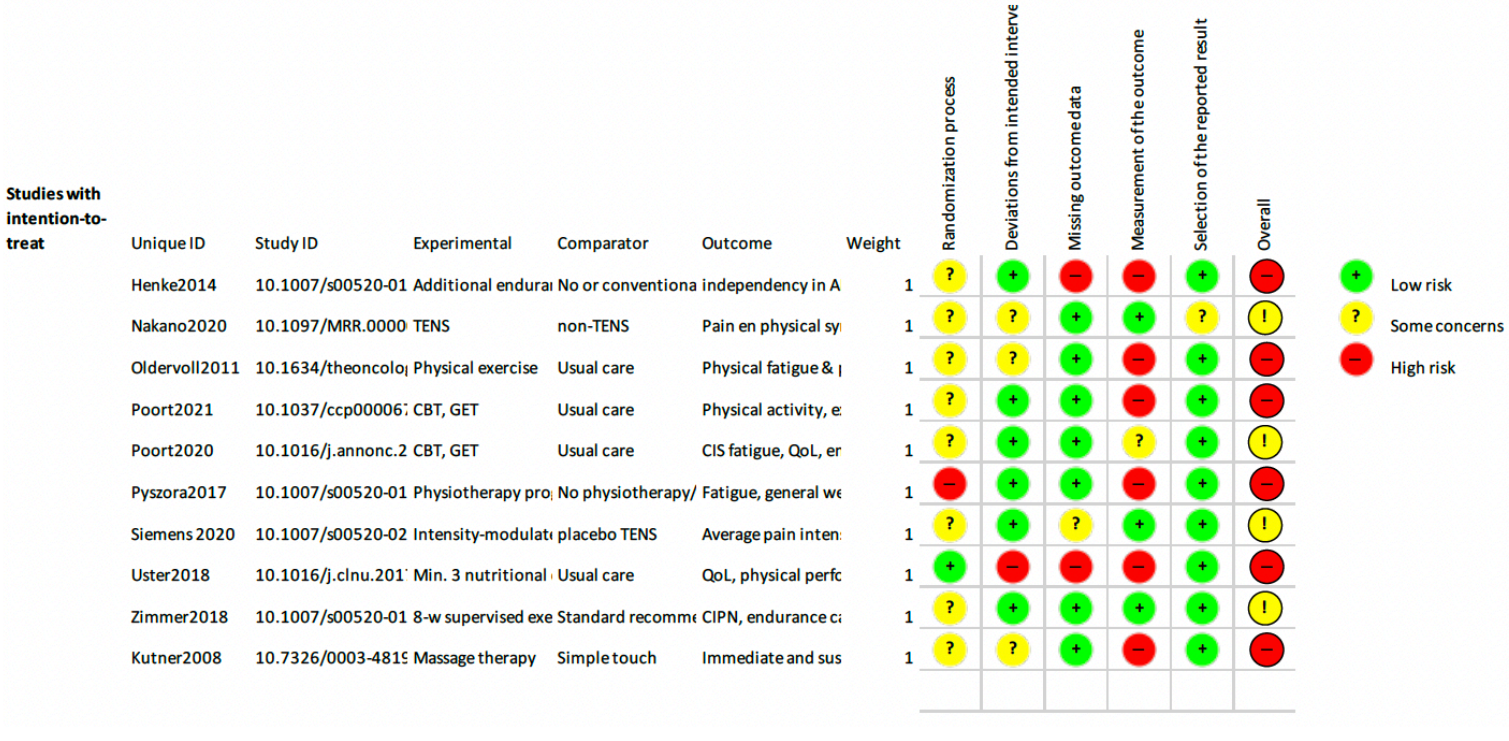

Figure 2. Risk of bias figure

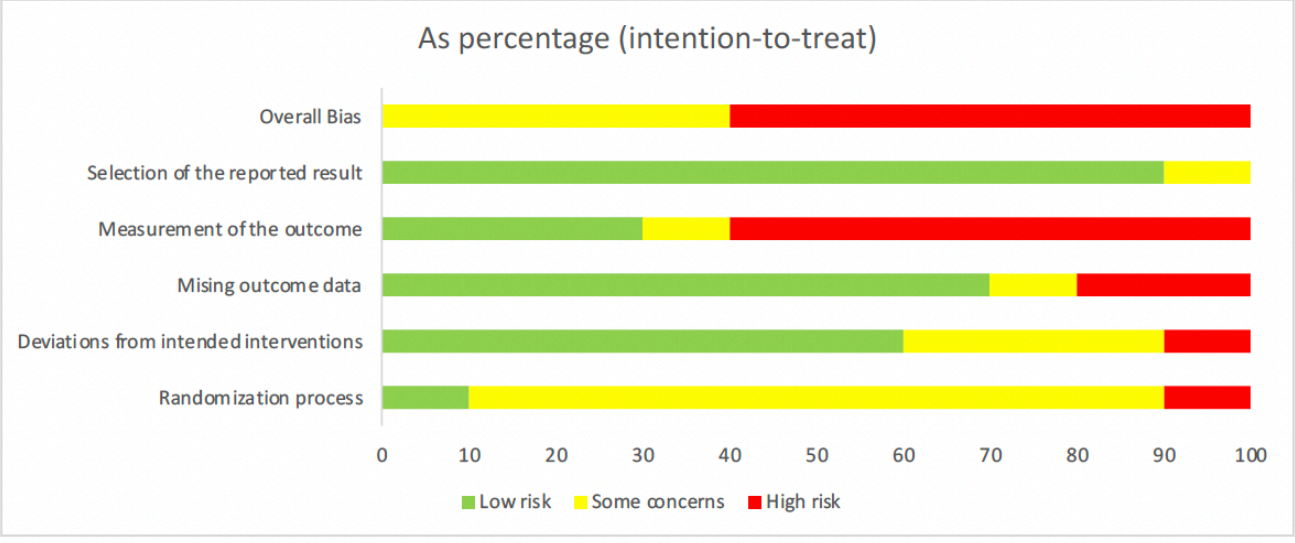

Figure 3. Summary Risk of Bias – as percentage

RESULTS

Methodological quality

In most of the studies the bias is caused by 'measurement of the outcome' (Figure 3). Interventions such as massage and physical activity, are very difficult to blind, which accounts for the large proportion of overall bias. It is both difficult to blind the evaluator as well as the instructor and participant/patient, which also raised some concerns in some studies regarding 'Deviations from intended interventions'.

Furthermore, the randomization processes also caused many concerns. Information regarding the randomization process is often incomplete or missing, or the process was not completely random. Nevertheless, quite a few studies used a randomization process arranged by computer. Also, the large variability in physical capacity between the intervention and control groups at baseline, which can be explained by the small sample size, raised some concerns as well.

'Selection of the reported result' and 'Missing outcome data' provided lowest risk. Even though the latter causes some concerns. This due to some patients dropping out and not showing up for one or more post measurements. This is something inevitable and is partly due to the population under review. However, analyses were often conducted to determine whether the studies obtained the same results even without those who discontinued the study as when they were included. This in turn reduced the risk of bias. As already mentioned, no issues were found in any of the studies that might indicate an increased risk of bias for the 'Selection of the reported result' component.

The distribution in terms of overall risk of bias can be seen in Figure 2.

The biggest shortcoming is the lack of studies within this population and the small sample sizes, causing dropouts or missing outcome data to have a greater impact on the result.

Content analysis of the included articles

Given that in this review the literature was searched on the role of the physiotherapist in palliative, oncology care, it consequently stands to reason that this role, which consists of multiple interventions, as well as impacts multiple outcomes. Outcomes were therefore all collected by study (Appendix 2), displaying in the left part of the sixth column the significantly positive outcomes (with the significance level being $p = 0.05$) and in de right part the non-significant outcomes ($p>0.05$).

Due to the large number of outcomes of the studies, they were divided into 3 different categories, i.e., physical, psychosocial/mental and QoL (Appendix 4).

Within the domain of physical outcomes, the greatest number of positive significant effects was found. Many results were found poorly within a single study, those discussed in multiple studies produced different results (Appendix 2). Muscle strength and peripheral neuropathy were significantly affected by physiotherapy by both the study by Henke et al. [7] and Zimmer et al. [13]. These studies both applied exercise therapy as intervention.

Furthermore, inconsistent agreement regarding the observed effects among studies exploring similar outcomes was observed. On the results of the 6MWT, the study by Henke et al. [7] found a significant positive effect after the exercise program, but in the study by Zimmer et al. [13], this effect was not significant. A positively significant result was again found on the outcomes physical functioning and dyspnea in the study by Henke et al. [7] and was not found significant either in the studies by Nakano et al. [11] and Uster et al. [17]. In contrast, nausea was significantly positively affected by TENS used in the study by Nakano et al. [11] and in the studies by Henke et al. [7] and Uster et al. [17] this effect was not significant. However, these are 3 studies that discussed different interventions within the domain of physiotherapy. (Appendix 2). On fatigue, only a positively significant influence of the physiotherapy program was found in the study by Pyszora et al. [12], the studies by Henke et al. [7], Nakano et al. [11], Oldervoll et al. [18] and Uster et al. [17] could not significantly prove this positive effect. Physiotherapy had a significant positive effect on the outcome pain, both in

the study by Kutner et al. [8] and in the study by Nakano et al. [11]. These studies included TENS and massage, not an exercise program. No significant effect on this was found in the studies by Henke et al. [7], Pyszora et al. [12] and Uster et al. [17]. Nakano et al. [11] also found a positive effect on patients' mean pain, although this was not significant in the studies by Kutner et al. [8] and Siemens et al. [16].
Within the domain of psychosocial/mental outcomes and QoL-related outcomes, no outcome was significantly positively confirmed by multiple different studies. We refer to Appendix 2 for the outcomes that were found to be significant but were only discussed by a single study.
For the other non-significant results that did not contradict within the different studies, please refer to the column 6 (right part) in Appendix 2.
The exact significance values (overall difference), as well as the within-group differences, grouped by study, if described in the studies, can be found in Appendix 2 & 3.

AUTHOR, YEAR	*SAMPLE SIZE TOTAL (BASELINE)*	*SAMPLE SIZE I (BASELINE)*	*SAMPLE SIZE C (BASELINE)*	*RETENTION TOTAL (%)*	*RETENTION I (%)*	*RETENTION C (%)*	*DROPOUT TOTAL (%)*	*DROPOUT I (%)*	*DROPOUT C (%)*
HENKE ET AL. (2014)	n=44	n=20	n=20	65,90%	75%	55,00%	34,09%	25,00%	45,00%
KUTNER ET AL. (2008)	n=380	n=188	n=192	70,00%	71,28%	68,75%	30,00%	28,72%	31,25%
NAKANO ET AL. (2020)	n=24	N/A	N/A	83,33%	N/A	N/A	16,67%	N/A	N/A
OLDERVOLL ET AL. (2011)	n=231	n=212	n=110	70,56%	64,46%	77,27%	29,44%	35,54%	22,73%
POORT ET AL. (2021)	n=134	CBTn=46 & GETn=42	n=46	61,19%	GET: 69,00% CBT: 83,00%	N/A	38,81%	GET: 31,00% CBT: 17,00%	N/A
POORT ET AL. (2020)	n=134	CBTn=46 & GETn=42	n=46	61,19%	GET: 69,00% CBT: 83,00%	N/A	38,81%	GET: 31,00% CBT: 17,00%	N/A
PYSZORA ET AL. (2017)	n=60	n=30	n=30	96,67%	96,67%	96,67%	3,33%	3,33%	3,33%
SIEMENS ET AL. (2020)	n=25	IMT-PBTn=13 & PBT-IMTn=12	N/A	80%	84,62% (IMT-PBT) & 75% (PBT-IMT)	N/A	20%	15,38% (IMT-PBT) & 25% (PBT-IMT)	N/A
USTER ET AL. (2018)	n=58	n=29	n=29	75,86%	82,76%	68,97%	24,14%	17,24%	31,03%
ZIMMER ET AL. (2018)	n=30	n=17	n=13	80%	88,24%	69,23%	20%	11,76%	30,77%

Appendix 1. Sample size and population information

STUDY (AUTHOR & YEAR)	PATIENT POPULATION	SAMPLE SIZE	INTERVENTION	COMPONENTS OF THE INTERVENTION	OUTCOMES	
					Significant, positive effect (p<0,05)	No significant effect (p>0,05)
HENKE ET AL. (2014)	Lung cancer patients in stages IIIA/IIIB/IV (NSCLC & SCLC)	n=44	Additional strength & endurance training + breathing techniques	Endurance training: 6 min. walk in hallway & stair walking exercise moderate intensity; strength training: 4 endurance strength exercises at 50% of 1RM; breathing exercises	6MWT Staircase walking Biceps curl Triceps extension Bridging Abdominal exercise Physical functioning: p=0,025 Cognitive functioning: p=0,050 Dyspnea Financial difficulties Coughing Hemoptysis: p=0,019 Peripheral neuropathy: p=0,050 Alopecia Pain in arms or shoulder: p=0,048	Role functioning Emotional functioning Social functioning Fatigue Nausea Pain Insomnia Appetite loss Constipation Diarrhea Sore mouth Dysphagia Pain in chest Pain in other body parts
KUTNER ET AL. (2008)	Patients with advanced cancer (lung, breast, pancreas, colorectal & prostate)	n=380	Six 30-minute massage over two weeks	Light/gentle effleurage, petrissage and myofascial trigger point release. Individual therapist judgment dictated the rhythm/rate/stroke frequency, sequence/mix of strokes, time spent in each stroke, stroke length and body area massaged.	Mood Pain	Heart rate Respiratory rate Mean pain Worst pain: p=0,53 Pain interference: p=0,60 Global Distress Index: p=0,97 Physical symptoms Psychological symptoms: p=0,50 Overall QoL: p=0,73 Physical Well-Being Existential: p=0,53 Support: p=0,36 Parenteral Morphine Equivalents: p=0,17
NAKANO ET AL. (2020)	Advanced cancer patients receiving palliative care (esophagus, head and neck, breast, kidney, lymphoma, prostate, liver, lung & other)	n=24	TENS	TENS applied to four sites, HF for all treatments except constipation, LF for constipation; 30 min applied 1x/day by physical therapist	Average pain: p<0,01 Pain: p<0,01 Nausea/vomiting: p=0,04 Appetite loss: p=0,02	Maximum pain Opioid Fatigue Dyspnea Insomnia Constipation Physical function Emotion function
OLDERVOLL ET AL. (2011)	Cancer patients with advanced disease (gastrointestinal, breast, lung, urological, gynecological, hematological & other (+ metastases))	n=231	Physical exercise	2 exercise sessions/week over an 8-week period; in groups of 2-8 persons supervised by a physiotherapist; 50-60 min./session with a warm-up, circuit training with six stations & stretching/relaxation; the program was tailored to the individual patient's level of physical functioning	Shuttle walk test: p=0.001 Sit-to-stand: p=0.05 Maximal stepping: p=0.04 Handgrip strength: p=0.001 Body weight: p=0.01	Total fatigue: p=0.12 Physical fatigue: p=0.20 Mental fatigue: p=0.13

POORT ET AL. (2021)	Patients with advanced cancer who reported severe fatigue (breast, colorectal, prostate & other (melanoma, sarcoma, renal cell, bladder, cervix/endometrial, or ovarian cancer))	n=134	CBT & GET	CBT: max 10 individual A-hr sessions (modules) over 12 weeks delivered at the patients local hospital; GET: 12-week supervised exercise program, weekly 2-hr sessions of individually graded aerobic and resistance training and second weekly session to repeat the training and increase physical activity	CIS-fatigue: p=0,003 Fatigue: p=0,005 Physical functioning: p=0,036 Emotional functioning: p=0,022	QoL: p=0,011 Functional impairments: p=0,060
POORT ET AL. (2020)	*Idem Poort et al. (2021)*				Fatigue self-efficacy Perceived physical activity	Emotional functioning Fatigue-catastrophizing Objective physical activity Exercise capacity
PYSZORA ET AL. (2017)	Patients with advanced cancer receiving palliative care (alimentary system, urogenital system, lung, CNS, mammary gland, hematological, indefinite origin, mouth & skin (tumor locations))	n=60	Physiotherapy program	3x/week for 2 weeks; 30 min.; incl. active exercises, myofascial release and proprioceptive neuromuscular facilitation (PNF) techniques	Fatigue: p<0,01 Drowsiness: p<0,05 Well-being: p<0,01	Pain: p=0,2 Nausea: p=0,1 Depression: p=0,8 Anxiety: p=0,9 Appetite: p=0,4 Breathlessness: p=0,7
SIEMENS ET AL. (2020)	Patients in specialist palliative care with advanced cancer pain (lung, pancreas, mamma, prostate, rectum & miscellaneous)	n=25	Intensity-modulated high TENS (IMT)	At the site of pain; patients were instructed by an experienced researcher; the IMT was 100Hz with a 'strong, but comfortable' intensity, decreased 40% every 0,5s to prevent habituation	/	Average pain: p=0,6590 Worst pain: p=0,7125 Least pain: p=0,6295 QoL: p=0,8252 General activity: p=1,000 Mood: p=0,7351 Walking ability: p=0,3229 Normal work: p=0,1745 Relations: p=0,5790 Sleep: p=0,3279 Enjoyment of life: p=0,9185
USTER ET AL. (2018)	Palliative cancer patients (colorectal, oesophago-gastric, NSCLC, SCLC, pancreas & others)	n=58	A min. of 3 standardized individual nutritional counseling sessions and participation in a 60 min. exercise program twice/week	Nutritional intervention: min. 3 sessions; it compromised an extensive initial nutritional assessment followed by individual nutritional measures; physical intervention: 2/week, in groups of 2-6 patients, supervised by an experienced physiotherapist, 60 min, included warm-up exercises (cycling ergometer), strength	Nausea and vomiting: p<0,01 Daily protein intake: p=0,01	Global health/QoL: p=0,72 Physical functioning: p=0,34 Role functioning: p=0,26 Emotional functioning: p=0,12 Cognitive functioning: p=0,53 Social functioning: p=0,72 Fatigue: p=0,75 Pain: p=0,42 Dyspnea: p=0,86 Sleep disturbance: p=0,18

				training exercises (6 stations covering the large muscle groups) & balance training exercises (Airex Balance mat)		Appetite loss: p=0,14 Constipation: p=0,14 Diarrhea: p=0,19 Finance: p=0,65 Daily energy intake: p=0,17 Total length of unexpected hospital stays p=0,185 Survival rate: p=0,25
ZIMMER ET AL. (2018)	Metastasized colorectal cancer patients (cecum/colon, rectosigmoid junction & rectum)	n=30	8-week, multimodal exercise program	Balance training, coordination practices, endurance training, resistance training and cool-down	Muscle strength - Bench press: p=0,014 - Leg press: p=0,011 - Lat pulldown: p=0,031 CIPN (Peripheral neuropathy)	Balance: p=0,650 6 MWT: p=0,432

Appendix 2. Summary of Findings

	OUTCOME	WITHIN-GROUP DIFFERENCES*	
		Intervention group	Control group
HENKE 2014	6MWT Staircase walking Biceps curl Triceps extension Bridging Abdominal exercise (EORTC QLQ C-30) QoL Physical functioning Role functioning Emotional functioning Cognitive functioning Social functioning Fatigue Nausea Pain Dyspnoea Insomnia Appetite loss Constipation Diarrhoea Financial difficulties (EORTC QLQ LC-13) Dyspnoea (LC) Coughing Hemoptysis Sore mouth Dysphagia Peripheral neuropathy Alopecia Pain in chest Pain in arms or shoulder Pain in other body parts t0: Baseline, first day of chemotherapy t1: After 3 cycles of chemotherapy	↑ 6MWT → t0: 378,35 (106,71) → t1: 397,06 (102,56) Staircase walking → t0: 130,24 (51,18) → t1: 136,18 (47,53) Biceps curl → t0: 25,35 (10,42) → t1: 27,41 (9,75) Triceps extension → t0: 25,47 (10,70) → t1: 27,12 (9,81) Bridging → t0: 11,82 (6,88) → t1: 13,94 (6,69) Abdominal exercise → t0: 10,24 (5,72) → t1: 11,71 (5,67) QoL → t0: 52,08 (21,84) → t1: 57,81 (17,34) Emotional functioning → t0: 69,27 (17,67) → t1: 70,31 (24,53) Fatigue → t0: 43,75 (28,82) → t1: 50,69 (27,51) Nausea → t0: 12,50 (27,55) → t1: 15,62 (22,33) Pain → t0: 22,92 (30,96) → t1: 25,00 (29,19) Financial difficulties → t0: 20,83 (34,16) → t1: 62,50 (29,50) Sore mouth → t0: 4,17 (11,39) → t1: 16,67 (36,51)	↑ Fatigue → t0: 59,83 (29,93) → t1: 64,10 (36,61) Nausea → t0: 8,97 (17,50) → t1: 32,05 (41,65) Diarrhea → t0: 12,82 (28,99) → t1: 17,95 (25,88) Financial difficulties → t0: 25,64 (30,89) → t1: 61,54 (40,47) Hemoptysis → t0: 10,26 (28,50) → t1: 17,95 (32,25) Dysphagia → t0: 20,51 (28,99) → t1: 25,64 (36,40) Peripheral neuropathy → t0: 30,77 (37,17) → t1: 46,15 (37,36) Alopecia → t0: 2,56 (9,25) → t1: 51,28 (37,55) Pain in arms or shoulder → t0: 33,33 (38,49) → t1: 35,90 (37,17) Pain in other body parts → t0: 56,41 (39,40) → t1: 58,97 (38,86) = Appetite loss → t0: 58,97 (43,36) → t1: 58,97 (41,17) Constipation → t0: 46,15 (44,18) → t1: 46,15 (48,19) ↓

		Dysphagia → t0: 20,83 (36,26) → t1: 29,17 (38,25) Peripheral neuropathy → t0: 6,25 (18,13) → t1: 20,83 (26,87) Alopecia → t0: 8,33 (25,82) → t1: 37,50 (40,14) Pain in other body parts → t0: 31,25 (28,46) → t1: 50,00 (34,43) ↓ Physical functioning → t0: 75,42 (28,46) → t1: 74,58 (21,94) Role functioning → t0: 66,67 (32,20) → t1: 59,37 (32,19) Cognitive functioning → t0: 86,45 (19,45) → t1: 79,17 (31,91) Social functioning → t0: 75,00 (29,19) → t1: 67,71 (29,48) Dyspnea → t0: 37,50 (23,96) → t1: 35,42 (30,96) Insomnia → t0: 52,08 (36,45) → t1: 37,50 (34,16) Appetite loss → t0: 39,58 (40,77) → t1: 37,50 (41,94) Constipation → t0: 37,50 (40,14) → t1: 33,33 (32,20) Diarrhea → t0: 14,58 (34,36) → t1: 10,58 (34,36) Dyspnea (LC) → t0: 30,56 (19,25) → t1: 23,61 (20,64) Coughing → t0: 45,83 (31,91) → t1: 37,50 (36,26) Hemoptysis → t0: 6,25 (13,44) → t1: 0,00 (0,00) Pain in chest → t0: 14,58 (24,25) → t1: 12,50 (26,87) Pain in arms or shoulder → t0: 22,92 (33,82) → t1: 10,42 (20,07)	6MWT → t0: 240,83 (150,50) → t1: 193,33 (162,78) Staircase walking → t0: 70,42 (50,74) → t1: 52,08 (55,85) Biceps curl → t0: 14,17 (9,04) → t1: 11,75 (10,39) Triceps extension → t0: 16,25 (10,93) → t1: 11,08 (9,00) Bridging → t0: 9,25 (7,24) → t1: 7,08 (7,45) Abdominal exercise → t0: 6,83 (6,87) → t1: 5,00 (5,94) QoL → t0: 50,64 (28,15) → t1: 44,23 (29,54) Physical functioning → t0: 55,38 (29,86) → t1: 48,20 (32,90) Role functioning → t0: 53,85 (40,34) → t1: 51,28 (39,36) Emotional functioning → t0: 58,33 (29,27) → t1: 57,05 (28,64) Cognitive functioning → t0: 79,49 (18,20) → t1: 57,69 (33,10) Social functioning → t0: 69,23 (31,80) → t1: 60,26 (41,69) Pain → t0: 51,28 (43,81) → t1: 46,15 (34,80) Dyspnea → t0: 64,10 (34,59) → t1: 51,28 (35,00) Insomnia → t0: 69,23 (31,80) → t1: 53,85 (39,76) Dyspnea (LC) → t0: 58,97 (31,22) → t1: 45,30 (34,08) Coughing → t0: 51,28 (29,24) → t1: 28,21 (29,96) Sore mouth → t0: 17,95 (32,25) → t1: 12,82 (28,99) Pain in chest → t0: 25,64 (30,89) → t1: 17,95 (29,24)
KUTNER **2008**	*Immediate effects* Mood (MPAC) Pain (MPAC) Heart rate Respiratory rate *Sustained effects* Mean pain (BPI) Worst pain (BPI) Pain interference (BPI)	*Immediate effects* Mood: 1,58 (1,40-1,76) Pain: 1,87 (-2,07, -1,67) Heart rate: 4,20 (-4,9, -3,50) Respiratory rate: 1,46 (-1,75, -1,17) *Sustained effects* Mean pain: 0,33 (-0,54, -	*Immediate effects* Mood: 0,97 (0,78, 1,16) Pain: 0,97 (-1,18, -0,76) Heart rate: 3,28 (-4,04, -2,57) Respiratory rate: 1,15 (-1,4§, -0,84) *Sustained effects* Mean pain: 0,40 (-0,62, -

	Global Distress Index (MSAS) Physical symptoms (MSAS) Psychological symptoms (MSAS) Overall QoL (MQOL) Physical Well-Being (MQOL) Existential (MQOL) Support (MQOL) Parenteral Morphine t0: Baseline t1: 2 weeks	0,12) Worst pain: 0,74 (-1,05, -0,43) Pain interference: 0,33 (-0,61, -0,05) Global Distress Index: 0,11 (-0,19, -0,03) Physical symptoms: 0,10 (-0,18, -0,02) Psychological symptoms: 0,09 (-0,22, 0,04) Overall QoL: 0,36 (0,04, 0,68) Physical Well-Being: 0,26 (-0,11, 0,63) Existential: 0,01 (-0,22, 0,20) Support: 0,17 (-0,39, 0,05) Parenteral Morphine: 0,007 (-0,09, 0,77)	0,18) Worst pain: 0,60 (-0,92, -0,28) Pain interference: 0,43 (-0,72, -0,14) Global Distress Index: 0,11 (-0,20, -0,02) Physical symptoms: 0,07 (-0,15, 0,008) Psychological symptoms: 0,16 (-0,29, -0,02) Overall QoL: 0,29 (-0,03, 0,61) Physical Well-Being: 0,44 (0,07, 0,81) Existential: 0,08 (-0,13, 0,29) Support: 0,02 (-0,24, 0,20) Parenteral Morphine: 0,11 (0,006, 0,21)
NAKANO **2020**	Average pain (NRS) Maximum pain (NRS) Opioid (mg/day) Pain (QLQ-C15-PAL) Fatigue (QLQ-C15-PAL) Nausea/vomiting (QLQ-C15-PAL) Appetite loss (QLQ-C15-PAL) Dyspnea (QLQ-C15-PAL) Insomnia (QLQ-C15-PAL) Constipation (QLQ-C15-PAL) Physical function (QLQ-C15-PAL) Emotion function (QLQ-C15-PAL) t0: Baseline t1: Post intervention	Average pain: 1,9 (SD 2,6) Maximum pain: 1,0 (SD 2,3) Opioid: 6,9 (SD 15,4) Pain: 24,6 (SD 22,5) Fatigue: 0,3 (SD 24,5) Nausea/vomiting: 12,5 (SD 25,3) Appetite loss: 11,7 (SD 19,6) Dyspnea: 5,0 (SD 22,3) Insomnia: 1,7 (SD 20,2) Constipation: 6,7 (SD 27,8) Physical function: 7,3 (SD 18,5) Emotion function: 2,9 (SD 23,1)	Average pain: 0,2 (SD 2,2) Maximum pain: 0,1 (SD 2,5) Opioid: 9,20 (SD 19,8) Pain: 3,3 (SD 26,0) Fatigue: 6,1 (SD 28,5) Nausea/vomiting: 2,5 (SD 19,0) Appetite loss: 4,9 (SD 34,7) Dyspnea: 6,7 (SD 25,6) Insomnia: 15,0 (SD 42,5) Constipation: 3,3 (SD 26,2) Physical function: 1,7 (SD 14,7) Emotion function: 7,1 (SD 25,5)
OLDERVOLL **2011**	Total fatigue Physical fatigue Mental fatigue Shuttle walk test Sit-to-stand Maximal stepping Handgrip strength Body Weight t0: Baseline t1: 8 weeks	↓ Total fatigue Physical fatigue Mental fatigue ↑ Shuttle walk test Sit-to-stand Maximal stepping Handgrip strength Body weight	↓ Total fatigue Physical fatigue Mental fatigue Shuttle walk test Maximal stepping Handgrip strength Body weight ↑ Sit-to-stand
POORT **2021**	Objective physical activity (actigraphy) Exercise capacity (6-MWT) Fatigue self-efficacy (SES) Fatigue-catastrophizing (FCS) Perceived physical activity (CIS physical activity) Emotional functioning (EORTC-QLQ EF) t0: Baseline	<u>CBT:</u> Fatigue severity: → t0: 44,8 (1,1) → t1: 30,0 (2,1) Objective physical activity: → t0: 53,2 (3,2) → t1: 57,3 (3,3) Exercise capacity: → t0: 415,0 (14,9) → t1: 431,2 (16,7)	Fatigue severity: → t0: 48,6 (1,1) → t1: 38,3 (2,2) Objective physical activity: → t0: 51,0 (53,3) → t1: 55,3 (3,4) Exercise capacity: → t0: 436,7 (15,5) → t1: 437,8 (17,3) Fatigue self-efficacy:

	t1: 14 weeks t2: 18 weeks t3: 26 weeks	Fatigue self-efficacy: → t0: 17,8 (0,6) → t1: 20,9 (0,6) Fatigue-catastrophizing: → t0: 22,5 (1,4) → t1: 19,2 (1,3) Perceived physical activity: → t0: 15,1 (0,8) → t1: 10,8 (0,9) Emotional functioning: → t0: 65,5 (4,4) → t1: 80,7 (3,6) <u>GET:</u> Fatigue severity: → t0: 46,0 (1,1) → t1: 33,1 (2,2) Objective physical activity: → t0: 56,5 (3,4) → t1: 53,9 (3,5) Exercise capacity: → t0: 435,5 (15,8) → t1: 443,2 (17,6) Fatigue self-efficacy: → t0: 20,6 (0,6) → t1: 20,1 (0,7) Fatigue-catastrophizing: → t0: 19,2 (1,5) → t1: 18,8 (1,4) Perceived physical activity: → t0: 15,4 (0,8) → t1: 12,4 (0,9) Emotional functioning: → t0: 70,8 (4,7) → t1: 76,6 (3,8)	→ t0: 18,8 (0,6) → t1: 19,2 (1,3) Fatigue-catastrophizing: → t0: 22,5 (1,4) → t1: 19,0 (1,3) Perceived physical activity: → t0: 15,4 (0,8) → t1: 13,5 (0,9) Emotional functioning: → t0: 65,1 (4,6) → t1: 73,5 (3,7)
POORT **2020**	14-week fatigue severity (CIS-fatigue) Fatigue (EORTC-QLQ-C30) QoL (EORTC-QLQ-C30) Physical functioning (EORTC-QLQ-C30) Emotional functioning (EORTC-QLQ-C30) Functional impairments (SIP8) t0: Baseline t1: 14 weeks t2: 18 weeks t3: 26 weeks	<u>CBT</u> CIS-fatigue: → t0: 43,96 (7,83) → t1: 31,72 (28,36 to 35,09) <u>GET:</u> CIS-fatigue: → t0: 45,74 (6,24) → t1: 34,25 (30,79 to 37,71)	CIS-fatigue: → t0: 47,07 (6,60) → t1: 38,95 (35,58 to 42,32)
PYSZORA **2017**	Cancer-related fatigue (CRF) & impact on daily functioning (BFI) Pain (ESAS) Fatigue (ESAS) Nausea (ESAS) Depression (ESAS) Anxiety (ESAS) Drowsiness (ESAS) Appetite (ESAS) Well-being (ESAS) Breathlessness (ESAS) (Satisfaction (satisfaction scores)) **t0: Baseline** t1: day 1	BFI (all questions): → t0: 6,4 (SD 1,0) → t6: 4,4 (SD 1,4) Pain: → t0: 1,5 (SD 1,9) → t6: 1,2 (SD 1,5) Fatigue: → t0: 6,8 (SD 1,1) → t6: 4,6 (SD 1,6) Nausea: → t0: 0,4 (SD 1,0) → t6: 0,3 (SD 0,8) Depression: → t0: 2,9 (SD 2,3) → t6: 2,7 (SD 2,1)	BFI (question 1 and 3): → t0: 6,13 (SD 1,4) → t6: 5,9 (SD 1,44) Pain: → t0: 1,7 (SD 2,1) → t6: 1,7 (SD 2,0) Fatigue: → t0: 6,5 (SD 1,4) → t6: 6,3 (SD 1,2) Nausea: → t0: 1,1 (SD 2,2) → t6: 0,9 (SD 2,0) Depression: → t0: 2,9 (SD 2,5) → t6: 2,8 (SD 2,6)

	t2: day 3 t3: day 5 t4: day 8 t5: day 10 **t6: day 12**	Anxiety: → t0: 2,7 (SD 2,3) → t6: 2,5 (SD 2,1) Drowsiness: → t0: 3,6 (SD 2,9) → t6: 2,3 (SD 2,1) Appetite: → t0: 4,3 (SD 2,9) → t6: 3,1 (SD 2,5) Well-being: → t0: 4,8 (SD 0,9) → t6: 3,0 (SD 1,2) Breathlessness: → t0: 1,0 (SD 1,8) → t6: 0,8 (SD 1,5)	Anxiety: → t0: 2,7 (SD 2,5) → t6: 2,5 (SD 2,5) Drowsiness: → t0: 4,0 (SD 2,7) → t6: 3,8 (SD 2,7) Appetite: → t0: 4,0 (SD 3,0) → t6: 3,8 (SD 2,8) Well-being: → t0: 5,3 (SD 1,3) → t6: 5,0 (SD 1,3) Breathlessness: → t0: 0,9 (SD 1,6) → t6: 0,9 (SD 1,6)
SIEMENS **2020**	Average pain (NRS) Worst pain (NRS) Least pain (NRS) QoL (EORTC QLQ-C30) General activity (NRS) Mood (NRS) Walking ability (NRS) Normal work (NRS) Relations (NRS) Sleep (NRS) Enjoyment of life (NRS) t0: Baseline t1: Post intervention	*Change scores within treatment IMT:* Average pain: 0,9 (-1,4 to -0,4) Worst pain: 1,3 (-2,0 to -0,6) Least pain: 0,7 (-1,2 to -0,2) Pain relief with TENS: 0,4 (-0,3 to 1,0) QoL: 1,4 (-2,8 to 0,0) General activity: 0,9 (-2,2 to 0,4) Mood: 1,8 (-3,3 to -0,3) Walking ability: 2,4 (-3,8 to -1,0) Normal work: 0,4 (-1,5 to 0,8) Relations: 1,2 (-2,2 to -0,1) Sleep: (-2,3 to 0,6)	<u>IMT-PBT</u> Average pain: 0,5 (SD 1,4) Worst pain 0,0 (SD 2,6) Least pain: 0,1 (SD 2,0) QoL: 0,6 (SD 2,0) General activity: 0,5 (SD 4,5) Mood: 0,5 (3,9) Walking ability: 2,2 (SD 4,5) Normal work: 3,4 (SD 5,5) Relations: 0,6 (SD 3,6) Sleep: 1,7 (SD 3,1) Enjoyment of life: 0,1 (SD 5,1) <u>PBT-IMT</u> Average pain: 0,2 (SD 1,6) Worst pain 0,6 (SD 3,6) Least pain: 0,3 (SD 1,7) QoL: 1,0 (SD 1,7) General activity: 0,7 (SD 5,1) Mood: 0,1 (4,1) Walking ability: 0,6 (SD 3,5) Normal work: 0,6 (SD 3,8) Relations: 1,7 (SD 2,1) Sleep: 0,3 (SD 3,9) Enjoyment of life: 0,1 (SD 3,5)
USTER **2018**	QoL (EORTC-QLQ-C30) Physical performance (hand-grip strength, 6-MWT, timed sit-to-stand test, 1 RM leg press) Nutritional status (body weight, BIA) Dietary intake (three-day dietary record) Clinical data (unexpected hospital days, performance status) t0: Baseline t1: 3 months later t2: 6 months later	Global health/QoL: 4,5 (SD 3,4) Physical functioning: 0 (SD 3,3) Role functioning: 5,3 (SD 5,2) Emotional functioning: 2,1 (SD 3,3) Cognitive functioning: 7,5 (SD 3,3) Social functioning: 3,9 (SD 4,6) Fatigue: 1,5 (SD 4,4) Nausea and vomiting: 4,2 (SD 3,0) Pain: 14,2 (SD 5,7) Dyspnea: 0,2 (SD 4,3) Sleep disturbance: 5,1 (SD 5,1) Appetite loss: 14,2 (SD 6,3) Constipation: 9,2 (SD 5,2) Diarrhea: 7 (SD 4,9) Finance: 4,4 (SD 3,5) Daily protein intake: 6 (SD 4) Daily energy intake: 129 (SD 6)	Global health/QoL: 2,7 (SD 4,0) Physical functioning: 8,7 (SD 3,8) Role functioning: 7,1 (SD 6,2) Emotional functioning: 0,2 (SD 4,2) Cognitive functioning: 1,1 (SD 3,9) Social functioning: 9,3 (SD 5,6) Fatigue: 2,2 (SD 5,2) Nausea and vomiting: 9,7 (SD 3,8) Pain: 16 (SD 6,8) Dyspnea: 0,5 (SD 5,0) Sleep disturbance: 6,7 (SD 6,0) Appetite loss: 11,6 (SD 7,6) Constipation: 15,7 (SD 6,5) Diarrhea: 18,7 (SD 5,7) Finance: 3,1 (SD 4,0) Daily protein intake: 2 (SD 5) Daily energy intake: 11 (SD 130)
ZIMMER **2018**	CIPN (FACT/GOG-NTX) Endurance capacity (6MWT) Strength (h1RM) Balance (GGT-Reha) t0: Baseline t1: After intervention t2: 4 weeks follow-up	<u>I (t1-t0):</u> TOI: → t0: 75,059 (SD 14,818) → t1: 77,353 (SD 11,837) PWB: → t0: 22, 941 (SD 3,832) → t1: 23,177 (SD 3,746) FWB: → t0: 19 (SD 5,303)	<u>C (t1-t0):</u> TOI: → t0: 71,577 (SD 13,035) → t1: 64,436 (SD 11,570) PWB: → t0: 19,577 (SD 5,392) → t1: 19,385 (SD 3,709) FWB: → t0: 17,923 (SD 6,238)

→ t1: 18,9412 (SD 5,984)
NTX:
→ t0: 33,118 (SD 8,162)
→ t1: 35,2353 (SD 6,600)
SocWB:
→ t0: 23,072 (SD 3,797)
→ t1: 22,873 (SD 3,878)
EmoWB:
→ t0: 17,412 (SD 5,075)
→ t1: 17,647 (SD 4,834)
FACT_G:
→ t0: 82,425 (SD 15,465)
→ t1: 82,637 (SD 15,432)
GGT-Reha:
→ t0: 54,88 (SD 16,677)
→ t1: 58,94 (SD 12,750)
6MWT:
→ t0: 477,735 (SD 91,911)
→ t1: 502,176 (SD 62,072)
h1RM…
… bench press:
→ t0: 38,061 (SD 12,767)
→ t1: 49,089 (SD 23,840)
… leg press:
→ t0: 142,156 (SD 44,125)
→ t1: 180,886 (SD 66,619)
… lat pulldown:
→ t0: 29,655 (SD 9,131)
→ t1: 38,416 (SD 14,004)
Sign. differences mentioned:
NTX: 2,12 (median: 2)
GGT-Reha (advanced static balance): 1,88 (median: 2)
h1RM…
…bench press: 38,06 (median: 37,21)
…leg press: 38,73 (median: 19,84)
…lat pulldown: 8,76 (median: 6,92)
6MWT: 24,44 (14)

I (t2-t1):
Sign. differences mentioned:
h1RM…
…bench press: 1,22 (+5,92)
…lat pulldown: 2 (-3,89)

I (t2-t0):
TOI:
→ t0: 75,059 (SD 14,818)
→ t2: 75,402 (SD 13,553)
PWB:
→ t0: 22, 941 (SD 3,832)
→ t2: 22,294 (SD 4,312)
FWB:
→ t0: 19 (SD 5,303)
→ t2: 19,108 (SD 5,373)
NTX:
→ t0: 33,118 (SD 8,162)
→ t2: 34 (SD 7,365)
SocWB:
→ t0: 23,072 (SD 3,797)
→ t2: 22,741 (SD 4,227)
EmoWB:
→ t0: 17,412 (SD 5,075)
→ t2: 17,647 (SD 4,358)
FACT_G:
→ t0: 82,425 (SD 15,465)
→ t2: 81,7902 (SD 15,425)
GGT-Reha:
→ t0: 54,88 (SD 16,677)
→ t2: 61,41 (SD 13,482)
6MWT:

→ t1: 16,077 (SD 6,238)
NTX:
→ t0: 34,077 (SD 7,297)
→ t1: 28,974 (SD 9,920)
SocWB:
→ t0: 24,231 (SD 2,454)
→ t1: 24,128 (SD 3,032)
EmoWB:
→ t0: 18,139 (SD 3,739)
→ t1: 18,308 (SD 4,171)
FACT_G:
→ t0: 80,547 (SD 12,789)
→ t1: 77,897 (SD 12,032)
GGT-Reha:
→ t0: 44 (SD 16,289)
→ t1: 47,15 (SD 12,844)
6MWT:
→ t0: 459,654 (SD 74,061)
→ t1: 478,154 (SD 75,172)
h1RM…
… bench press:
→ t0: 40,215 (SD 19,145)
→ t1: 38,242 (SD 15,022)
… leg press:
→ t0: 166,717 (SD 56,304)
→ t1: 160,339 (SD 54,137)
… lat pulldown:
→ t0: 30,501 (SD 10,308)
→ t1: 32,936 (SD 11,254)
Sign. differences mentioned:
NTX: 5,11 (median: -3)
1hRM…
…lat pulldown:
2,44 (2,11)
6MWT: 18,5 (21)

C (t2-t0):
TOI:
→ t0: 71,577 (SD 13,035)
→ t2: 63,508 (SD 9,758)
PWB:
→ t0: 19,577 (SD 5,392)
→ t2: 18,077 (SD 3,475)
FWB:
→ t0: 17,923 (SD 6,238)
→ t2: 16 (SD 5,686)
NTX:
→ t0: 34,077 (SD 7,297)
→ t2: 29,431 (SD 9,332)
SocWB:
→ t0: 24,231 (SD 2,454)
→ t2: 23,603 (SD 2,947)
EmoWB:
→ t0: 18,139 (SD 3,739)
→ t2: 18,231 (SD 3,833)
FACT_G:
→ t0: 80,547 (SD 12,789)
→ t2: 75,910 (SD 10,464)
GGT-Reha:
→ t0: 44 (SD 16,289)
→ t2: 46,38 (SD 13,156)
6MWT:
→ t0: 459,654 (SD 74,061)
→ t2: 482,154 (SD 82,641)
h1RM…
… bench press:
→ t0: 40,215 (SD 19,145)
→ t2: 36,361 (SD 12,645)
… leg press:
→ t0: 166,717 (SD 56,304)
→ t2: 159,991 (SD 62,154)

		→ t0: 477,735 (SD 91,911) → t2: 519,059 (SD 68,958) h1RM… … bench press: → t0: 38,061 (SD 12,767) → t2: 46,356 (SD 24,223) … leg press: → t0: 142,156 (SD 44,125) → t2: 179,664 (SD 68,196) … lat pulldown: → t0: 29,655 (SD 9,131) → t2: 36,413 (SD 13,290) *Sign. differences mentioned:* TOI: 8,07 (median: -8)	… lat pulldown: → t0: 30,501 (SD 10,308) → t2: 31,217 (SD 11,594) *Sign. differences mentioned:* TOI: 8,07 (median: -8) NTX: 4,65 (median: 3)

*** Legend arrows:**

↑ : Post-measurement is more/higher than pre-measurement
↓ : The post-measurement is less/lower than the pre-measurement
= : There is no difference between the pre- and post-measurement

Appendix 3. Within-group differences of the outcomes

PHYSICAL	PSYCHOSOCIAL/MENTAL	QOL
6mwt	Role functioning	QoL
Staircase Walking	Emotional functioning	Insomnia
Biceps Curl	Social functioning	Appetite loss
Triceps Extension	Financial difficulties	Impact on daily functioning (BFI)
Bridging	Global distress index	Well-being
Abdominal Exercise	Psychological symptoms	Normal work
Physical Functioning	Existential	Sleep
Fatigue	Cognitive functioning	Enjoyment of life
Nausea	Support	Dietary intake
Dyspnea	Mental fatigue	Nutritional status
Constipation	Fatigue catastrophizing (FCS)	Total length of unexpected hospital stays
Diarrhea	Fatigue self-efficacy (SES)	Survival rate
Coughing	Depression	
Hemoptysis	Anxiety	
Sore Mouth	Drowsiness	
Dysphagia	Mood	
Peripheral Neuropathy	Relations	
Pain In Chest		
Pain In Arms Or Shoulder		
Pain In Other Body Parts		
Muscular Strength		
Heart Rate		
Respiratory Rate		
Physical Symptoms		
Physical Well-Being		
Physical Fatigue		
Shuttle Walk Test		
Maximal Stepping		
Objective Physical Activity		
Exercise Capacity		
Perceived Pa (Cis Pa)		
14-Week Fatigue Severity		
Funtional Impairments (Sip8)		
Cancer Related Fatigue (Crf)		
Breathlessness		
General Activity / Level Of Daily Pa		
Walking Ability		
Endurance Capacity		

Balance	
Clinical Data	
Sit To Stand Test	
Hand Grip Strength	
Daily Protein Intake	
Pain	
Average / Mean Pain	
Worst / Maximum Pain	
Least Pain	
Pain Interference	
Parental Morphine	
Alopecia	

***THE DIVISION MAY APPEAR RATHER ARTIFICIAL. IT IS POSSIBLE THAT CERTAIN OUTCOMES COULD ALSO BE PLACED WITH OTHER CATEGORIES. THIS DIVISION IS MERELY A TOOL TO BETTER RANK THE OUTCOMES AND KEEP THE TABLES AND DESCRIPTIONS CLEAR.**

DISCUSSION

This systematic review investigated what physiotherapy can do within palliative, oncology care.

Generalizing results and comparing studies with each other was very limited, given the heterogeneity of the included studies. Furthermore, it was not possible to perform a meta-analysis due to this limitation. This again emphasizes the need for new large studies of good quality and the development of general guidelines on physical therapy in palliative oncology.

The main findings are the following.

Both the study by Henke et al. [7] and the study by Zimmer et al. [13] showed a significant effect of exercise therapy on both muscular strength, and peripheral neuropathy. Therefore, the effect was confirmed by both studies.

Pain reduction was significant in the studies by Nakano et al. [11] and Kutner et al. [8], the two included studies that focused on no exercise program but physical applications (i.e., TENS) and massage therapy. The studies by Henke et al. [7], Pyszora et al. [12] and Uster et al. [17], also examined the effect on pain, but the effect of their exercise therapy was not significant.

However, it is important to reiterate the artificial division of the three categories outlined in Appendix 4. Pain serves as an illustrative example of outcomes that may be categorized under physical domains in palliative care, while also exerting a significant negative influence on multiple dimensions of QoL. In the realm of palliative care, pain is commonly categorized as a physical outcome rather than solely under the QoL category. While QoL encompasses various aspects of well-being, including physical, psychological, and social dimensions, pain itself is tied to the physical domain. However, it is essential to acknowledge that pain does have a profound negative influence on a patient's overall QoL. This complex relationship highlights the interconnectedness of different outcome categories and their impact on one another. Just as pain can affect multiple facets of a patient's life, other outcomes may also transcend their assigned categories. The concept of the 'total pain' exemplifies this notion, emphasizing that various dimensions of suffering should be considered holistically. [23]

Furthermore, the effect on mean pain was examined by the studies of Nakano et al. [11], Kutner et al. [8] and Siemens et al. [16], but only in the study of Nakano et al. [11] was this mean pain reduction found to be significant. The effect on CRF has been examined by many studies, since it is, after all, one of the most commonly reported symptoms. Although this was examined both by Henke et al. [7], Nakano et al. [11], Oldervoll et al. [18], Pyszora et al. [12] and Uster et al. [17], only a significant improvement was found in the study by Pyszora et al. [12]

Henke et al. [7] found a significant, positive improvement on the outcomes physical functioning and dyspnea, while this was not significant in the study by Nakano et al. [11] and Uster et al. [17]. Notwithstanding, Henke et al. [7] and Pyszora et al. [12] found no significant improvement on nausea, but did in the study by Nakano et al. [11]. Cognitive functioning and financial difficulties were both positively significantly affected in the Henke et al. [7] study, although this was not significant in the study by Uster et al. [17]. A significant positive effect was also found on performance on the 6MWT in the Henke et al. [7] study, which in contrast was not found significant in the Zimmer et al. [13] study. Finally, the study by Kutner et al. [8] found significant improvement on patients' mood, although again this effect was not significant in the study by Siemens et al. [16]

If the outcomes were to be divided into three major groups, clearly most of the significant improvements/effects occurred within the physical outcomes. The majority of the included studies accordingly used an exercise program as an intervention. Previous research underlined indeed the positive effects of exercise on physical performance and function in advanced cancer patients. [24]

Although it is already known from other studies that included cancer patients, but at a less advanced stage, that exercise can be beneficial. Exercise also seems feasible and can both improve physical performance and reduce or stabilize disease-specific symptoms in the palliative stage. This can also be seen in the included studies. Physical activity is cost-effective and easy to apply as a supportive management tool. Patients who actively engage in physical activity have the opportunity to actively improve their living situation. This strengthens resilience to life-shortening diseases. Further research should address which exercise principles are most beneficial. [7, 9, 10, 12, 13, 17, 18, 24].

Massage and other relaxation-related techniques are also known to be beneficial in the oncological population. Because of the high stress levels, anxiety, and pain they often experience, this can indeed provide relief. Massage therapists are already commonly employed in oncology services and palliative centers [25, 26]. In the palliative population, there is some remaining uncertainty about the long term and specific effects of massage therapy. Also due to the little

study material available on this topic, and the low methodological quality, small sample sizes, and high drop-out rates of the studies that are available. Something that was recurring in the included articles [8, 27].
Kutner et al. [8], Oldervoll et al. [18], and Poort et al. [9, 10] all 4 possess the rather larger sample sizes of all 10 included RCTs. Only the blinding, randomization and/or no standardization of the intervention sometimes caused a risk of bias there. In general, it is suspected that this overestimated the effect. The other studies all had small sample sizes (n<60) and suffered from high drop-out rates as well. Likewise, risks of bias were present in the randomization process and/or blinding of reviewers, patients and/or therapists. Furthermore, both by drop-outs, and even at baseline, large differences could already be noticed between intervention and control group (in favor of the intervention group). However, it is difficult to estimate the direction of effect bias, because all these studies have little power to reinforce these presumptions.
Generally, drop-out rates in trials with advanced cancer patients show a marked difference compared to trials with tumor patients in earlier stages. The drop-out rate in exercise interventions in a curative treatment setting was reported to be 10–13% [24, 28, 29]. In the included studies, all rates often exceed 13%. Most of the time as a result of expected drop-out because of disease progression and health deterioration. This would seem to be valuable information when designing new studies, such as for calculating sample size. To clearly establish the impact on the primary endpoint and avoid contamination, approximately 25% more patients should be included [30].
While the studies may not always show significant improvement, they can still provide stagnation of symptoms. The presence of this phenomenon is evidently reflected in the results of the study. Although positive improvement is desirable in any context, it is particularly crucial in palliative care to prioritize the comfort of patients. The occurrence of symptom stagnation can hold significant implications within a population that typically experiences progressive deterioration.
The continued expansion and optimization of palliative care in cancer patients is imperative, considering the evolving nature of cancer. With more effective therapies available, people are increasingly living with cancer as a chronic disease, with all its associated side effects, requiring comprehensive and ongoing support to address their physical, emotional, and psychosocial needs. By further developing and refining palliative care services, healthcare providers can ensure that cancer patients receive the necessary holistic care and support to enhance their QoL throughout their cancer journey.
Given that specialized palliative care does appear to be effective according to most studies, the benefits do outweigh the costs. It is also stated that patients with advanced illness receiving home palliative services have greater odds of dying at home and experience lower symptom burden compared with usual care. [31] The effectiveness of the interventions likewise reduces the burden on the healthcare system, making specialized palliative care cost-effective. [32]
In fact, palliative care is most frequently found to be less costly relative to comparator groups, and in most cases, the difference in cost is significant. [33] Another not inconsiderable socio-economic impact is the reduction of depression scores, depression, and stress burden in the terminal decline analysis in the patient's family and/or caregivers. As a matter of fact, (early) palliative care interventions have a significant impact on these three previous ones. Therefore, palliative care for family and caregivers should be initiated as early as possible to maximize benefits. [34]
Although there is still much unclarity in the existing literature, these results seem promising. They may provide the impetus for even more studies and research, which can then eventually lead to the writing of guidelines and thereby make palliative care multidisciplinary and organized. The results also suggest that physiotherapy should become an integral part of palliative, oncological care.
In general, the different studies possess a large heterogeneity, have small sample sizes, high dropout rates and large inter-group differences at baseline. The risk of bias seems to be present in most studies. Drawing conclusive findings from studies with limited statistical power poses considerable challenges. These limitations can be seen as learning objectives and opportunities for the future, when creating new protocols and conducting new studies.

CONCLUSION

Based on the results of this systematic review of the literature it is suggested that physiotherapy can have positive effects on various physical, mental, and QoL-related outcomes in this population, but largely proved most effective on physical symptoms.
The studies consistently indicated positive effects of physiotherapy interventions on muscle strength and peripheral neuropathy. Pain and fatigue emerged as two commonly investigated outcomes, but while some studies reported a positive effect on these outcomes, others did not yield similar findings. The studies that employed physical applications and massage as interventions were more inclined to observe a positive impact on pain and nausea.
Exercise therapy emerged as a particularly effective intervention, as well as cognitive behavioral therapy and graded activity, improving different physical outcomes.
In contrast, there was a lack of significant findings in the domain of psychosocial/mental outcomes, with no outcome being consistently supported by multiple studies.
Overall, our review highlights the potential benefits of physiotherapy interventions in improving physical outcomes for palliative care oncology patients. However, the scarcity of studies and small sample sizes limit the generalizability of these findings. Future research should focus on conducting larger-scale RCTs with rigorous methodology to further explore the role of physiotherapists and physiotherapy in palliative care for oncology patients.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES

1. Institute N-NC. What Is Cancer? [Website]. United States: NIH - National Cancer Institute; 2021 [updated 11/10/2021. Available from: https://www.cancer.gov/about-cancer/understanding/what-is-cancer.
2. Stewart BWK, P. World Cancer Report: International Agency for Research on Cancer; 2018 [Available from: https://www.iarc.who.int/wp-content/uploads/2018/07/WorldCancerReport.pdf
3. Kanker St. Kanker in cijfers: Stichting tegen Kanker; [Available from: https://www.kanker.be/alles-over-kanker/kanker-cijfers.
4. Kaasa S, Loge JH, Aapro M, Albreht T, Anderson R, Bruera E, *et al*. Integration of oncology and palliative care: a Lancet Oncology Commission. *Lancet Oncol*. 2018;19(11):e588-e653.
5. België G. Zorg rondom het levenseinde 2019 [updated 24/04/2023. Available from: https://www.gezondbelgie.be/nl/performantie-van-het-belgische-gezondheidssysteem/specifieke-zorgdomeinen/zorg-rondom-het-levenseinde.
6. Eijrond E. Behoefte aan palliatieve zorg (2019): hoeveel personen? : Palliaweb; 2020 [Available from: https://palliaweb.nl/getmedia/12a8b323-7b55-4b50-b6bc-58239ccf76e/20200701-Infographic-Doodsoorzaken-en-Behoefte-palliatieve-zorg-4.pdf.
7. Henke CC, Cabri J, Fricke L, Pankow W, Kandilakis G, Feyer PC, et al. Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV. *Support Care Cancer*. 2014;22(1):95-101.
8. 8. Kutner JS, Smith MC, Corbin L, Hemphill L, Benton K, Mellis BK, *et al*. Massage therapy versus simple touch to improve pain and mood in patients with advanced cancer: a randomized trial. *Ann Intern Med*. 2008;149(6):369-79.
9. Poort H, Müller F, Bleijenberg G, Verhagen S, Verdam MGE, Nieuwkerk PT, *et al*. Condition or cognition? Mechanism of change in fatigue in a randomized controlled trial of graded exercise therapy or cognitive behavior therapy for severe fatigue in patients with advanced cancer. *J Consult Clin Psychol*. 2021;89(9):731-41.
10. Poort H, Peters M, van der Graaf WTA, Nieuwkerk PT, van de Wouw AJ, Nijhuis-van der Sanden MWG, *et al*. Cognitive behavioral therapy or graded exercise therapy compared with usual care for severe fatigue in patients with advanced cancer during treatment: a randomized controlled trial. *Ann Oncol*. 2020;31(1):115-22.
11. Nakano J, Ishii K, Fukushima T, Ishii S, Ueno K, Matsuura E, *et al*. Effects of transcutaneous electrical nerve stimulation on physical symptoms in advanced cancer patients receiving palliative care. *Int J Rehabil Res*. 2020;43(1):62-8.
12. Pyszora A, Budzyński J, Wójcik A, Prokop A, Krajnik M. Physiotherapy programme reduces fatigue in patients with advanced cancer receiving palliative care: randomized controlled trial. *Support Care Cancer*. 2017;25(9):2899-908.
13. Zimmer P, Trebing S, Timmers-Trebing U, Schenk A, Paust R, Bloch W, *et al*. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. *Support Care Cancer*. 2018;26(2):615-24.
14. Jensen W, Baumann FT, Stein A, Bloch W, Bokemeyer C, de Wit M, *et al*. Exercise training in patients with advanced gastrointestinal cancer undergoing palliative chemotherapy: a pilot study. *Support Care Cancer*. 2014;22(7):1797-806.
15. López-Sendín N, Alburquerque-Sendín F, Cleland JA, Fernández-de-las-Peñas C. Effects of physical therapy on pain and mood in patients with terminal cancer: a pilot randomized clinical trial. *J Altern Complement Med*. 2012;18(5):480-6.
16. Siemens W, Boehlke C, Bennett MI, Offner K, Becker G, Gaertner J. Transcutaneous electrical nerve stimulation for advanced cancer pain inpatients in specialist palliative care-a blinded, randomized, sham-controlled pilot cross-over trial. *Support Care Cancer*. 2020;28(11):5323-33.
17. Uster A, Ruehlin M, Mey S, Gisi D, Knols R, Imoberdorf R, *et al*. Effects of nutrition and physical exercise intervention in palliative cancer patients: A randomized controlled trial. *Clin Nutr*. 2018;37(4):1202-9.
18. Oldervoll LM, Loge JH, Lydersen S, Paltiel H, Asp MB, Nygaard UV, *et al*. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. *Oncologist*. 2011;16(11):1649-57.
19. Tan SB, Tan TT, Tan MP, Loo KK, Lim PK, Ng CG, *et al*. Contributing and Relieving Factors of Suffering in Palliative Care Cancer Patients: A Descriptive Study. *Omega* (Westport). 2022;85(3):732-52.
20. Wilcock A, Hussain A, Maddocks M. Holistic Needs of People with Thoracic Cancer Identified by the Sheffield Profile for Assessment and Referral to Care Questionnaire(©). *J Palliat Med*. 2019;22(9):1120-3.
21. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, *et al*. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc*. 2019;51(11):2375-90.
22. Physiotherapy A-BCIGO. ABCIG Oncology Physiotherapy 2023 [Available from: https://axxon.be/abcigsite/nl/12-abcig-oncology-physiotherapy/home/#:~:text=De%20rol%20van%20de%20kinesitherapeut%20in%20het%20kankertraject%20is%20veelzijdig,een%20medische%20historiek%20van)%20kanker.
23. Jespersen E, Minet LR, Nissen N. Symptoms of total pain experienced by older people with advanced gastrointestinal cancer receiving palliative chemotherapy. *Eur J Cancer Care* (Engl). 2022;31(6):e13674.
24. De Lazzari N, Niels T, Tewes M, Götte M. A Syste-

matic Review of the Safety, Feasibility and Benefits of Exercise for Patients with Advanced Cancer. *Cancers* (Basel). 2021;13(17).
25. Hilfiker R, Meichtry A, Eicher M, Nilsson Balfe L, Knols RH, Verra ML, *et al*. Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. *Br J Sports Med*. 2018;52(10):651-8.
26. Lee SH, Kim JY, Yeo S, Kim SH, Lim S. Meta-Analysis of Massage Therapy on Cancer Pain. *Integr Cancer Ther*. 2015;14(4):297-304.
27. Candy B, Armstrong M, Flemming K, Kupeli N, Stone P, Vickerstaff V, *et al*. The effectiveness of aromatherapy, massage and reflexology in people with palliative care needs: A systematic review. *Palliat Med*. 2020;34(2):179-94.
28. Bullard T, Ji M, An R, Trinh L, Mackenzie M, Mullen SP. A systematic review and meta-analysis of adherence to physical activity interventions among three chronic conditions: cancer, cardiovascular disease, and diabetes. *BMC Public Health*. 2019;19(1):636.
29. Steins Bisschop CN, Courneya KS, Velthuis MJ, Monninkhof EM, Jones LW, Friedenreich C, *et al*. Control group design, contamination and drop-out in exercise oncology trials: a systematic review. *PLoS One*. 2015;10(3):e0120996.
30. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. *Cancer*. 2013;119(5):1098-105.
31. Gomes B, Calanzani N, Higginson IJ. Benefits and costs of home palliative care compared with usual care for patients with advanced illness and their family caregivers. *Jama*. 2014;311(10):1060-1.
32. Higginson IJ, Evans CJ. What is the evidence that palliative care teams improve outcomes for cancer patients and their families? *Cancer J*. 2010;16(5):423-35.
33. Smith S, Brick A, O'Hara S, Normand C. Evidence on the cost and cost-effectiveness of palliative care: a literature review. *Palliat Med*. 2014;28(2):130-50.
34. Dionne-Odom JN, Azuero A, Lyons KD, Hull JG, Tosteson T, Li Z, *et al*. Benefits of Early Versus Delayed Palliative Care to Informal Family Caregivers of Patients With Advanced Cancer: Outcomes From the ENABLE III Randomized Controlled Trial. *J Clin Oncol*. 2015;33(13):1446-52.