Physical therapist-guided exercise programs for patients with cancer: towards further tailoring and implementation

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GENERAL INTRODUCTION

Cancer in women and its treatment

Cancers that are specifically common in women are breast cancer and gynecological cancers. Breast cancer is the most prevalent cancer in women, with an incidence of 18.000 new diagnoses per year in the Netherlands [1] . Of all cancer diagnoses in women, 28% is breast cancer.

In the Netherlands, 1 in 7 women are diagnosed with breast cancer at some point in their lives. Thanks to advances in early detection and medical treatments, the 5-year survival rate has improved substantially in the past decades. Nowadays, 95% of patients diagnosed with stage I and 32% of patients diagnosed with stage IV are alive 5 years after diagnoses [1] . Most patients with breast cancer (around 90%) are treated with surgery, and additionally receive radiotherapy (64%), hormonal therapy (53%), chemotherapy (30%) and/or targeted therapy (11%) [1]. In case patients are diagnosed with stage IV breast cancer, treatment is given with palliative intent aimed at prolonging life while maintaining quality of life. The median survival after diagnosis of metastatic cancer is around 3 years, but there is a strong heterogeneity in survival, and 7% of patients will survive for over 10 years [1, 2].

The incidence of gynecological cancer in the Netherlands is 4.800 per year. The second most prevalent type is ovarian cancer with an incidence of 1.300 per year in the Netherlands [1]. Because symptoms of ovarian cancer appear relatively late, it is most often diagnosed when the cancer is in an advanced stage. Consequently, the estimated 5-year overall survival of ovarian cancer is 38% [1]. Treatment for ovarian cancer consists of the (neo)adjuvant chemotherapies paclitaxel and carboplatin, and (interval) debulking surgery [3].

Both breast cancer and ovarian cancer and their treatments have several side effects. Surgery in patients with breast cancer can lead to limited range of motion and pain of the shoulder and arm, or the development of lymphedema after axillary lymph node dissection [4]. In patients diagnosed with late-stage ovarian cancer (2B or higher), surgery mainly includes resection of the ovary, fallopian tube, uterus and omentum, with or without resection of lymph nodes, and additional intraperitoneal chemotherapy (OVHIPEC) [3]. Surgery can result in wound problems, weakening of the abdominal muscles, and lymphedema in abdomen and legs [5-7]. Treatment with chemotherapy can lead to several short- and long-term side-effects in both patients with breast and ovarian cancer, such as neutropenia, pain, neuropathy, fatigue and declined physical fitness [8-10].

Physical exercise, physical therapy and cancer

In 2018, the American College of Sports Medicine organized the second roundtable meeting with exercise oncology experts with the aim to formulate evidence-based exercise guidelines for patients with cancer. Strong evidence shows that exercise interventions can reduce fatigue, anxiety and depressive symptoms, and improve physical functioning and health-related quality of life [11]. Four randomized controlled exercise trials (RCTs) carried out in the Netherlands between 2010 and 2018 [12-15] reported beneficial outcomes on quality of life, physical fitness and/or fatigue contributing to this evidence base.

In these trials, but also in clinical practice in the Netherlands, such exercise programs are guided by physical therapists. Physical therapists in the Netherlands receive four years of Higher Vocational Education (HBO) and are movement experts who strive to improve quality of life through targeted exercise, hands-on care (i.e. manual lymph drainage or mobilization techniques), and patient education. This four years of education is considered to enable physical therapists to play a role in the detection and management of many symptoms related to cancer treatment, including pain and reduced physical fitness. However, there is also consensus within the profession that more specialized knowledge and skills about cancer treatments and their side-effects (such as lymphedema, neuropathy) are desirable to support patients with cancer before, during and following cancer treatment [16].

In the Netherlands, oncology-specific knowledge and skills can be increased through a diversity of postgraduate educational programs, or via one of two available Master programs. Oncology physical therapy is a recognized specialty, requiring master-level specialization. Nowadays, an established nationwide network with over 500 physical therapists with various levels of specialization in oncology, working in over 700 locations in the Netherlands (Onconet) contributes to the quality of healthcare for patients with cancer. Several postgraduate courses are offered to obtain or refresh knowledge and skills towards the treatment of patients with cancer. In these courses, casuistry is often used as a method to improve the clinical decision-making skills of physical therapists specializing in oncology.

The process of decision making, particularly when exercise prescriptions need to be tailored to comorbidities and side-effects of cancer treatment [17], requires complex clinical reasoning [18]. The physical therapist needs to use clinical expertise to effectively integrate information on (i) clinical state and circumstances, acquired via history taking and physical examination; (ii) patient values, preferences and actions; and (iii) scientific evidence [19]. This process of clinical reasoning, described as a core competency of professional practice, is mostly an implicit and often automatic process [20]. It would be of interest to capture the underlying cognitive processes of physical therapists involved

in clinical reasoning when treating patients with cancer in order to make them more explicit [21]. The think aloud method can be used to elicit expert knowledge which can subsequently be used in future exercise protocols [22]. During the think aloud method, participants are asked to verbalize everything that goes through their minds, and they are instructed not to interpret or analyze their thinking [23]. In this case, healthcare professionals can be asked to literally think aloud while evaluating casuistry in order to obtain insight into their cognitive processes during clinical reasoning.

Exercise and advanced cancer

The majority of exercise trials in patients with cancer investigated the effects of exercise in early stages of the disease [11, 24]. Consequently, evidence on the effects of exercise interventions in patients with advanced disease is limited. Patients with advanced cancer report overlapping symptoms compared to patients treated with curative intent [25]. But, distinctively, patients with advanced breast cancer may suffer from bone metastases, which occur in around 70% of cases, and these might interfere with exercise interventions [26]. Bone metastases tend to accelerate the breakdown of normal bone (osteolytic bone metastases), or in some cases overstimulate the production of new bone with a poor organized microstructure (osteoblastic metastases) [27]. The safety of exercise for patients with advanced cancer has been a matter of debate, in particular with regard to the presence of bone metastases. Over the past years, it has been shown that exercise is safe for patients receiving palliative treatment and that it is feasible and benefits physical functioning, also in patients with bone metastases [28-30].

At the time of starting the studies contained in this thesis, the best available evidence suggested that exercise for patients with bone metastases was likely safe when adequate supervision is provided, and when the program is tailored to avoid (over)loading the locations with bone metastases. Consequently, physical therapists may need to acquire extra skills for this specific tailoring compared to skills needed to guide patients treated with curative intent. Insight in the educational needs and perceived barriers is needed to optimally educate the physical therapists to guide patients with advanced cancer.

From “one size fits all” to tailored exercise programs

Despite the overall beneficial effect of exercise on aerobic fitness, fatigue and quality of life in patients with cancer [11], the effects vary between subgroups of patients [24]. Results from a meta-analysis on individual patient data from 34 RCTs demonstrated the largest effects of exercise interventions when the exercises were performed under supervision of an experienced physical therapist or exercise physiologist [31-33]. Results also showed that the largest effects on muscle strength and aerobic fitness were produced by including

resistance and aerobic exercises respectively [31]. Effects of exercise on physical fitness during treatment, and fatigue during and after treatment, were dependent on baseline values [24] and effects on aerobic fitness were larger for younger patients [34]. The greatest benefits on fatigue were observed in those with high levels of fatigue prior to exercise. Conversely, during cancer treatment, patients with a low baseline aerobic fitness did not show significant improvements in aerobic fitness, while significant benefits were found for patients with a higher aerobic fitness level at baseline [24].

These findings emphasize the need to move from a "one size fits all" approach to personalized exercise prescriptions tailored to the characteristics, needs, capabilities and preferences of individual patients, and to specific outcomes (e.g. aerobic fitness, fatigue). Moreover, exercise should be tailored to existing comorbidities and dynamically changing side-effects, which requires proper considerations for adjustments [17]. Additionally, physical therapists need to deliver tailored care targeting a patient's individual treatment goal [35]. For example, patients can strive to maintain or regain functional independence and the ability to perform daily activities (e.g., walking the stairs, standing while cooking), strive for participation (e.g. return to work or sports club), or have a more generic wish to maintain physical fitness. From clinical and teaching experience, we know that physical therapists consider designing goal directed exercise interventions for patients with metastatic disease challenging. At the same time, exercise programs as described in the literature tend to be of a more generic nature.

Implementation of exercise interventions

Despite the evidence on the positive effects of exercise interventions during and after cancer treatment, exercise is still not part of standard care. As emphasized in the recently published American Society of Clinical Oncology (ASCO) guidelines on exercise and nutrition during treatment for cancer, oncology providers should recommend regular aerobic and resistance exercise during active treatment with curative intent [36].

Improving implementation requires insights in implementation barriers and facilitators [37]. A commonly used framework to evaluate implementation is the RE-AIM framework [38]. This framework evaluates implementation of interventions by examining the **R**each (number, proportion and representativeness of individuals willing to participate in an intervention), **E**ffectiveness (the impact of an intervention on important outcomes), **A**doption (the number, proportion and representativeness of settings and, in this case, physical therapists), **I**mplementation (in this case: the fidelity of intervention delivery by physical therapists and adequacy of adaptations to the intervention and implementation strategies), and **M**aintenance (the extent to with behavior is sustained and a program becomes institutionalized) [38].

The previously-mentioned Dutch exercise oncology trials have been run as pragmatic trials. The purpose of such RCTs is to inform about decisions made in practice and to examine how effective a treatment actually is in routine everyday practice [39]. Hence, information from these trials can be useful to evaluate strengths, weaknesses and opportunities for further implementation of exercise in Dutch clinical oncology practice.

Objectives and outline of this thesis

The overall aim of this thesis was to improve the development and facilitate implementation of tailored exercise interventions for patients with cancer. Specifically, this thesis aimed to:

1. Improve physical therapist-guided tailored exercise programs for patients with metastatic breast cancer.
2. Gain insight into the process of clinical reasoning towards exercise prescription in the context of a trial that can be useful for description and fidelity assessment of interventions and training of healthcare professionals.
3. Identify the lessons learned from state-of-the-art of exercise interventions in the Netherlands and to describe opportunities for future implementation in oncology clinical practice.

Chapter 2 describes the results of a mixed methods study to identify physical problems, functional limitations, and preferences for physical therapist-guided exercise programs in patients with metastatic breast cancer. **Chapter 3** presents the educational needs of physical therapists with regard to the guidance of patients with metastatic cancer. **Chapter 4** presents the results of an observational study examining the feasibility and outcomes of goal-directed, physical therapist-guided exercise interventions for patients with metastatic breast cancer. **Chapter 5** provides a practical illustration of the complex clinical reasoning process of physical therapists and dietitians when tailoring exercise and dietary interventions to specific side effects of patients with ovarian cancer. **Chapter 6** evaluates the implementation in clinical practice of the exercise programs studied in four Dutch exercise oncology trials, and discusses the opportunities and challenges for implementing exercise interventions in oncology clinical practice. Finally, **Chapter 7** summarizes and discusses the findings of this thesis, and provides future directions on how to improve the implementation of tailored physical therapist-guided exercise programs for patients with cancer.

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2

PHYSICAL PROBLEMS, FUNCTIONAL LIMITATIONS AND PREFERENCES FOR PHYSICAL THERAPIST-GUIDED EXERCISE PROGRAMS AMONG DUTCH PATIENTS WITH METASTATIC BREAST CANCER: A MIXED METHODS STUDY

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ABSTRACT

Purpose

In this study we aimed (1) to identify the most prevalent physical symptoms and functional limitations that limit physical activity of patients with palliative treatment for metastatic breast cancer (MBC) and (2) to identify their preferences for exercise based physical therapy programs, as a first step towards the development of physical therapist (PT)-guided exercise programs for patients with MBC.

Methods

We performed a mixed-methods study that comprised a cross-sectional survey and two focus group sessions among patients with MBC. Survey results were analyzed using descriptive statistics. The focus groups were audio-taped, transcribed verbatim and analyzed independently by two researchers, using directed content analysis.

Results

A total of 114 women (response rate 61%) completed the survey (mean age 63.5, SD 10.2). Eighty-six percent of the women reported at least some level of physical problems limiting their ability to be physically active, of whom 46% reported substantial problems. The most prevalent problems were fatigue, painful joints, painful muscles and shortness of breath. Uptake of exercise appeared to be limited. Exercise preferences varied strongly. Fifty-three percent indicated a preference for some form of PT-supervision, and 34% for a prolonged period of time (>8 weeks). Focus group results clarified that patients' preferences for supervision, by PTs with special qualifications in oncology, were related to feelings of insecurity about their ability to self-manage physical functioning.

Conclusions

Patients with MBC experience a broad range of physical health problems that limit their ability to be physically active. While preferences vary strongly, patients with MBC would value the availability of high quality, PT- guided, tailored exercise programs.

KEYWORDS

Metastatic Breast Cancer; Exercise; Physical therapy; Functional Limitations; Quality of Life

INTRODUCTION

Currently, exercise is recognized as a key element in cancer rehabilitation to reduce symptoms and improve physical functioning, mood, and quality of life [1-3]. Few programs are however available specifically for patients with metastatic breast cancer (MBC). Yet, the need for such programs is growing, as survival rates of patient with MBC are increasing; nowadays, median survival is approximately 3 years, with 11% of patients surviving for more than 10 years after diagnosis [4]. The limited availability of exercise programs for patients with MBC is likely due, in part, to reluctance of health care providers to recommend exercise to this population [5] and to the limited evidence available regarding both the feasibility and effectiveness of exercise programs for patients with advanced cancer. Also, patients with MBC may not be aware of the possibility of exercising safely, and the potential benefits involved. Findings from systematic reviews suggest that exercise is feasible and safe for patients with advanced cancer and may prevent or delay decline in aerobic fitness, muscle strength, and physical functioning. Also, it may improve physical wellbeing, fatigue, depression, and overall quality of life [6-8].

The exercise interventions for patients with MBC studied, to date, were designed to improve muscle strength and/or aerobic capacity, and all of them have employed generic exercise interventions. Tailoring of these programs consisted of adjusting intensity of the exercises to exercise tolerance or capacity [9,10]. From a rehabilitation perspective, tailoring of exercise should go beyond adjusting exercise intensity to patients' current fitness. In particular, FITT-factors (frequency, intensity, type, and timing) of exercise should be chosen in relation to the specific activities of daily living, or specific target symptoms that the intervention is intended to improve. The symptoms and limitations MBC patients experience in activities of daily living may be very heterogenous, and may require exercise programs that employ a highly personalized and functional approach.

To our knowledge, no study has yet documented the range of functional limitations experienced by patients with MBC. Additionally, in order to successfully implement any exercise program, it is important that it aligns not only with the needs of patients, but also with their preferences. Studies on preferences for exercise programs have primarily been carried out among early stage cancer patients or in mixed advanced cancer populations [11,12]. To our knowledge, no study has investigated specifically the preferences of patients with MBC.

In the context of a health innovation program for physical therapy (PT) for MBC patients in the Netherlands, we conducted a study with the objective of: (1) identifying the most prevalent physical symptoms and functional limitations among patients with MBC and (2) gaining insight into the preferences of these patients for PT-guided exercise programs.

METHODS

Study design

This convergent, parallel, mixed methods study comprised quantitative and qualitative elements. The quantitative substudy consisted of a cross-sectional survey about the physical symptom burden, functional limitations and exercise programming preferences of patients with MBC. The qualitative substudy employed focus groups to gain insight into the most prevalent themes regarding exercise programming preferences. The institutional review board of The Netherlands Cancer Institute approved the study and all patients provided written informed consent prior to participation.

Survey

Eligible patients were those who were under treatment for MBC during the study period, in one of these four hospitals in the Netherlands: the Netherlands Cancer Institute (NKI), the Amsterdam University Medical Center (Amsterdam UMC), Amstelland hospital, and Rijnstate hospital. These are a specialized cancer hospital, an academic hospital and two general community hospitals, respectively. Exclusion criteria were the following: being terminally ill, unable to read and write in Dutch, receiving treatment with intent to cure for oligometastases, and having severe cognitive or psychiatric comorbidities. We approached all eligible patients by mail, after obtaining approval of their treating oncologist. Consenting patients could complete the survey on paper or online, depending on their preference. The survey consisted of 119 questions, most with multiple choice response options. The questions were divided into eight categories relevant to the development of an exercise-based PT program: (1) patient characteristics (e.g., sociodemographics and clinical characteristics); (2) current level of physical activity (PA) and physical fitness; (3) current engagement in professionally supported or supervised exercise programs; (4) perceived social support regarding PA; (5) physical problems (including fatigue) limiting PA; (6) health-related quality of life (HRQOL); (7) personal goals and preferences for PT-guided exercise programs, including preferred frequency, duration and intensity, need for direct supervisions, and willingness to incur costs for participation; and (8) interest in and preferences regarding e-Health.

The survey also included five existing questionnaires. For comorbidity, we used the Charlson Comorbidity Index, which was adapted to this specific patient population based on the advice of an oncologist (GS) [13]. Specifically, we eliminated comorbidities already covered by our in- and exclusion criteria and added a number of comorbidities that might hinder exercise. The Physical Activity Scale for Elderly (PASE) questionnaire was used to measure the level of self-reported PA. This questionnaire was developed for use in individuals aged 65 years or older and has been used previously in cancer populations [14, 15]. The PASE sum score is computed by multiplying the hours per week spent on occupational, household and leisure activities by empirically derived item weights and summing over all activities. The recall period is 7 days, and higher scores indicate a

higher level of PA [16]. Physical fatigue was assessed with the 4-item Short Fatigue Questionnaire, which ranges from 4 to 28, with higher scores representing more severe fatigue [17]. The problem list of the Patient Specifics Complaints Instrument (PSC) [18], was used to identify the activities that respondents had experienced problems with in the past week. The PSC was originally developed to support goal setting for treatment of low back pain but is, in a slightly adapted version, currently widely used in cancer rehabilitation in the Netherlands [19]. HRQOL was assessed with the EORTC QLQ-C30. We used the 5 functional scales (physical, role, emotional, cognitive and social functioning) and the summary score of this questionnaire, as well as the global health status/QoL score. All scales range from 0 to 100, with higher scores indicating better outcomes [20].

Data handling and analysis

The survey data were analysed with IBM SPSS (version 22.0), using descriptive statistics of the sample, including frequencies and percentages for categorical data and mean/median with standard deviation and ranges for continuous data.

Focus groups

We used two convenience sampling strategies to recruit patients for the focus groups. First, we distributed flyers in the NKI and Amsterdam UMC about the aim, intended content, date, and location of the focus groups. Second, we recruited patients through social media (Facebook and a Dutch website of the breast cancer patient association).

Both focus groups were held in the NKI and lasted 2 h. The focus groups were moderated by the first (MT) and second author (WG). A patient advocate with metastatic breast cancer who was part of the research team was also present. At several points during the focus groups, the patient advocate summarized the findings and asked the participants if they agreed. All patients consented to having the sessions audiotaped.

Prior to the focus groups, we developed a topic list consisting of eight pre-conceived themes regarding the preferences for PT-guided exercise programs: (1) experiences with exercise and relaxation exercises; (2) desired/anticipated outcomes of PT-guided exercise programs; (3) functional limitations prohibiting or restricting exercise; (4) preferences for type(s) of exercise program(s), for example, group/non group, delivery mode; (5) preferences for supervision during exercise programs; (6) preferences for alternative types of exercise, such as relaxation exercises and yoga; (7) preferences for e-Health applications; and (8) additional topics including the role of the general practitioner/oncologist, willingness to pay for these programs, and willingness to travel to a specialized PT-practice. Directly following the focus groups, patients completed a brief questionnaire assessing sociodemographic and clinical characteristics, and current levels of PA.

Data analysis

MT transcribed the audio-recorded focus groups verbatim. MT and WG independently analyzed and coded the transcripts, using directed content analysis [21]. MT deductively categorized the codes into the preconceived eight themes. If necessary, we added categories to expand the framework. In case of disagreement during the coding process, differences were discussed until consensus was reached. Selected quotes are presented to highlight the findings.

RESULTS

Survey

Clinical and sociodemographic characteristics and level of physical activity

One hundred ninety MBC patients were invited for the survey, of whom 114 (61%) completed the questionnaire. All respondents were female, with a mean age of 63.5 years (SD 10.2) and a third had a college degree or higher. On average, patients had been diagnosed with MBC 4.3 years earlier (SD 4.0). At the time of the survey, 24% were receiving chemotherapy, 56% hormonal therapy, and 14% targeted therapy. Musculoskeletal and cardiovascular conditions were the most prevalent reported comorbidities. The self-reported median PA score on the PASE was 96.7 (IQR 50.7–156.2), and the mean summary score of the EORTC QLQ-C30 was 80.3 (SD: 13.8) (Table 1).

Table 1. Sociodemographic and clinical characteristics of the survey respondents (N=114).

Age in years: mean (SD, range, missing)	63.5 (10.2; 34-91; 5)
Educational level N (%)	
Primary / middle school	42 (37%)
Highschool	33 (29%)
College / university	37 (32%)
Missing	2 (2%)
Time since diagnosis in years (SD) Missing (%)	12.2 (8.6) 9(9%)
Time since metastatic disease in years (SD) Missing (%)	4.3 (4.0) 8 (7%)
Current treatment	
hormonal therapy	64 (56%)
chemotherapy	27 (24%)
targeted therapy	16 (14%)
immunotherapy	2 (2%)
Missing	9 (8%)
Location metastases	Number of patients (%)
Bone	76 (67%)

Lung	32 (28%)
Liver	31 (27%)
Brain	8 (7%)
Missing	2 (2%)
Number of comorbidities: mediaan (SD, range) Missing (%)	(1.4; 0-7) 1(1%)
Type of comorbidities*	Frequency (%)
Musculoskeletal	53 (49%)
Cardiovascular	28 (24%)
Gastrointestinal	15 (13%)
Pulmonary	10 (9%)
Metabolic disease	9 (8%)
Migraine/headache	6 (5%)
Mental illness	3 (3%)
Missing	1 (1%)
Quality of Life (EORTC QLQ-C30)**	Mean (SD; 95%CI)
Global health status/QoL Missing (%)	69.5 (17.7; 66.1-72.9) 0 (0%)
Physical Functioning Missing (%)	73.4 (19.3; 69.7-77.2) 3 (3%)
Role Functioning Missing (%)	76.1 (28.1; 70.7-81.5) 3 (3%)
Emotional Functioning Missing (%)	79.7 (17.6; 76.3-83.1) 3 (3%)
Cognitive Functioning Missing (%)	83.2 (20.1; 79.3-87.1) 1 (1%)
Social Functioning Missing (%)	82.2 (23.0; 77.8-86.7) 3 (3%)
Physical fatigue (Short Fatigue Questionnaire)***	Median (IQR)
Summary score	15 (11 - 19)
Missing (%)	3 (3%)
Physical Activity Scale for the Elderly (PASE)****	Median (IQR)
Summary score	96.7 (50.7 – 156.2)

*Self-reported comorbidities measured with a modified Charlson Index. ** Values are 0-100 with higher scores representing better functioning or quality of life. *** Scores range from 4 to 28 with higher scores representing more severe fatigue **** PASE sum score which can range from 0 to 793, with higher scores indicating greater physical activity.

Physical problems and functional limitations

Full details of reported physical problems and functional limitations (PCS) are provided in Figures 1 and 2. The majority of patients (86%) reported some degree of physical problems that limited their PA. The level of interference with PA was reported as “none” by 13%, “a little” by 40%, “quite some” by 36% and “severe” by 10% of the patients. The

most frequently reported physical barriers to being physically active were fatigue (54%), painful joints (42%), painful muscles (29%) and dyspnea (25%). Almost half of the patients reported problems with running and standing upright for a longer period of time (58% and 55%, respectively). Among less frequently reported activities, lifting and carrying heavy objects (35% and 24%), playing sports (33%), performing domestic work (32%) and picking something up from the ground (24%) were also reported as being problematic.

Figure 1. Physical symptoms limiting physical activity

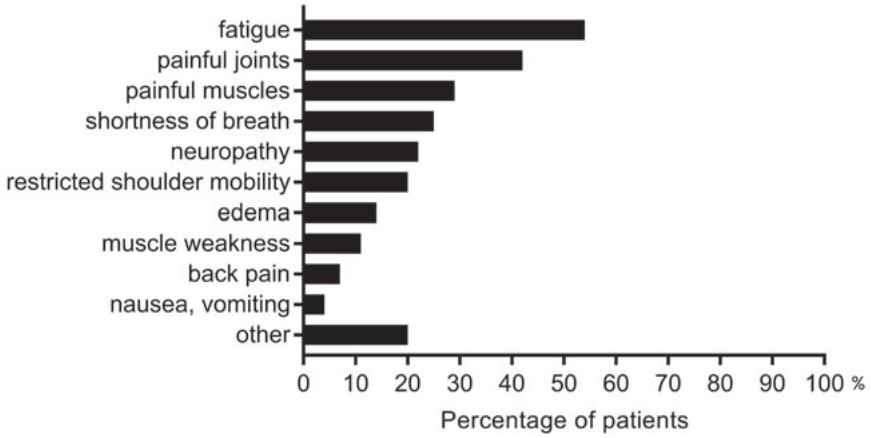
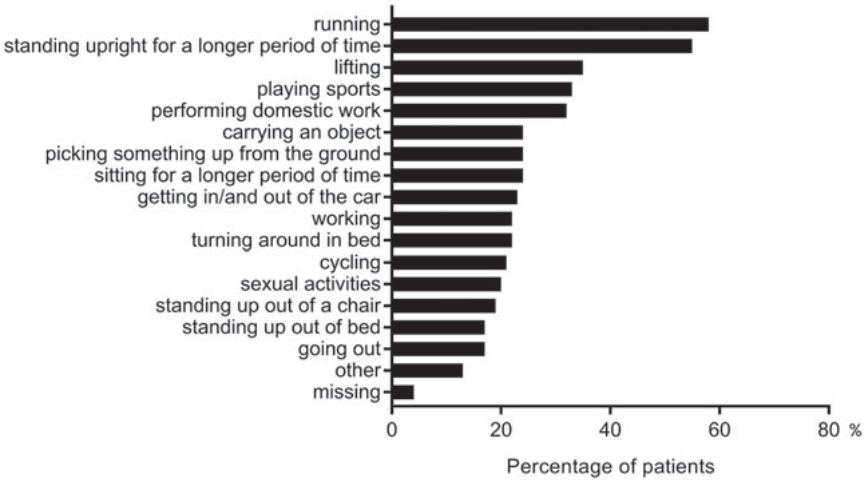


Figure 2. Problematic activities and movements in the past week (Patient Specific Complaints results)

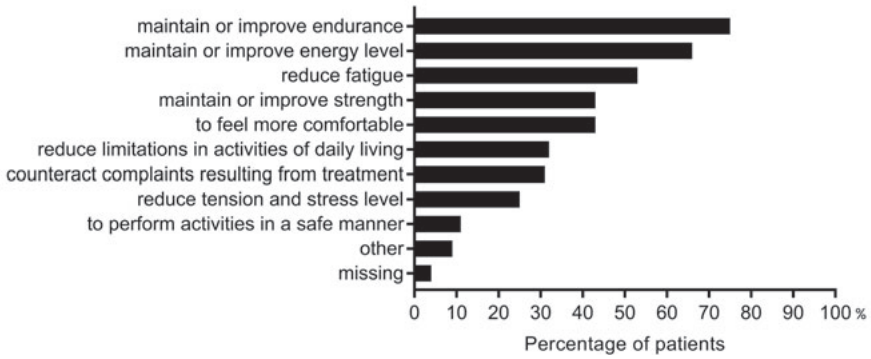


Preferences for exercise programs and PT-guidance

Preferences for PT-guided exercise programs were heterogeneous (see Figure 3 and Table 2 for full details). For two items, responses were unavailable for 1/5 of patients because of a technical error (Table 2).

One-third of the patients indicated a preference for exercising in a group. Patients who wanted to exercise in a group preferred exercising with other patients with MBC or other patients with cancer over exercising with partners, friends, or patients with other diseases.

Figure 3. Goals with physical therapy



The majority of patients reported an intention to exercise once (22%) or twice (29%) a week and to do this at a low (40%) or moderate (49%) intensity level.

The majority of patients (68%) preferred regular contact with and supervision by a PT rather than exercising on their own at home. One-quarter of the patients indicated that they only wanted to exercise under supervision; 25% wanted at least weekly supervision and 22% percent wanted less frequent supervision. Eighteen percent indicated no need for direct PT supervision. Regarding program duration, 34% preferred an exercise program > 8 weeks, 18% < 8 weeks, while 42% had no preference or did not know. Nearly all patients were willing to travel an extra distance to be supervised by a PT with additional training in oncology. Finally, 18% of patients indicated that they would be willing to incur some costs for participating in such a program, 57% reported that they might be willing to do so, and 19% stated that they would not be willing to participate if there were costs involved. A third of the patients expressed an interest in e-Health support.

Focus groups

In total, ten patients participated in the two focus groups (4 and 6 patients, respectively). All participants were female, and the majority had a college education and considered themselves to be “fairly fit”. Other patient characteristics are reported in Table 3. The main themes that were discussed during the focus groups were barriers to and facilitators of exercise interventions (e.g., costs and level of oncology-qualification of a PT) and preferences for exercise interventions (e.g., duration and frequency).

Table 2. Preferences for an exercise based physical therapy program (N = 114)

Variable	N	%
Preferences for type of exercises		
Being active in own environment (walking, cycling, swimming etc)	60	53
Fitness training (endurance)	51	45
Yoga	43	38
Fitness training (strength)	21	18
Aerobics/steps	11	10
Games	8	7
Bootcamp activities (easy to follow, but intensive endurance and strength work-out)	7	6
I don't know	15	13
Other	9	8
Missing	3	3
Preferences for the composition to be physically active in		
A group	33	29
Individually	31	27
With one other person	16	14
No preference / missing	34	30
Preferences for the composition of the group to be physically active with*		
Peers	34	30
With other cancer patients, including patients without metastatic breast cancer	29	25
With friends or acquaintances	14	12
With other patients (e.g. patients with diabetes, pulmonary complaints)	13	11
With sport 'buddies', or as part of a sports club	13	11
With partner	8	7
Missing	7	6
Preference for frequency of exercise during the week		
Once a week	25	22
Twice a week	33	29
Three times a week	5	4
More than 3 times a week	2	2
I don't know	23	20
Missing (due to technical error in the survey)	26	23
Preference for intensity of exercise		
Mild intensity (no increase in heart rate or breathing frequency)	45	40
Moderate intensity (increased heart rate and breathing frequency)	56	49
High intensity (sweating and shortness of breath)	2	2
Missing	11	10
Preference for the duration of the exercise program		
Maximum of 4 weeks	3	3
4-6 weeks	6	5
6-8 weeks	9	8

Table 2. Preferences for an exercise based physical therapy program (N = 114) *(continued)*

Variable	N	%
More than 8 weeks	39	34
I don't know	48	42
Missing	9	8
Preference for exercise under supervision of a physical therapist		
Only under the supervision of a physical therapist	28	25
Weekly supervision of a physical therapist	28	25
Every 2 weeks contact with a physical therapist	16	14
Every 3 weeks contact with a physical therapist	5	4
Maximum of 3 contacts with a physical therapist	4	4
I don't need supervision of a physical therapist	20	18
Other:		
Depends on type of activities	2	2
Can also be supervised by a fitness instructor	1	<1
Don't know	1	<1
Missing	9	8
Acceptable travel time to a physical therapist with additional oncology training		
0-15 minutes	54	47
15-30 minutes	35	31
30-45 minutes	9	8
Other:		
n/a, treatment at home	2	2
No traveling time accepted	3	3
In own town	1	<1
Don't know	1	<1
Missing	9	8
Interest in additional relaxation exercises		
Yes	48	42
No	37	33
No preference	5	4
Missing (due to a technical error in the survey)	24	21
Interest in e-Health support		
Very attractive	4	4
Attractive	34	30
Not attractive	14	12
No opinion	58	51
Missing	4	4
Willingness to pay for possible costs		
No participation in case of costs	22	19
Possible participation in case of costs	65	57
Willing to participate despite costs	20	18
Missing	7	6

*response options are not mutually exclusive

Table 3. Characteristics of focus group participants (N = 9)

Age in years: mean (SD, range)	52 (SD: 8.0, range: 41-64)
Educational level (n=)	
Primary/ middle school	2
Highschool	1
College/university	6
Current treatment (n=)	
Hormonal therapy	5
Targeted therapy (herceptin)	1
Both Targeted therapy & Hormone therapy	1
Both Chemotherapy & Targeted therapy	1
Missing	1
Self-perceived fitness (n=)	
Fairly unfit	2
Fairly fit	6
Very fit	1
Currently active in a supervised exercise program (n=)	3
Internet use (n=)	
(almost) Every day	7
About 1 day per week	1
Missing	1

Background information for one participant is missing.

Barriers and facilitators for a physical therapy programs

Only one of the focus group participants reported having received a referral from their treating physician to an exercise program. Participants wished that they had been better informed about the possibilities of exercise and physical therapy, in general. Other barriers mentioned to starting or continuing an exercise program were costs and lack of expertise and/or experience of their PT in working with patients with MBC. In addition, most participants indicated they would be willing to travel an extra distance for a PT with special training in oncology.

Reasons for pursuing a PT-guided exercise program were the possibility to maintain and gain insight into their own fitness, to achieve goals concerning activities of daily living, to stay motivated to be physically active, and to be able to consult someone about physical complaints. As one participant put it:

"...if you have someone who sees you weekly, a permanent coach (...) who sees - by the way you walk and move - how you feel, if you are all right (...) that makes me feel like there is also someone else (...) who keeps an eye on your body."

Preferences for the content of PT-guided exercise programs

The majority of participants reported that support should be individually tailored with regard to the exercise content, intensity, and duration. Some participants preferred exercising with peers, while others did not. Participants expressed a wish for a long period of PT-guidance, a "lifetime coach". One of the primary reasons for this was that they felt insecure about their future perspective and their physical well-being. Because of their declining physical fitness, they would rather be supervised by a PT and considered themselves unable to exercise by themselves in, for example, a fitness center. Preferences for the frequency and intensity of PT sessions differed between patients, depending on their physical fitness and priority setting. Patients prioritized exercise in comparison with social activities in different ways, depending on their health status and feelings of enjoyment and reward they got from exercising. One woman, who considered herself quite fit and was still working, expressed this as follows:

"... when I have walked 5 kilometers, I am completely broken, exhausted, super proud, and I can't do anything else that day. So that means, for example, that I can't visit a friend later that day – but I don't mind. My achievement matters more to me."

Another participant, with a poorer health status, prioritized her social life as more important than exercise;

"I tend to consider my social life as more important, and I feel that by being socially involved I become more active and get more energy."

The majority of participants believed that e-Health could be a useful addition to supervised exercise, as it could reduce the burden of traveling and facilitated scheduling the exercises at times that would suit them. However, they also stressed that e-Health should not fully replace face-to-face contact with the PT.

The participants reported several physical complaints that might interfere with an exercise program, including fatigue and neuropathy. They stressed the importance of proper adjustment of the exercise intervention to these physical complaints and to their overall health condition.

Finally, the majority of the participants was interested in relaxation exercises. They reported elevated levels of stress and insomnia, which they thought could be reduced with such exercises.

DISCUSSION

In this study, our goal was to gain insight into the physical symptoms and functional limitations of patients with MBC, and into their preferences regarding PT-guided exercise programs. We found that the large majority of MBC patients experiences physical problems that are barriers to PA or exercise. Preferences with regard to PT-guided exercise programs varied but, in general, patients seem to favor group-based exercise and frequent contact with a PT. Also, many patients indicated a preference for programs of longer duration (> 8 weeks).

Many of the physical problems reported by patients in this study (fatigue, painful joints and muscles, shortness of breath) have also been reported in previous studies among patients with MBC [22-28]. While these symptoms are perceived as barriers to PA, they have also been demonstrated to respond well to exercise [29-31]. Yet, patients in the focus groups reported lack of referral to exercise programs, and only 20% of the survey respondents were currently participating in an exercise program. Clearly, there is a need for increased awareness among patients with MBC and their health care providers about the feasibility and potential benefits of exercise, despite the presence of advanced disease.

Despite their reported physical limitations and low uptake of exercise, the median (IQR) PASE score of respondents to the survey was relatively high (96.7 [50.7–156.2]). To put this in perspective: the median PASE score was 65.7 in a heterogeneous sample of lung cancer patients [15], and 86 and 97, respectively, in two measurements of a group with mixed cancer diagnoses and a younger mean age (50 years) compared to our respondents [14].

Median EORTC QLQ-C30 global health status/QOL and cognitive and social functioning scale scores were comparable to reference values available for patients with MBC [32]. However, median EORTC QLQ-C30 scores of our sample were lower for physical functioning (73.4 vs. 86.7) and higher for emotional (79.7 vs. 66.7) and role functioning (76.1 vs. 66.7) as compared to reference values [32]. This suggests that our study participants were less physically fit, but had better psychosocial functioning than oncology peers.

Many of the patients, both in the survey and the focus groups, expressed a preference for exercise supervision by a qualified PT. From the focus groups we learned that this was related to feelings of uncertainty about their future, in general, and the anticipated decline in their physical fitness and health state in particular. The majority of patients in our sample (67%) had bone metastases. Bone metastases can cause pain and anxiety, and represent a risk for fractures. Supervision by a qualified PT may decrease feelings of uncertainty with regard to the safety of exercising. Several recent studies have proposed ways of tailoring resistance exercise based on the location of the metastases in patients with prostate or breast cancer, with promising results [33-35].

Although they valued supervision, only 8% of the survey respondents was prepared to travel more than 30 min to a physical therapist. Although there undoubtedly are sociocultural and geographical differences with regard to what is considered acceptable, travel time has been recognized as an important barrier to uptake of physical exercise by cancer patients [36, 37].

e-Health could be an interesting addition to home-based exercise, reducing the practical barrier of travel while maintaining the benefits of supervision. One-third of the survey respondents indicated an interest in e-Health, while half of the patients did not have an opinion on e-Health, which may be due to unfamiliarity with the concept. Further feasibility studies are needed to explore the acceptability, feasibility, and uptake of such interventions for exercise supervision of patients with advanced cancer. e-Health could potentially also reduce the costs associated with exercise programs. This could be important not only from a societal perspective, but also because many patients indicated that they were unwilling to pay for taking part in an exercise program, or would only accept a limited amount of out-of-pocket expenses.

Although our study provides useful insights that can help to shape exercise-based PT interventions for patients with MBC, some limitations should be noted. There is a potential risk for selective response of patients who are relatively exercise-minded. This risk may be higher for the focus groups than for the survey sample, due to our sampling strategy. Focus group participants were also relatively highly educated, and only one was currently under active chemotherapy treatment, which may have been reflected in their views and preferences. Overall, participants also reported relatively high levels of PA, and they had a relatively good prognosis, as reflected in their time since diagnosis. We collected data on physical symptoms and functional limitations by self-report. Performance-based measures would have strengthened the study, but for feasibility reasons, this would likely have resulted in a much smaller sample size. The focus groups were led by a physical therapist. This may have introduced some social desirability bias, in particular with regard to the discussion of topics directly related to physical therapy, although this did not withhold participants to express their concerns about lack of expertise of PTs. For two questions, there were missing data due to a technical error. However, these missing responses can be considered “missing completely at random” and therefore, it is unlikely that this resulted in bias [38]. The study also has some notable strengths, which include rich data resulting from collecting both quantitative and qualitative data.

In conclusion, patients with MBC experience a range of physical problems that limit their daily activities, and that represent a barrier to exercise. Uptake of exercise in this population appears to be limited, which is due, in part, to lack of referral by their health care providers. Our results also suggest that increased availability of high-quality, easily accessible, supervised and personalized programs would be welcomed by many women with MBC, and could improve exercise uptake in this population.

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3

EDUCATION NEEDS OF DUTCH PHYSICAL THERAPISTS FOR THE TREATMENT OF PATIENTS WITH ADVANCED CANCER: A MIXED METHODS STUDY

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ABSTRACT

Background

The survival rates for patients with advanced cancer have increased over time. Many patients experience symptoms and functional limitations that impair activities of daily living and limit quality of life. A number of these health problems are amenable to physical therapy treatment. However, physical therapists caring for patients with advanced cancer require special training and skills.

Objective

The study aimed to assess the educational needs and clinical uncertainties of Dutch physical therapists in relation to treatment of patients with advanced cancer.

Design

This was a mixed methods study.

Methods

A survey and two focus groups were conducted among physical therapists working in primary care who had previously received at least basic oncology training.

Results

A total of 162 physical therapists completed the survey. The most frequently reported educational needs were related to effective interprofessional collaboration (61.7%), knowledge of medical treatment (49.4%) and current evidence on physical therapy interventions in this population (49.4%). In the focus groups physical therapists (N=17), voiced uncertainties about treating patients with bone metastases, setting realistic goals, when and how to end a treatment episode, interprofessional collaboration, finding and using evidence, and using clinimetrics.

Conclusion

These results support the need for specific education programs for physical therapists working with advanced cancer patients to increase the availability of high-quality oncology rehabilitation for this population.

INTRODUCTION

Many patients with advanced disease experience symptoms and functional limitations as a result of their disease and its treatment(s). These symptoms and impairments can lead to restrictions in activities of daily living and may decrease quality of life [1-7] . For example, in a recent study among patients with advanced breast cancer, we found that 86% reported at least some level of physical problems limiting their ability to be physically active, and 46% reported substantial problems [8]. The most prevalent problems reported in that study were fatigue, painful joints, painful muscles and shortness of breath [8]. In general, these health problems are likely to be amenable to physical therapy interventions [9-11]. However, due to the presence of distant metastases, and the complex medical treatment, restrictions or contra-indications for physical therapy interventions may apply. Also, physical therapists need to take into account the high physical and psychosocial burden associated with advanced cancer when examining and treating these patients. Physical therapists therefore require specific knowledge and skills for treating patients with advanced cancer. This is particularly true for exercise prescription, because both the disease and its treatment may alter exercise tolerance and exercise response, as well as increase the risk of adverse events.

The limited available evidence suggests that exercise is feasible and safe for patients with advanced cancer and that it may prevent or delay declines in aerobic fitness, muscle strength and physical functioning, while improving physical wellbeing, fatigue, depression and overall quality of life [12-14]. Yet, in daily practice and outside of the realm of the clinical trial setting, physical therapists caring for patients with advanced cancer may have been uncertain about exercise as a treatment for patients with advanced cancer. In a small cross-sectional study among Irish physical therapists, 80% reported needing further information about prescribing physical activity to patients with advanced cancer [15].

In the Netherlands, physical therapy is a 4 year study at a university of applied sciences. Currently, oncology is not part of the standard curriculum of physical therapy education. Although several post-graduate educational programs for physical therapists in oncology are currently available, few physical therapists have received specific training in exercise prescription for patients with advanced disease. This topic is currently covered only in 4-year MSc-level specialty courses for oncologic physical therapy. At the same time, it is important for patients with cancer - especially those with advanced disease - to be treated close to (or inside) their homes[8]. This then calls for a dense network of sufficiently skilled physical therapists across the country to adequately support these patients.

As part of an innovation project to increase the availability of such physical therapy services in the Netherlands, we aimed to develop an educational module on exercise prescription for patients with advanced cancer, for physical therapists who have received only basic oncology training. Because it is unknown to what extent these physical

therapists experience uncertainties regarding the management of patients with metastatic disease and what educational needs (if any) they have, we designed a convergent, parallel mixed-methods study, consisting of a survey and focus group discussions, with the objective to explore these issues in depth.

METHODS

Survey

We approached all physical therapists of the Onconet network (N=401), a rapidly growing national network of physical therapists offering exercise interventions for patients during and/or after cancer treatment. Although some physical therapists in the network received a master's degree in oncologic physical therapy, the majority had received only basic oncology training (+/- 60 hours), which does not cover advanced cancer.

The survey covered the following topics: (1) general information about the physical therapist (i.e. years of experience in cancer care); (2) information exchange with referring health professionals; (3) the diagnostic process; (4) the therapeutic process; (5) inter-professional collaboration (with general practitioners/ family physicians, oncologists and oncology nurses); (6) e-Health (e.g. remote coaching using apps or online exercise programs, or video consultation); (7) reimbursement and (8) educational needs. For the diagnostic process, we focused on physical therapists' perceived competence and their desire to improve their knowledge and skills with regard to generating a physical therapy-diagnosis based on clinical history taking and physical examination. For the therapeutic process, the focus was on the current offer of interventions, on whether physical therapists feel compelled to avoid or adjust the interventions they apply, and on safety issues they encounter during treatment of patients with advanced cancer, in particular in relation to exercise-based interventions.

Data handling and analysis

The survey data were analyzed descriptively with IBM SPSS (version 22.0), including frequencies and percentages for categorical level data and medians and ranges for interval-level data. We performed an exploratory post-hoc analysis to examine potential differences in educational needs between physical therapists with and without a master's degree in oncologic physical therapy. We used chi-squared tests for these analyses, and considered p-values < 0.05 statistically significant.

Focus groups

For practical reasons, it was decided a priori to schedule two focus groups. We aimed to include approximately 7 participants per group to ensure adequate participation of all members while also achieving sufficient coverage of the topics to be discussed. [16] We recruited physical therapists via an invitation e-mail that was sent to all OncoNet physical

therapists. The focus groups, which were held in the NKI in Amsterdam and lasted about two hours, were moderated by the first and second author (M.T. and W.G.). M.T. is an experienced physical therapist in the field of oncology and a junior researcher in the field of cancer rehabilitation. W.G. is a postdoctoral researcher with a focus on exercise and cancer. The participating physical therapists were not familiar to either researcher. All physical therapists consented to having the sessions audiotaped.

Prior to the focus groups, we developed a topic list consisting of 6 themes regarding the physical therapists' experience with supervising patients with advanced cancer, and their perceived need for improving the physical therapy process. The following themes were included: (1) clinical history taking and diagnostic process; (2) current offer of interventions and experience with the target group; (3) general perspectives on physical therapy-interventions in patients with advanced cancer, including avoidance of specific interventions, and on the role of the physical therapist; (4) e-Health; (5) communication with referring health care provider; and (6) educational needs. For this paper, we report on identified uncertainties and perceived level of professional competence for working with this population, and on educational needs - regardless of the theme under which they were reported. Directly following the focus groups, physical therapists completed a brief questionnaire assessing their experience in working with patients with cancer, specifically metastatic cancer.

Data analysis

MT transcribed the audiotaped focus groups verbatim. The transcripts were analyzed and coded by M.T. and a second investigator (D.B.) independently, using directed content analysis [17]. In case of disagreement during the coding process, differences were discussed until consensus was reached. Codes were then deductively categorized by MT into the 6 preconceived themes. If necessary, we added categories to expand the framework. Finally, codes and categories were discussed with a senior researcher (M.S.) as an additional validation step. Selected quotes are presented to highlight the findings.

RESULTS

Participant characteristics

A total of 162 physical therapists (40.3%) completed the online survey. The majority worked in a primary care private practice (83.3%). Slightly one-half of the physical therapists (58.0%) had more than over 6 years of experience working with cancer patients. A total of 19% had a master's degree in oncologic physical therapy. Full sample characteristics are shown in Table 1.

In total, 17 physical therapists participated in two focus groups (2 men and 15 women). The participants were aged a median of 43 years (range: 28-59) and had a median of 7

years of experience in working with cancer patients (range: 1-20). Seven of these physical therapists had a master's degree in oncologic physical therapy (41%).

Table 1. Characteristics of survey respondents[a]

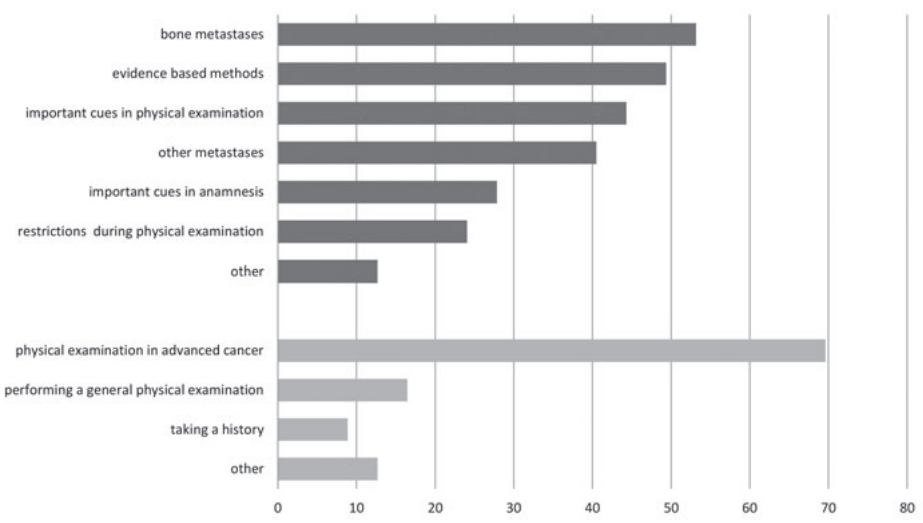
Work setting	N(%)
Primary care private practice	135 (83.3)
Hospital	12 (7.4)
Primary care multidisciplinary health care centre	11 (6.8)
Other:	4 (2.5)
Additional education	
MSc Oncology Physical Therapy	31 (19.1)
Years since receiving MSc	
>4 years	5 (16.1)
2 years	6 (19.4)
1 year	11(35.5)
<1 year	9 (29.0)
Years of working experience with oncology patients	
<1 year	2 (1.2)
1-3 years	30 (18.5)
4-6 years	36 (22.2)
7-9 years	31 (19.1)
>9 years	63 (38.9)
Number of new oncology patients –all disease stages- treated per year	
< 5 patients	5 (3.1)
5-10 patients	24 (14.8)
11-20 patients	54 (33.3)
21-30 patients	28 (17.3)
31-40 patients	15 (9.3)
41-50 patients	11 (6.8)
> 50 patients	25 (15.4)
Number of new oncology patients -with advanced disease- treated per year	
1-2	20 (12.3)
3-5	55 (34.0)
6-10	44 (27.2)
11-15	20 (12.3)
16-20	11 (6.8)
>20	12 (7.4)

[a] N=162 physical therapists

Diagnostic process

More than one-half of the physical therapists rated their own knowledge of the physical therapy diagnostic process for patients with advanced cancer as optimal (3.7%) or good (54.3%). Thirty-eight percent rated their knowledge as adequate and another 4.3% as moderate. None of the respondents reported their knowledge as completely insufficient. Almost four percent (3.7%) of the respondents rated their diagnostic skills for working with patients with advanced cancer as optimal, 56.8% as good, 36.4% as adequate, and 3.1% as moderate. Again, none of the respondents reported their skills as insufficient. The respondents who rated their knowledge and/or skills as less than "good" (n=79, 48.8%) were asked to provide more details about their educational needs (see Figure 1). Fifty-three percent (n=42) of these physical therapists indicated a need for additional knowledge about bone metastases. Seventy percent (n=55) wanted to improve their skills specific to carrying out a physical examination in patients with advanced cancer. In particular, this concerned skills in exercise testing (n=39), clinical reasoning (n=28), keeping an overview of the diagnostic process (n=25), and performing passive range of movement examinations (n=12).

Figure 1. Desired areas in which to improve knowledge (dark grey bars) and skills (light grey bars) in the diagnostic process. Percentages are relative to subgroup of physical therapists who rated their knowledge or skills less than good (n=79).



Insecurities about exercise testing were also clearly expressed in the focus groups. These were related to the safety of some tests (e.g., a direct 1-repetition maximum strength test or the Steep Ramp cycle ergometer test) in patients with bone metastases. With regard to clinical reasoning, uncertainty was voiced in the focus groups about the setting of realistic goals. Due to the uncertain prognosis and the anticipated decline in patients' overall health condition, physical therapists felt unsure about what improvement (or

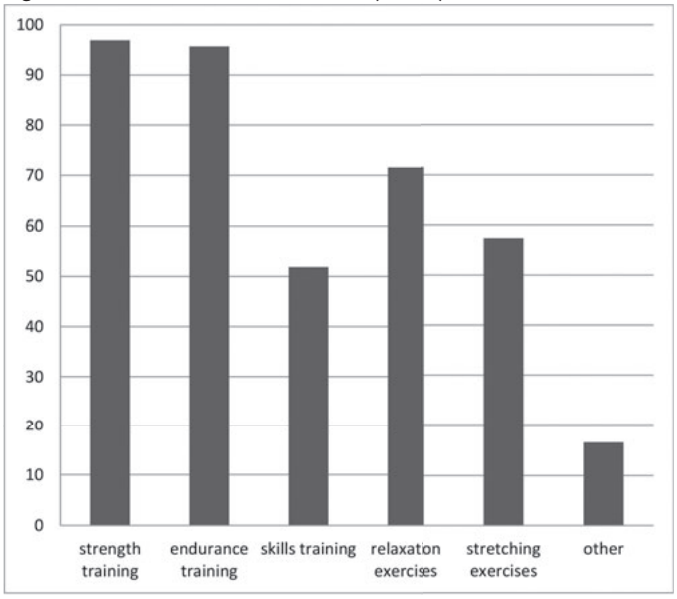
maintenance) of physical functions and activity levels can be expected. Also, focus groups participants indicated concerns with using “clinimetrics” (physical testing and self-reported questionnaires) and then sharing the results with the patients. As one physical therapist put it:

“I don’t find the general questionnaires difficult to work with, but it is unpleasant to perform exercise tests on someone if you know that their physical condition is deteriorating. That can be very demotivating, so I tend to forgo those tests because, to me, there is no point in confirming what I already know. “

Therapeutic process

The large majority of physical therapists reported offering exercise interventions to patients with advanced cancer, including both strength training (96.9%) and endurance training (95.7%). Further details are presented in Figure 2. Respondents experienced several challenges in treating patients with advanced cancer. More than one-half of the physical therapists (57.4%, n=93) experienced insecurity about the acceptable work load level, 24.7% (n=40) about the use of strength training equipment in this population, and 22.2% (n=36) about the types of exercises to use. Only 18.5% (n=30) reported having no challenges at all. Overall, 91.3% of physical therapists reported having issues relating to intervention safety. Safety issues were reported as a reason for avoiding certain types of exercise, and led to challenges regarding exercise programming; see Figure 3b. The risk of fractures was the most commonly reported issue (76.4%). Seventeen percent of the respondents reported that they dealt with this issue by adjusting exercises to each individual patient and to the localization of the metastases.

Figure 2. Exercise interventions used (n=162)

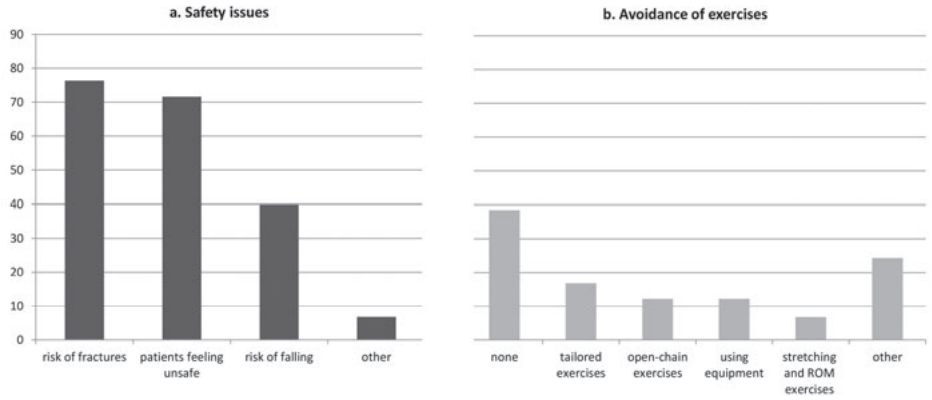


In the focus groups, several issues concerning safety were also raised. Participants reported that the limited information provided by the referring health professional was a major barrier to decision making, especially with regard to the choice and intensity of exercises. Also, they experienced problems with a lack of clarity in the recommendations and cautions provided to the patient by treating physicians. As stated by one participant:

But still....the surgeon might say: "don't do it (exercise), absolutely not!", but then the radiotherapist says: "if you don't do anything, then you can be sure you won't get better". So, everyone gets a bit anxious.

This conflicting information is one of the reasons physical therapists experienced difficulties with efficiently prescribing an adequate level of exercise. Instead, they relied on an often extensive process of trial and error to establish the most appropriate intensity level for individual patients, usually erring on the side of caution. One of the participants of the focus groups often resorted to a "graded activity-like" approach, to make sure patients would not be overloaded.

Figure 3. Safety issues experienced (dark grey bars) and avoidance of exercises used (light grey bars) during treatment (n=148)



Data on the use of e-Health was missing for 48% of the respondents. Of those who responded to the question, only 17 reported the use of e-Health interventions for this population. Educational needs with regard to the use of e-Health were reported by 40.1 % (n=65) of the survey respondents.

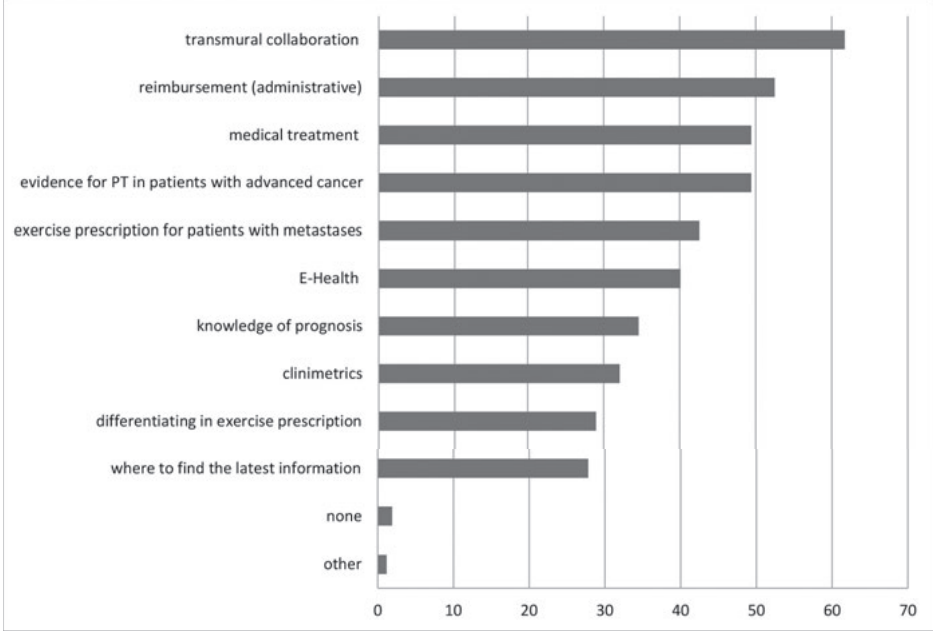
Two additional themes emerged in the focus groups. The first was insecurity about judging newly developing symptoms, especially pain. On the one hand, the physical therapists worried about symptoms they could not immediately explain, and felt a responsibility to act adequately on these. On the other hand, they did not want to worry the patient unduly. For example, one respondent said:

"When a patient develops pain in another location then where you know the metastases are located, the first thing you worry about is that it might be a new metastasis. Yet, you don't want to worry the patient. So at which point do you bring up that they should talk to the oncologist about it ? That is something I struggle with."

Second, the participants expressed difficulties about when and how to end a treatment episode, including when to refer to a different discipline (e.g. a psychologist). Several reasons were provided for these difficulties. One reason was the changing role of the physical therapy during the course of treatment; what starts off as a treatment with a focus on physical functions, may develop into a relationship that is characterized mainly by providing coaching and psychological support. In such a relationship, physical therapists can find it difficult to state that there is no further indication for physical therapy interventions, as they fear this may lead to negative thoughts and emotions on the part of the patient. This was expressed by one of the participants as follows:

"When you reach the point where, as a physical therapist, you say: I have done all I can, and I will not come to see you anymore, people tend to think, 'now I am really going to die' "

Figure 4. Educational needs (n=162)



Other educational needs and clinical uncertainties

Using the combined data from the survey and the focus groups, we identified several overarching educational needs (Figure 4). The educational need reported most frequently in the survey was how to establish effective interprofessional collaboration (61.7%). In clinical practice, most collaborations are with the oncology nurse; both in the diagnostic (37.0%) and therapeutic process (41.4%). One-half of the survey respondents (51.9%) reported that the frequency of contact with health care professionals, in general, is insufficient. This is in line with the findings from the focus groups in which some physical therapists expressed the desire to improve both the quality and quantity of communication with other health professionals, in particular with the referring physician. Moreover, the partitioning and alignment of responsibilities across health care providers was experienced as unclear, which led to uncertainty on the side of physical therapists about when to refer a patient to another discipline. This was stated by one of the participants as follows:

"Are you going to consult someone else, or are you going to solve this all by yourself? I would like that to be part of an educational program: multidisciplinary working."

In the focus groups, the degree of satisfaction with interprofessional collaboration varied and seemed to be related to regional differences in the organization of interprofessional care. For example, some PTs indicated that they could easily contact an oncology nurse in the hospital, while others could not.

The second-most important educational need was for increasing knowledge of medical decision making in palliative care and of the medical treatment of patients with advanced cancer (49.4%). Also, 49.4% of the PTs wanted to increase their knowledge of current evidence for efficacy and safety of PT interventions in this population. The focus group participants also emphasized the need for knowledge of, or access to, evidence on safety, feasibility and effectiveness of exercising with bone metastases. Specifically, the PTs recommended creation of a knowledge base, accessible via a web portal, where they could find the latest evidence on physical therapy treatment of patients with advanced cancer. Finally, in both the survey (52.5%) and the focus groups, PTs expressed administrative problems related to getting reimbursed for services provided. This typically reflected lack of clarity with regard to reimbursement rules.

Differences in educational needs between Master's level oncology physical therapists and physical therapists with only basic oncology training

In the survey sample, the only significant difference in educational needs between physical therapists with and without a master's degree in oncologic physical therapy was with regard to the use of clinimetrics (5.0% vs 47.0%, respectively; p=.035). In the focus groups, the PTs with a Master's degree in oncology expressed more self-confidence and less need for education in the provision of basic psychosocial support, compared to those without an advanced degree.

DISCUSSION

In this study, our aim was to gain insight into the experiences, uncertainties and the educational needs of physical therapists working with patients with advanced cancer. We found that more than one-half of the physical therapists felt quite confident about their abilities in the diagnostic process. Nevertheless, almost all physical therapists in the survey and focus groups also expressed several educational needs and uncertainties, with regard to either the diagnostic process, the treatment process, or both. The most important educational needs concerned how to establish effective interprofessional collaboration, increasing background knowledge of medical treatment, increasing knowledge about the safety and feasibility of examining and exercising patients who have bone metastases, and increasing knowledge of the current evidence for the efficacy of physical therapy interventions in this population. Moreover, physical therapists reported uncertainties regarding setting realistic goals, ending a treatment episode, and judging and acting on newly occurring symptoms.

To the best of our knowledge, this is the first study specifically aimed at identifying educational needs of physical therapists in the context of treating patients with advanced cancer. Consequently, the possibilities for comparison with the literature are limited. Our findings are in agreement with a recent mixed methods study among chartered physical therapists in Ireland.[15] In that study, physical therapists were asked to provide physical activity prescriptions for two patients with advanced cancer, based on clinical vignettes. They expressed concerns regarding prescribing physical activity to patients with advanced cancer and, as in our study, in many cases this was related to the presence of bone metastases or the increased risk of falling.

The few available exercise intervention studies in patients with bone metastases suggest that exercise is safe. This includes targeted strength and aerobic exercise prescriptions, provided that these are properly adjusted to the individual patient [18, 19]. The exercise prescription strategies proposed in those studies were based on the localization of the metastasis, excluding specific exercises or exercise modes (i.e. weight-bearing vs. non-weight baring). Although more research is needed to confirm and expand on these results, it seems useful to familiarize physical therapists working with patients with advanced cancer with these strategies. The clinical reasoning of physical therapists may be prone to omission bias; the tendency to avoid actions that might be harmful even if not-acting may be equally harmful [20]. Such bias may result from conscientious adherence to the medical principles “primum non nocere” (first, do no harm) and “in dubio abstine” (when in doubt, do not act). However, given the expected decline in physical fitness, reduced functioning, and increased risk of falling that results from physical inactivity, not using exercise as a therapy may ultimately do more harm than good. Providing evidence of safety and practical guidelines for safe exercise prescription may reduce doubts, and thus reduce underutilization of exercise interventions.

Few of the physical therapists reported to use e-Health, while 40.1% expressed educational needs on its use in this population. In a previous study, we showed that one-third of patients with metastasized breast cancer were interested in the use of e-Health [8]. Also, travel time to a qualified physical therapist was reported as a barrier to supervised exercise in that study. Thus, improving the knowledge and skills of physical therapists for using e-Health applications for patients with advanced cancer may improve the quality and accessibility of care.

Some of the uncertainties experienced by the physical therapists in our study appeared not to be related specifically to cancer, but to general competencies such as finding and using relevant evidence, goal setting, using clinimetrics and discussing the results, providing psychosocial care, communication skills, and transmural collaboration. The complexity of (advanced) cancer obviously puts higher demands on such generic competencies. Providing evidence-based guidelines and decision support may reduce some of these uncertainties within the context of advanced cancer. Skills related to

delivering basic psychosocial care and communication can be developed as well, even in a relatively brief training course [21].

The barriers to effective delivery of care that arise from problems with interprofessional collaboration cannot be targeted with education alone. Currently, around 550 physical therapists are registered in the Onconet network, of whom approximately 100 have a master's degree in oncologic physical therapy. This network covers the majority of the Netherlands and is growing. Yet, the results from our study suggest that, to improve accessibility to physical therapy care for patients with (advanced) cancer, regional initiatives to improve interprofessional collaboration among hospital-based and primary care-based health care providers are needed, in addition to continuing education of these physical therapists.

One-half of the survey respondents reported educational needs with regard to reimbursement regulations. Rather than demonstrating lack of knowledge on the part of the physical therapists, the experienced difficulties with understanding and appropriate use of reimbursement rules may also reflect the health care system in the Netherlands, which has not yet incorporated into its reimbursement policies the fact that many patients with advanced cancer may live longer and consequently have extended supportive care needs. Thus, to improve the accessibility of care for this vulnerable population of patients, health care insurance regulations need to be reevaluated.

Some limitations of this study should be noted. First, we performed this research within the context of the development of an educational program for physical therapists without a master's degree in oncology. To explore differences between physical therapists with basic oncology training and those with advanced oncology training, we invited both groups to participate in the survey and the focus groups. Although the number of physical therapists with a master's degree responding to the survey was comparable to that in the target population, the number of physical therapists with a master's degree in the focus groups was relatively high (41%). This may have been reflected in the views expressed and themes identified. Second, although we did our best to create and maintain a safe atmosphere during the focus groups, it might be difficult for physical therapists to fully expose their uncertainties in front of colleagues. However, given the similarity in the themes derived from the focus groups and the results of the survey, we believe that such a "social desirability" factor did not play a prominent role in the group dynamics. Third, we did not explicitly query educational needs with regard to psychosocial care in our survey. However, this emerged as a theme in the focus groups. Additional research is needed to examine if this is an educational need that is widely endorsed by physical therapists working with patients with advanced cancer. Finally, differences in educational systems and delivery of care for patients with advanced cancer exist between countries, which may limit the generalizability of our findings to some extent. Nevertheless, as far as we are aware, specific education on the physical therapy treatment of patients

with advanced cancer is currently lacking from education for entry level to practice in most countries, and postgraduate courses on the topic are also not widely available. We therefore believe that our findings regarding clinical uncertainties are currently likely generalizable to physical therapists in many other countries. Notable strengths of the study include the triangulation achieved by combining survey and focus group data, and the focus on obtaining actionable information.

In conclusion, our results suggest that Dutch physical therapists working with patients with advanced cancer have a wish to improve their knowledge and skills with regard to the treatment of these patients. Some of these skills can be covered in relatively short-term courses and by establishing treatment guidelines and protocols. This could lead to relatively quick improvements in the quality of care. At the same time, to fully address the quality and accessibility of physical therapy-care for patients with advanced cancer, a number of problems need to be addressed at the level of the regional and national health care systems.

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4

FEASIBILITY AND OUTCOMES OF A GOAL-DIRECTED PHYSICAL THERAPY PROGRAM FOR PATIENTS WITH METASTATIC BREAST CANCER

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ABSTRACT

Purpose

To evaluate the feasibility and outcomes of a tailored, goal-directed and exercise-based physical therapy program for patients with metastatic breast cancer (MBC).

Methods

This was an observational, uncontrolled feasibility study. The physical therapy intervention was highly tailored to the individual patient's goals, abilities, and preferences, and could include functional, strength, aerobic, and relaxation exercises. Feasibility outcomes were participation rate (expected: 25%), safety and adherence (percentage of attended sessions relative to scheduled sessions). Additional outcomes were goal attainment, self-reported physical functioning, fatigue, health-related quality of life, and patient and physical therapist satisfaction with the program.

Results

Fifty-five patients (estimated participation rate: 34%) were enrolled. Three patients did not start the intervention due to early disease progression. An additional 22 patients discontinued the program prematurely, mainly due to disease progression. Median intervention adherence was 90% and no major intervention-related adverse events occurred. A goal attainment score was available for 42 patients (of whom 29 had completed the program and 13 had prematurely dropped out). Twenty-two (52%) of these patients achieved their main goal fully or largely and an additional 15 patients (36%) partially. Eighty-five percent would "definitely recommend" the program to other patients with MBC. We observed a modest improvement in patient satisfaction with physical activities (Cohen's d_z 0.33).

Conclusion

The tailored intervention program was feasible in terms of uptake, safety and outcomes, and was highly valued by patients and physical therapists. However, disease progression interfered with the program, leading to substantial dropout.

INTRODUCTION

With increasing life expectancy of patients with metastatic breast cancer (MBC), there is an increasing demand for multiple and or prolonged periods of supportive care. Metastatic disease can negatively affect physical fitness [1] and quality of life [2]. Pain and fatigue are the two most common symptoms, but patients can also suffer from joint pain, nausea, depression, anxiety, drowsiness, and shortness of breath [3, 4]. These symptoms are a barrier to being physically active and performing usual activities of daily living [5].

In the context of early stage breast cancer, there is an ever growing body of evidence supporting the potential of physical exercise to alleviate treatment-related symptoms and functional limitations [6]. Patients who take part in physical exercise programs during or after primary breast cancer treatment have better physical fitness, experience less fatigue, and report better quality of life [7]. There are also indications that better physical fitness and higher levels of physical activity are associated with improved survival[8-10]. Also, some studies indicate that there may be positive effects of relaxation and body-awareness interventions in reducing symptom burden [11, 12].

In advanced breast cancer, the empirical support for the feasibility and effectiveness of exercise and rehabilitation is limited [13, 14]. To date, the studies performed in advanced cancer are to a large extent “intervention centered”; although exercise parameters are tailored to patients’ capacity, the intervention itself is rather uniform [13, 14]. We would argue that tailoring the program to individual patients’ unique goals and preferences needs special consideration in the palliative phase. The aim is to precisely target those aspects of functioning in daily life that are most valuable to the individual, and thus most likely to improve their quality of life. Such a goal-directed program does not yet exist, and in general, the range of exercise and rehabilitation interventions available for this patient population is currently limited and fragmented. At the same time, patients with MBC have expressed an interest in exercise-based rehabilitation programs [5].

Given this background, we developed a patient-centered and goal-directed exercise program entitled “*Veerkracht”* (which translates to “resilience”) to improve physical functioning in relation to daily activities, regular physical activity, and/or intentional exercise. The program is based on a comprehensive literature review, surveys, focus group sessions with patients [5] and physical therapists working with patients with cancer [15], and our own clinical experience. In the current feasibility study, we carried out an initial evaluation of the *Veerkracht* program in terms of process measures (i.e., program uptake and adherence), and preliminary indicators of outcome, in particular goal attainment and changes in health-related quality of life (HRQoL) of patients with MBC.

METHODS

Design and patients

In this single-arm feasibility study we recruited patients from seven Dutch hospitals: The Netherlands Cancer Institute, Amsterdam University Medical Center (location VUMC), Amstelland hospital, Rijnstate hospital, Northwest Hospital Group (location Alkmaar), Zaans Medical Center and Spaarne hospital. The recruitment strategies differed between these hospitals. In the Netherlands Cancer Institute and Rijnstate hospital, all eligible patients who were under current care of the hospital were evaluated for eligibility for inclusion by their treating physician and then approached by a letter. In the other hospitals, the treating physician approached eligible patients during their regular outpatient appointments. Patients were also recruited via a closed-group Facebook page for patients with advanced breast cancer and via the website of the Dutch Breast Cancer Association. Finally, physical therapists involved in the study could refer potentially eligible patients.

Eligible patients had been diagnosed with metastatic breast cancer, were at least 18-years of age, had a WHO performance score 0–2, had either self-reported functional problems with activities of daily living or were on active chemotherapy, and expressed a desire to participate in a physical exercise program. Patients had to be able to read and write Dutch and have health insurance coverage for physiotherapy treatment or be willing to participate partially at their own expense. To reduce the financial barrier for patients with insufficient insurance coverage, a fixed financial contribution was available via "Tegenkracht", a Dutch sports and cancer foundation. Patients with significant cognitive impairment, symptomatic heart disease, or complex and/or multi-morbid conditions requiring multidisciplinary rehabilitation were excluded. We aimed to recruit a minimum of 40 patients in 18 months.

Intervention

During a comprehensive intake performed by the physical therapist, program goals were set using a stepwise approach, "Patient-specific goal setting (PSG)", as proposed by Stevens et al. [16]. The steps included the following: (1) identifying health-related problems in activities in daily life; (2) prioritizing the most important activities to be targeted by the intervention; (3) scoring the perceived ability to perform these activities on a Numeric Rating Scale (0 = impossible to perform to 10 = easy to perform); (4) translating the selected activities into specific treatment goals; and (5) planning treatment. A tailored, exercise-based physical therapy program was then provided that best targeted the patients' goal(s).

Tests of physical fitness and functioning were used to measure baseline capacity, identify targets for therapy, and to evaluate the treatment outcome at the functional level. The physical therapist selected from a core set of tests those tests that where most relevant to the patient's goals. Thus, the tests could differ from patient to patient. Also,

the frequency, duration, and specific content of the program were determined for each patient individually, again depending on the patient's goals and clinical status. Program content could include resistance and/or aerobic exercises, functional exercises (e.g., stair climbing), and/or relaxation exercises. Also, the program could be offered with differing degrees of supervision, ranging from fully supervised/in-person to fully home-based, and included the optional use of e-Health (Physitrack, Physitrack Ltd., London, UK). Specific exercise libraries were prepared within Physitrack using both readily available exercises and exercises that were added specifically for this patient population. Detailed information about the program modules and their rationale are presented in Appendix 1.

Education of physiotherapists

All participating physical therapists had previous training in working with oncology patients via the Onconet network (Appendix 2). They received an additional, full-day training session specifically targeted at providing the *Veerkracht* program. This training session included medical background information on MBC, goal setting in the context of MBC, physical testing procedures, and the use of the Physitrack e-Health platform. Additionally, the physical therapists were instructed on study procedures, received a *Veerkracht* practice guide, and a subscription to *Physitrack,* with access to the *Veerkracht* library of exercises.

Assessments

At baseline (pre-intervention), participants completed a questionnaire assessing sociodemographics, activities of daily living, and HRQoL. The program was evaluated by two main sets of outcomes: process-related outcomes and outcomes related to satisfaction with and preliminary results of the intervention.

Process related outcomes

Uptake was expressed as the number of patients who were actually enrolled in the program as a fraction of all eligible patients. In our earlier survey on exercise preferences of patients with MBC, we found that about 25% would appreciate a fully physical therapist-supervised program [5], so accordingly, we anticipated an uptake of around 25%. Due to the differences in recruitment strategies across hospitals, complete and detailed data on the number of eligible and invited patients could only be collected in three of the participating hospitals (Netherlands Cancer Institute, Rijnstate hospital, and NWZ). Therefore, uptake was estimated based on the numbers from these hospitals.

Safety was evaluated based on the occurrence of any serious adverse events (SAEs) or of adverse events (AEs) that were directly related to the *Veerkracht* intervention and that occurred during or shortly after the sessions (e.g., cardiovascular events or falls resulting in fractures, but also muscle pain or joint pain). We used a selection of the Common Terminology Criteria for Adverse Events (CTCAE) v.4.03, including muscle pain, joint pain, back pain, bone pain, pain in extremities, hypotension, and lymphedema. We

only registered grade 2 complications (moderate symptoms and limited in instrumental ADL) or worse.

Adherence of patients to the prescribed intervention program was expressed as the percentage of planned sessions that were attended. Prior to the study, we defined program feasibility as reaching a minimal adherence level of 70%.

Outcomes related to satisfaction with and preliminary results of the intervention
Satisfaction of patients was measured by a short, study-specific questionnaire that covered the intake procedure and the applicable intervention components (exercise, relaxation, e-Health, etc.). The physical therapists' satisfaction was evaluated via an online questionnaire and concerned the training that they received, the perceived usefulness of the study's practice guide, the intervention components, and the Physitrack e-Health platform.

Goal attainment for each goal was rated on a 4-point adjective scale, as evaluated by the patient and physical therapist together: (1) goal was not attained at all, (2) goal was partially attained, (3) goal was largely attained, (4) goal was fully attained. This approach is similar to the original goal attainment scaling method of Kiresuk and Sherman [17], but has the advantage of fitting into the workflow of physical therapists, who already use the PSG in routine clinical practice.

Activities of daily living and participation were measured with the "Utrecht scale for evaluation of rehabilitation-participation" (USER-P) [18]. This questionnaire was developed specifically to evaluate the outcomes considered most relevant to rehabilitation. It contains 32 questions about daily activities and participation, organized into three sub-scales assessing the frequency with which daily activities are performed (frequency), whether one perceives any impairments in activities of daily living (restrictions), and satisfaction with current activities of daily living (satisfaction) [18]. Higher scores indicate better levels of participation (higher frequency, less restrictions, higher satisfaction) [18].

HRQoL was assessed with the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire [19]. The QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included. An overall QLQ-C30 summary score can be calculated. For all scales, scores range from 0 to 100, with higher scores representing better functioning (functional scales and overall summary score) or more severe symptoms (symptom scales).

Statistical analyses

All analyses were performed with SPSS version 22 for Windows (IBM Corp. Somers, NY, USA). We calculated summary statistics for sociodemographic and clinical data. Satisfaction was analyzed at the individual item level; responses for all items are presented as raw scores. For goal attainment, we calculated the frequency and percentage of each score category for program completers, non-completers, and the combined group. To obtain an indication of changes in activities of daily living (USER-P) and HRQoL, we performed analyses on an intention to treat basis, including all available data at baseline and end of intervention, regardless of whether participants had followed the intervention as planned. Changes in physical test scores were calculated only for the most frequently used tests (≥ 10 pairs available). Mean changes with 95% confidence intervals were obtained from paired samples Student's t-tests. The standardized mean difference effect size (E.S.) for within-subjects designs (Cohen's dz) was calculated [20]. Effect sizes of 0.2, 0.5, and 0.8 represent small, moderate, and large effects, respectively [21].

RESULTS

Between January 2017 and June 2018, we included 55 patients. Their characteristics are presented in Table 1. During the study, three patients did not start the intervention due to early disease progression and an additional 22 prematurely discontinued their participation in the intervention, mainly due to disease progression (Figure 1).

Characteristics of the provided interventions

The average program duration was 12.0 (SD 5.5; range 2–29) weeks, with an average of 13.5 (SD 6.8; range 2-30) physiotherapy visits. Table 2 provides an overview of the provided intervention components. The most frequently used physical health-related tests and questionnaires were the 6-min walk test (6 MWT), the numeric pain rating scale (NPRS), indirect 1-RM strength testing of lower extremities, grip strength, and the multidimensional fatigue index questionnaire (MFI) [22] (Table 6 in Appendix 3).

Process measures

Uptake Based on the data of three hospitals (The Netherlands Cancer Institute, Rijnstate hospital and NWZ), an estimated 34% (95%CI 0.25 to 0.44) of eligible patients participated in the intervention, which exceeded our expected rate of 25%.

Safety Physical therapists reported ten grade-2 and four grade-3 adverse events (AEs) that were potentially related to the intervention. The grade 2 AEs consisted of transient muscle pain (n = 4), joint pain (n = 3,) back pain (n=2), and bone pain (n = 1). The grade 3 AEs consisted of muscle pain (n = 3) and bone pain (n = 1) interfering with daily activities. No hospitalizations were required for any of these AEs.

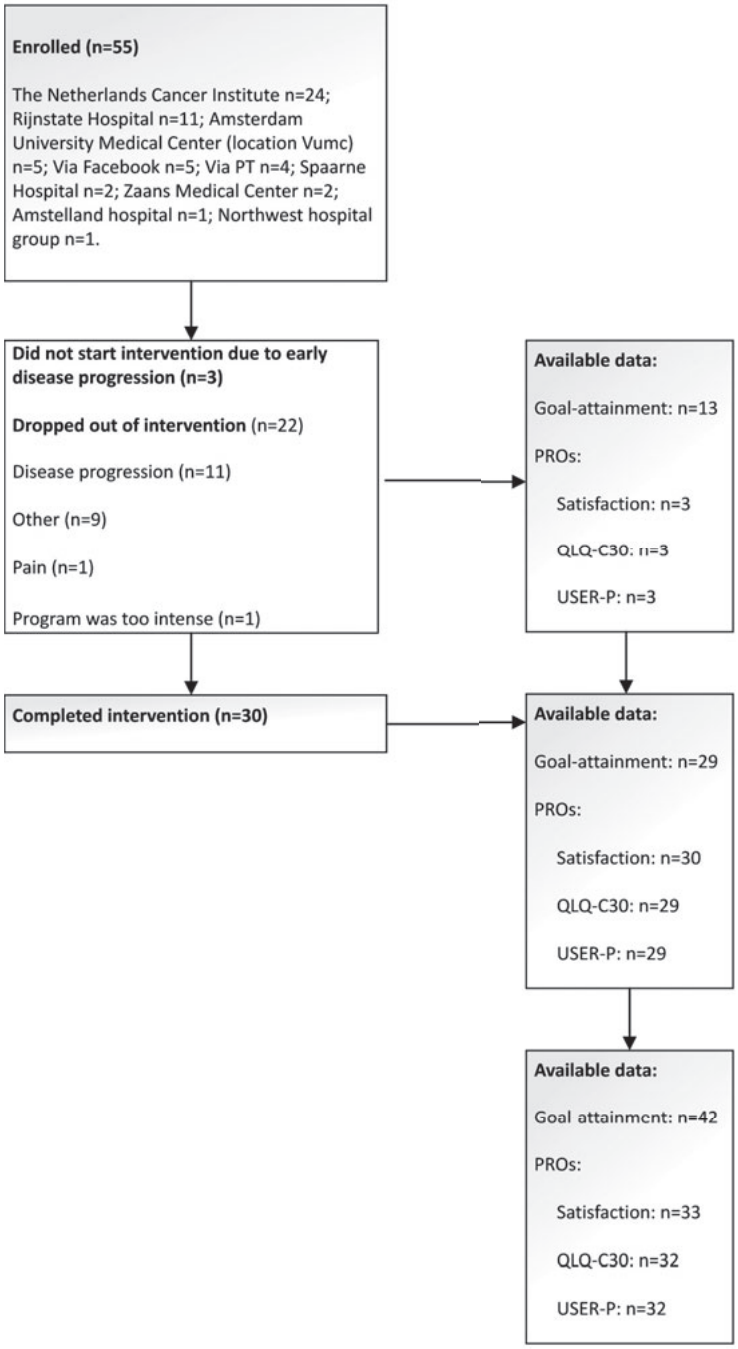
Adherence The median adherence rate of patients who completed the intervention was 90% (N = 36; IQR 80–100%). Reasons for canceling/not attending appointments were related to illness, personal factors unrelated to the disease, and hospitalization due to cancer.

Table 1. Patient characteristics

Sex, Female, n (%)	54 (98%)
Age, mean (SD)	58.1 (9.4)
Living situation, n (%)	
With partner	40 (73%)
Alone	15 (27%)
Educational Level, n (%)	
Primary/middle school	26 (47%)
High school	24 (44%)
College/University	5 (9%)
Time since diagnosis in years (SD)*	9.4 (7.3)
Time since metastatic disease in years (SD)*	3.1. (2.8)
Current treatment	
Hormone therapy	29 (53%)
Chemotherapy	21 (38%)
Targeted therapy	21 (38%)
Radiotherapy	2 (4%)
Missing	1 (2%)
Location metastases	
Bone	41 (75%)
Lung	23 (42%)
Liver	17 (31%)
Other	15 (27%)
Brain	2 (4%)
Number of comorbidities: median (range)**	1 (0-4)
Types of comorbidities, n	
Musculoskeletal	21 (38%)
Pulmonary	7 (13%)
Cardiovascular	4 (7%)
Other	27 (49%)
Missing	1 (2%)

* N=53, ** N=54

Figure 1 Flow of participants and data



Outcome measures

Goal setting and goal attainment

Most patients set 2 or more goals. We categorized these in line with predetermined categories that were already used in the practice guide for the physical therapists: (1) Sports/exercise and being physically active (n = 43) (e.g., "Improve my strength and endurance in two months so that I can walk my dogs 3 times a day for more for at least 30 minutes"; (2) activities of daily living (n = 31) (e.g., "walk two flights of stairs without being short of breath"; (3) maintaining posture (n = 10) (e.g., "standing upright for 30 minutes during cooking"); and (4) Relaxation (n = 1).

For all the patients that had a goal attainment outcome (regardless if they had completed the physical therapy intervention, intention to treat), 52% had attained their most important goal largely or fully. An additional 36% attained their goal partially. Of the 29 patients who completed the intervention, 66% attained their goal largely or completely. An additional 31% attained their goal partially. The results for the second and third goals (if applicable) were comparable (Table 3).

Satisfaction of patients

Thirty-three participants provided feedback regarding their satisfaction with the program. Of these, 28 (85%) indicated that they would "definitely recommend" (highest response category) the *Veerkracht* program to other patients in a comparable situation, 1 (3%) was likely to recommend, 2 (6%) were unlikely to recommend the program, and 2 patients (6%) did not know. Median satisfaction scores on all aspects were high and patients, on average, believed that the intervention contributed to their physical fitness and to their being able to perform their daily activities (Table 4).

Satisfaction of physical therapists

Twenty-one physical therapists (64%) completed the evaluation questionnaire. Of these, ten (48%) reported using the written practice guide very often, two (10%) often, eight (38%) occasionally, and one (5%) almost never (because she was already familiar with the content). Almost all of the physical therapists (n = 20, 95%) were (very) satisfied with the written guidebook. Cited benefits of the education session were improved skills in structured goal setting, being empowered to clearly communicate the boundaries of the intervention program with regard to goals and duration, and increased confidence in prescribing exercises for patients with bone metastases. Ten physical therapists had used the Physitrack e-Health platform and favorably rated its navigability and clear exercises. Some of the physical therapists mentioned the lack of integration/communication with the electronic medical record (EMR) as a drawback of the platform.

Estimate of effect on HRQoL, physical functioning, activities of daily living, and participation

At the group level, we observed a modest improvement in the satisfaction score of the USER-P (E.S. 0.33), and small but positive changes with regard to restrictions in activities of daily living (E.S. 0.16). Small but positive changes were also observed for global health status (E.S.0.14) and physical functioning (E.S. 0.11). All scores are reported in Table 5. Ten or more pre-posttest pairs were available for only one physical functioning test (6-min walking test). Walking distance increased for 16 patients an average of 73.8 m (95% CI: 37.1 ; 110.6) from 407 (SD 103) meters to 481 (SD 102) meters (E.S. 0.72).

Table 2. Intervention characteristics

Intervention component (not mutually exclusive)	Provided*, N (%);	Number of sessions median (range); N	Duration in weeks median (range) ; N	Frequency of sessions/wk median (range) ; N
Functional training				
Resistance training	41 (87.2%)	10.0 (2-24) N=37	12.0 (2-29); N=37	1.6 (0.6-2.0); N=33
Endurance training	42 (89.4%)	9.5 (2-27); N=38	11.0 (2-29); N=37	1.4 (0.5-2.0); N=32
Skill training	22 (46.8%)	6.5 (1-24); N=20	6.0 (0-24); N=19	1.2 (1-2); N=15
Relaxation exercises	13 (27.7%)	2.0 (1-12); N=9	2.0 (1-13); N=11	(1-12); N=11
Staying fit during chemotherapy				
Supervised moderate to high intensity program	4 (8.5%)	18.5 (7-24) N=4	22.0 (7-24) N=3	2.0 (1-2) N=3
Home based program	1 (2.1%)	Not reported	Not reported	Not reported
Education				
Information booklet	18 (40%)	Not applicable	Not applicable	Not applicable

*Data was available for 47 patients.

Table 3. Extent of goal attainment. *percentages are provided as fraction of total number of goals set

	Extent of goal attainment (All available goal attainment data/ intention to treat)					
	Fully, n (%)*	Largely, n (%)	Partly, n (%)	Not at all, n (%)	Not reported, n(%)	Valid/ Missing, n=
Goal 1 (main goal)	11 (26%)	11 (26%)	15 (36%)	5 (12%)		42/13
Goal 2	10 (24%)	9 (21%)	13 (31%)	6 (14%)	4 (7%)	42/13
Goal 3	5 (12%)	7 (17%)	5 (12%)	7 (17%)	18 (43%)	42/13
	Extent of goal attainment (For patients with goal attainment scoring after successful completion of the program)					
	Fully (%)	Largely (%)	Partly (%)	Not at all (%)	Not reported, n(%)	Valid/ Missing, n=
Goal 1 (main goal)	11 (38%)	8 (28%)	9 (31%)	1 (3%)		29/1
Goal 2	10 (34%)	8 (28%)	6 (21%)	1 (3%)	4 (14%)	29/1
Goal 3	5 (17%)	6 (21%)	2 (7%)	1 (3%)	15 (52%)	29/1
	Extent of goal attainment (for patients with premature goal attainment scoring due to disease progression or other cause of dropout)					
	Fully (%)	Largely (%)	Partly (%)	Not at all (%)	Not reported, n(%)	Valid/ Missing, n=
Goal 1 (main goal)	0 (0%)	3 (23%)	6 (46%)	4 (31%)		13/12
Goal 2	0 (0%)	1 (8%)	7 (54%)	5 (38%)		13/12
Goal 3	0 (0%)	1 (8%)	3 (23%)	6 (46%)	3 (23%)	13/12

DISCUSSION

The results of our study indicate that the *Veerkracht* program designed to support physical activity and daily functioning of patients with MBC via physical therapist-supervised interventions is largely feasible as rated by several process and safety indicators. Overall, patients and physical therapists were very satisfied with the program, and many patients were able to meet their goals. There was some indication of improved scores related to satisfaction with activities of daily living, and HRQOL scores remained unchanged. However, interference and dropout due to disease progression were substantial. An in-depth exploration of the underlying reasons for program cessation was beyond the scope of this study, so uncertainty remains with regard to whether or not—and how—the program

should or can be adapted to accommodate patients' shifting needs and perspectives at the time of disease progression.

Table 4. Satisfaction with and perceived benefits of the intervention as rated by patients

	N (net)*	Not applicable	Missing**	Median (IQR)***
How satisfied were you with …				
Initial meeting with PT (intake/goal setting)	33	-	-	9 (8-10)
strength training	21	12	-	9 (8-10)
endurance training	30	3	-	9 (8-10)
relaxation exercises	15	17	1	8 (8-9)
Web-based exercise	7	25	1	9 (7-10)
Supervision by physical therapist	33	-	-	10 (9 – 10)
To what extent did the program contribute to…				
Your physical fitness	32	-	1	8 (7-10)
Better perform activities of daily living	32	-	1	8 (7-9)
Perform social activities	32	-	1	7 (2-8)
your perceived quality of life	32	-	1	8 (7-9)

*Net number of patients that contribute to the score

**Numbers are related to total number of completed evaluation questionnaires.

*** Score ranges from 0 (worst possible score) to 10 (best possible score)

Aside from disease progression, some AEs occurred but most of these were minor and of the kind that can be expected when engaging in a training program (i.e., muscle aches following resistance training). In such cases, the physical therapist will adjust the training load as needed. In line with our findings, recent systematic reviews indicate that exercise interventions in this vulnerable population are generally safe [13, 14].

Regarding the efficacy of exercise interventions in advanced breast cancer, in previous studies, improvements were mainly observed for indicators of physical fitness, while results are ambiguous for fatigue and quality of life [13, 14]. Most, if not all, of the studies performed to date are to a large extent "intervention centered", using the same exercise program for all individuals. While this approach is useful to investigate the efficacy of exercise, it may underestimate the potential salutary effect of exercise-based interventions on quality of life and functioning in daily life for individual patients, as it does not adhere to the exercise principle of (task) specificity. The goal setting procedure used in our program ensured that patients and physical therapists were working towards the most relevant goals for each patient at that moment in time. While it is considered best practice in physical therapy, this approach is not very often taken in clinical studies. The heterogeneity in interventions applied makes it difficult, if not impossible, to tease out which program components contributed to the overall outcome, and how. Yet, the

outcomes obtained when using a tailored approach are probably a better reflection of what can be expected in clinical practice. In one recent oncology rehabilitation study including women with gynecological (i.e., cervical, endometrial, and ovarian) cancer [23], a goal setting and evaluation approach similar to ours was used. The study showed that women's goal setting and self-assessment of goal achievement were feasible in a hospital-based rehabilitation setting. Approximately 70% of the women achieved or exceeded their rehabilitation goals, which were not only limited to physical functioning but also included social, emotional, cognitive, existential, and sexual functioning goals [23]. In our study, for the overall group, we found a considerably lower rate of full goal attainment (±25% across all goals), with an additional 25 to 30% attaining their goal in large part. This may be related to the intervention, the different population (mainly curative vs. advanced disease), the differences in types of goals, or the slightly different method of goal setting and evaluation.

Table 5. Pre- and posttest values for the Utrecht Scale and the EORTC QLQ-C30; scores are presented as mean (SD)

Variable	T0 for all patients (MEAN,SD)	T0 for which a T1 was available (MEAN,SD)	T1(MEAN, SD)	Mean change T0-T1 (effect size)	95%CI of change
USER-P*	N=55	N=32	N=32	N=32	
Satisfaction	55.6 (20.3)	59.1 (19.4)	65.3 (17.7)	6.2 (0.33)	0.3; 12.0
Restrictions	73.3 (16.5)	74.9 (16.8)	77.6 (16.8)	2.7 (0.16)	-2.6; 8.1
Frequency	35.9 (10.0)	38.8 (9.6)	39.2 (9.8)	0.3 (0.04)	-3.9; 4.6
EORTC QLQ-C30*	N=55	N=31	N=31	N=31	
Global health status /QoL*	60.8 (17.0)	62.4 (16.6)	65.1 (22.0)	2.7 (0.14)	-6.1; 11.5
Physical functioning	69.4 (18.0)	73.1 (17.8)	75.1 (16.5)	1.9 (0.11)	-2.8; 6.7
Role functioning	64.2 (23.9)	64.5 (23.9)	66.1 (23.8)	1.9 (0.07)	-9.5; 12.7
Emotional functioning	69.3 (24.5)	72.0 (24.7)	70.7 (19.6)	-1.3 (-0.06)	-11.8; 9.1
Cognitive functioning	78.8 (22.8)	75.3 (25.4)	74.2 (20.6)	-1.1 (-0.05)	-8.1;6.0
Social functioning	70.4 (26.2)**	76.3 (25.4)	73.7 (23.9)	-2.7 (-0.11)	-13.2;7.8
Summary score	74.5 (12.4)***	76.5 (12.9)	77.5 (13.7)	1.0 (0.08)	-3.8:5.8

* Scores range from 0-100, with 0 indicating worst possible outcome and 100 indicating best possible outcome.

N=54, * N=52. The data are based on intention to treat analysis.

Our results also highlight the importance of educating physical therapists in providing guidance to patients with metastatic breast cancer. The physical therapists who participated in our study indicated that the 1-day educational session and the written manual increased their confidence, especially regarding training in the presence of bone metastases. This is important, as physical therapists often express uncertainty in this area [15, 24]. Targeted education and training can help to prevent inadequate exercise prescription resulting from unjustified fear of adverse events. The educational material developed for the "Veerkracht" program has now been embedded in the extensive oncology education program provided for physical therapists by the Dutch Institute of Allied Healthcare.

Limitations

Several uncertainties remain due to the scope and design of the study. First, because the study was uncontrolled, we cannot determine whether observed changes in physical function or HRQoL were due to the intervention, per se. Second, our goal attainment scaling method was somewhat subjective as there were no formal a priori operationalizations of "fully attained," "largely attained," or "partially attained" goals. However, our approach fits into the daily routine of physical therapists, and we would note that the validity of more formal procedures of goal attainment scaling remains ambiguous [25]. Though subjective, goal attainment scoring does measure what we believe needs to be measured, a perceived change in (patient-specific) functioning. Thus, it may be a more direct reflection of performance, whereas standardized functional measures rather reflect capacity. Thus, goal attainment scoring represents a valuable addition to functional testing [26]. Third, the heterogeneity of provided exercise interventions limits the reproducibility of this study. Lastly, getting the participating physical therapists to systematically collect and report process-related data proved to be challenging. Data collection in future similar studies might be improved by using electronic CRFs.

In conclusion, despite expected modest uptake and a high level of disease-related dropout, we found that a tailored, goal-directed physical therapy program for patients with MBC was safe, very well received by participating patients and physical therapists alike, and facilitated patients achieving their individual physical functioning-related goals. Finally, while our results are encouraging, the findings should ideally be confirmed by controlled studies that are able to accommodate the complex nature of the intervention [27].

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APPENDIX 1. DETAILED INFORMATION ON THE TAILORED INTERVENTION AND ITS COMPONENTS

General information

In an intake meeting patients' problems and goals are explored (see section 8.1.1 on goal attainment). Where necessary, regular clinimetric evaluations (e.g., function tests) can be used to explore underlying functional impairments. Subsequently, the physical therapist composes a tailored exercise program aimed at the specific goals and the underlying physical deficits of the patient. The intervention is thus different for each patient, but the program will contain one or more of the following components:

Overview of program modules

Exercise modules to target patient-specific functional goals

1. Resistance exercises including a range of exercises targeting the muscles that are limiting performance. This can include training on resistance exercise machines, training with dumbbells/free weights, or exercises with own body weight. PTs are educated to adjust resistance exercises in case of bone metastasis according to the protocol of Cormie et al. [28]
2. Aerobic exercises, including exercises targeting large muscles of the body such as swimming, rowing, cycling, walking, or running, performed at an intensity of 55-80% of the estimated maximal heart rate.
3. Functional skill exercises (deficient skills are trained in a systematic manner, e.g., balance training, stair climbing, transfer training [29].
4. Relaxation exercises (e.g., progressive muscle relaxation) [30].

Exercise modules to prevent functional decline during treatment (Modified versions of the OncoMove and OnTrack programs)

5. Modified OncoMove. OncoMove is based on the original program as described by van Waart et al. [31] and is adapted for our current population. It is a home-based, low-intensity, individualized, self-managed physical activity program as proposed by Mock et al. with the addition of behavioral reinforcement techniques. These comprise written information tailored to the individual's preparedness to exercise according to the transtheoretical model, and an activity diary that is discussed at each chemotherapy cycle. Specially trained physical therapists will encourage participants to engage in at least 30 min of physical activity per day, 5 days a week, with an intensity level of 12–14 on the Borg Scale of perceived exertion.
6. Modified OnTrack. OnTrack is a moderate-high intensity, combined resistance and aerobic exercise program, supervised by specially trained physical therapists. The participants attend two sessions per week. Six large muscle groups are trained for 20 min per session, with 2 series of 8 repetitions at 80% of 1 repetition maximum (1RM). (Indirect) 1RM testing repeated every 3 weeks. Each session incorporates 30

min of aerobic exercises, with an intensity of 50 to 80% of the maximal workload (Wmax) as estimated by the Steep Ramp Test. The intensity is adjusted using the Borg Scale, with a threshold of <12 for an increase and >16 for a decrease of intensity. Participants who follow this program will also be encouraged to be physically active 5 days a week for 30 min. OnTrack is based on the original program as described by van Waart et al. [31] and has been adapted for the metastatic setting. For example, the resistance training exercises of the original OnTrack protocol have been adapted to the special needs of metastatic breast cancer patients (e.g., strength training of areas with significant bone metastases is avoided according to the protocol of Cormie et al. [32].

7. Either the modified OncoMove or the OnTrack program can be offered to all patients who receive chemotherapy and do not have a specific functional goal, but are interested to stay physically active and physically fit. For those patients who wish to take part in this program, these modules will start as close to the start of chemotherapy as possible and will continue until 3 weeks after the last cycle of chemotherapy.

Generic module

Educational material (booklet) on the effects that cancer and its treatment can have on exercise capacity, what safe exercising means, how to determine the right exercise intensity, the importance of recuperation, what symptoms to look out for when exercising, and how physical exercise may influence symptom burden and affect quality of life.

Origin of program modules

The program modules were selected based on a needs assessment we performed through focus groups and a survey among 114 patients with metastatic breast cancer [6]. Intervention components 1–4 are, in fact, already part of daily practice of physical therapists and only require some modification for the special needs of metastatic breast cancer (points of attention include, for example, bone metastasis, impaired physical fitness, and/or diminished adaptive capacity due to the disease or its treatment). Components 5 and 6 have been successfully evaluated in the curative setting by van Waart et al. [31] and were consequently adapted for patients with metastatic disease. Component 7 is a component that is written specifically for the target population to enhance their knowledge of the effects of treatment on exercise capacity and the potential use of exercise to improve or maintain functional status. The novelty of the proposed intervention is that it adapts standard physical therapy interventions by using a structured intake procedure that includes an evaluation of adaptive capacity and safety that is specific to the target population, and by explicitly incorporating restrictions that are specific to the target population. The addition of an e-Health component is intended to provide additional support in learning, carrying out, and adhering to the exercise program.

Frequency, intensity, and duration of the program

PTs were trained to set proper treatment goals with the patient based on patient-dependent factors (e.g., personal goals, exercise history, preferences, context, and financial possibilities). Consequently, we did not give specific recommendations; there is no uniform recommendation with regard to frequency, intensity or amount of supervision on forehand. The total program duration will depend on the specific schedule and is anticipated to last a maximum of 12 weeks, but PTs could choose to alter this duration if needed.

The intervention components listed above are supported with an online platform, Physitrack. This is a secured platform that connects physical therapists and patients. Exercises deemed important and safe (as indicated by a previous survey and literature review) for patients with metastatic breast cancer have been added to the Physitrack's standard library of exercises. The physical therapist can provide patients with an exercise schedule through Physitrack as a supplement to face-to-face visits. In general, the goal is to have patients meet with the physical therapist at least once weekly, but this frequency may be adjusted according to the specific needs of the patients (e.g. traveling distance, physical functioning level).

APPENDIX 2: DETAILED INFORMATION ON THE ONCONET-NETWORK

Onconet is a nationwide network of physical therapists. These physiotherapists have received 67 h or more of additional training in subjects such as basic oncology, exercise oncology, behavioral support, dealing with cancer-specific side effects, dealing with comorbidity, using clinimetrics, and clinical reasoning in an oncology context. All the physical therapists in the network follow mandatory refresher courses and have to pass summative tests related to these courses. Patients and referrers can identify the nearest Onconet physical therapist using a searchable index on the Onconet website. Those who do not attend the refresher courses, or who fail the tests, are subsequently removed from the index. Currently, the network covers most of the populated areas in the Netherlands and an Onconet therapist is available anywhere within a 15′ commute for most people. Since September 2020, Onconet is a formal partner of the Oncology Section of the Royal Dutch Society of Physical Therapy (KNGF).

APPENDIX 3. FULL LIST OF PHYSICAL TESTS OR QUESTIONNAIRES USED

Table 6 - most frequently used physical health-related tests and questionnaires

Physical test or questionnaire	Number of times used at baseline	Number of times used during program	Number of times used at end of program
TUGT	5	1	4
SWT	1	0	1
6MWT	32	14	17
5TSTST	7	1	3
SPPB	1	0	0
1RM – LE	11	6	9
1RM – UE	6	4	5
1minRM	2	1	2
NPRS	11	5	5
BBS	1	0	1
SRT	8	6	6
Astrand	3	1	3
Handgrip strength	9	2	5
Microfet	3	1	2
MFI	10	3	5
VAS fatigue	3	1	2
AFQ	3	3	0

TUGT: timed up and go test. SWT: shuttle walk test. 6MWT: 6 minute walk test. 5TSTST: 5 times sit to stand test. SPPB: Short physical performance battery. 1RM-LE: 1 repetition maximum – lower extremities. 1RM-UE: 1 repetition maximum – upper extremities. 1minRM NPRS: numerical pain rating scale. BBS: Berg Balance Scale. SRT: Steep ramp test. Astrand: Astrand test. MFI: Multidemensional fatigue inventory. VAS fatigue: visual analogue scale for fatige. AFQ: abbreviated fatigue questionnaire.

5

TAILORING OF EXERCISE AND DIETARY INTERVENTIONS TO ADVERSE EFFECTS AND EXISTING COMORBIDITIES IN PATIENTS WITH CANCER RECEIVING CHEMOTHERAPY: A CLINICAL VIGNETTES STUDY AMONG EXPERT PHYSICAL THERAPISTS AND DIETITIANS

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ABSTRACT

Purpose

This study aims to capture the complex clinical reasoning process during tailoring of exercise and dietary interventions to adverse effects and comorbidities of patients with ovarian cancer receiving chemotherapy.

Methods

Clinical vignettes were presented to expert physical therapists (n=4) and dietitians (n=3). Using the think aloud method, these experts were asked to verbalize their clinical reasoning on how they would tailor the intervention to adverse effects of ovarian cancer and its treatment and comorbidities. Clinical reasoning steps were categorized in *questions* raised to obtain additional information; anticipated *answers*; and *actions* to be taken. Questions and actions were labeled according to the evidence-based practice model.

Results

Questions to obtain additional information were frequently related to the patients' capacities, safety or the etiology of health issues. Various hypothetical *answers* were proposed which led to different actions. Suggested *actions* by the experts included extensive monitoring of symptoms and parameters, specific adaptations to the exercise protocol and dietary-related patient education.

Conclusions

Our study obtained insight into the complex process of clinical reasoning, in which a variety of patient-related variables are used to tailor interventions. This insight can be useful for description and fidelity assessment of interventions and training of healthcare professionals.

INTRODUCTION

Exercise and dietary interventions are evidence-based methods to help maintain physical fitness and body composition during cancer treatment [1-4]. However, adverse effects of ovarian cancer and its treatment with cytotoxic agents, such as nausea, peripheral neuropathy and fatigue [5, 6] can affect adherence to exercise and dietary interventions [7]. In addition, some patients may already suffer from pre-existing comorbidities, such as hypertension or chronic lower respiratory diseases [8], which may hamper adherence to interventions. To optimize adherence to, and thereby the efficacy of, exercise and dietary interventions, it is important that these interventions are specifically tailored to the adverse effects of the treatment and pre-existing comorbidities of the individual patient. Rather than relying on intuitive and implicit decision-making, the process of tailoring interventions should be structured, explicit, and based on the best available evidence and/or best practice.

To provide structure to the tailoring of exercise prescriptions to comorbidities, the i3-S strategy was developed [9]. This strategy starts by defining optimal type and dose of exercise interventions for an index disease and determining the most common comorbidities of patients with that index disease. Subsequently, evidence-based recommendations regarding adequate adaptations to the exercise protocol for individual patients are made. The i3-S strategy has previously been used to generate recommendations for tailoring an exercise intervention to treatment adverse effects and comorbidities in patients with early-stage breast cancer [10]. The strategy has also been used to develop an exercise and dietary intervention for patients with ovarian cancer undergoing chemotherapy [8]. The protocols for these tailored interventions provide recommendations on how to deal with the most common adverse effects (e.g., ascites, fatigue) and comorbidities, so-called “if-then” scenarios. However, patients receiving cancer treatment often face varying and complex adverse effects of cancer and its treatment. Study protocols are unlikely to include all possible if-then scenarios. Adaptations to the intervention required by the clinical state of the patient, could then be considered protocol deviations, while in fact, they reflect good clinical care. Insight in the clinical reasoning process behind such protocol adaptations may illustrate tailoring of the intervention and may also inform future study protocols.

Clinical reasoning is the cornerstone of evidence-based practice, in which the healthcare professionals integrate best available evidence, the clinical state and circumstances of the patients, in combination with patient preferences and actions, to reach treatment decisions for individual patients [12]. The process of clinical reasoning is complex, mostly invisible, and often largely automatic [13]. In order to make it accessible to others in practice or research, it is important to make it more transparent and explicit, also within research protocols.

Evaluating intervention fidelity in research requires detailed information on why and how protocol adjustments were made. However, in patients receiving cancer treatment, adjustments made to exercise and dietary interventions with the objective of tailoring them to individual patients' needs and capabilities often have to some extent an inscrutable component. In order to gain insight into this component, we performed a qualitative study. We aimed to capture the clinical reasoning process undertaken by expert physical therapists and dietitians when faced with existing comorbidities and disease- and treatment-induced adverse effects of individual patients, which require tailoring of an exercise and dietary intervention during chemotherapy for ovarian cancer. Information about this process is useful when designing, adapting, and evaluating interventions, and when educating healthcare professionals who deliver these interventions.

METHODS

Study procedures

We selected three patients who participated in the intervention group of the Physical Activity and Dietary intervention in OVArian cancer (PADOVA) trial. PADOVA is a multicenter, randomized controlled trial examining the effectiveness of a combined exercise and dietary intervention compared to usual care (control group) during chemotherapy for adult patients with ovarian cancer. The PADOVA study has been approved by the medical ethical committee of the Amsterdam UMC and registered in the Netherlands Trial Register (NTR6300). Informed consent was obtained for all patients included in this study [8].

The three cases were selected based on the occurrence of significant adverse effects during ovarian cancer and its treatment, which had consequences for both the exercise and dietary intervention. For these three cases, baseline clinical characteristics such as age, International Federation of Gynecology and Obstetrics (FIGO) stage, type of treatment, comorbidities and adverse effects were collected from medical records. [8].

Combined Exercise and Dietary Intervention

The aims of the combined exercise and dietary intervention were to maintain physical fitness and function, prevent the loss of lean body mass and maintain a healthy body weight during (neo)adjuvant chemotherapy. The intervention started with the first cycle of chemotherapy and continued until three weeks after the chemotherapy administration [8].

The exercise intervention consisted of two one-hour sessions supervised by a physical therapist specialized in oncology in a practice close to the patients' home and included moderate-to-high intensity resistance and aerobic exercises. To ensure adequate training intensity over time, one repetition maximum (1RM) tests and a steep ramp (cycle ergometer) test were repeated every three or six weeks, respectively. The training load

of the resistance exercises was 70-80% of the 1RM with a gradual increase per week and exercises were performed in two sets of 8-10 repetitions. Aerobic exercises were conducted for 30 min per session, with an intensity of 50-80% of the maximal workload as estimated by the steep ramp test [14]. In addition, physical therapists were instructed to adjust training load to a Borg Scale of perceived exertion between 12 and 15.

The dietary intervention consisted of one counseling session per chemotherapy cycle and was provided by an oncology dietitian during face-to-face counseling sessions or by telephone [8]. Dietary counseling was tailored to the nutritional needs of each patient according to body composition, nutritional status and dietary intake during chemotherapy. Patients who were at risk of malnutrition were primarily counseled for prevention of weight loss by maintaining sufficient caloric and protein intake according to guidelines [8]. Patients who were not at risk of developing malnutrition were primarily counseled to meet the dietary guidelines set by the World Cancer Research Fund [15].

Data Collection and Analysis

Data on clinical state, clinical circumstances and the general wellbeing of the three different patients was collected by their physical therapists and dietitians delivering the interventions within the PADOVA trial. This data was summarized in clinical vignettes, which contained health data of the baseline visit, and subsequent time points during treatment at which a relevant change in clinical stage occurred.

The vignettes were presented to four physical therapists and three dietitians (further referred to as “the experts”). These experts were selected because they were specifically trained in the treatment of patients with cancer and had >10 years working experience in the field of oncology. None of the experts were involved in the exercise or dietary treatment of the selected patients.

The experts were asked whether and how they would adjust the dietary or exercise intervention using the think aloud method. This method consists of asking people to verbalize their thoughts while solving a complex problem [16]. In one-on-one sessions, guided by a researcher and recorded through video conferencing, they verbalized their reasoning process as they worked through the selected cases. The experts were told to think aloud repeatedly, and if they paused for longer than a few seconds the researcher reminded them to “keep thinking aloud”. The sessions were conducted in Dutch and transcribed verbatim.

MT and SS transcribed the data of the experts and analyzed this thematically. On an aggregate level, the data was classified into three clinical reasoning steps: 1) questions raised to obtain additional information about the described case; 2) the proposed possible answers to these questions; 3) the actions to be taken depending on these answers. Additionally, a group meeting with the experts and a researcher was held to discuss

contradictions between experts' opinions, to further clarify recommendations which were deemed unclear, and to fill in any blanks in the clinical reasoning process steps. Next, all questions raised were coded according to the domains from the evidence-based practice (EBP) paradigm [12] (i.e., clinical state and circumstances, evidence or patient preferences and actions), and thereafter inductively in further detail according to the type of question. Subsequently, actions were labeled inductively. Two researchers (MT and SS) performed the coding and results were discussed within the research group.

Selected cases

Two cases received neoadjuvant chemotherapy and one received adjuvant chemotherapy. The first case ("Amber") experienced significant ascites-related adverse effects (including symptoms of swollen abdomen, shortness of breath and a diminished nutritional intake) and fatigue. The second case ("Fatima") experienced fatigue, wound problems and joint pain and had a medical history with hypertension and Barret esophagus. The third case ("Wendy") drastically changed her nutritional intake after diagnosis and suffered from wound problems and fatigue after surgery. Detailed information about clinical characteristics, adverse effects and information registered by the physical therapists and dietitians are presented per case in appendix I.

RESULTS

An illustration of coded questions (step 1), possible answers (step 2) and proposed actions (step 3) raised by the experts is presented per vignette in table 1, and the complete overview can be found in appendix I.

The questions raised by the expert physical therapists were all labelled with the "clinical state and circumstances" label of the EBP paradigm. Further inductive coding of the questions regarding exercise (QE) within this label yielded seven different subcategories (short codes in appendix I); acuteness (QE1), etiology (QE2), exercise limitation (QE3), capacity (QE4), safety (QE5), costs and benefits of training (QE6) and exercise prescription (QE7). The majority of the questions raised by expert physical therapists were directed towards exercise capacity (e.g., "Does the ascites influence the patients' tidal volume during exercise?"), safety (e.g., "Is the wound area inflamed?") and etiology (e.g., "What is the reason for the fatigue?") (table 1 and appendix I). The raised questions, with hypothesized answers led to several different proposed actions, which were coded in eleven main categories and thirty-four subcategories. Actions regarding exercise (AE) mostly involved "adaptations to exercise protocol (AE1)", "extensive monitoring of symptoms (AE2)" and "patient education and advice (AE3)" (table 2).

Questions raised by expert dietitians were all labelled with the "clinical state and circumstances" label of the EBP paradigm. Further inductive coding of the questions

regarding diet (QD) within this label yielded five different subcategories (short codes); etiology (QD1), capacity (QD2), dietary limitation (QD3), safety (QD4) and dietary prescription (QD5). The questions mostly concerned etiology (e.g., "What is the cause of the increase in body weight?") and patients' capacity (e.g., "Would it be possible to increase the patients' dietary intake in calories and protein?"). Proposed actions regarding diet (AD) to these questions were coded in five main categories and eight subcategories (table 2) and mostly involved "patient education and advice (AD1)", "extensive monitoring of symptoms (AD2)" and "continuation of intervention according to protocol (AD3)".

Below, a summary of the specific questions asked (Step 1), possible answers formulated (Step 2), and the proposed actions taken (Step 3) for the adverse effects provided by experts, are presented for three prevalent adverse effects, that is ascites, fatigue and wound problems.

Ascites

Expert Physical Therapists
When Amber presented with ascites, the experts tended to raise questions to gather information on Ambers' capacity to exercise, in order to guide the exercise type, intensity and duration. Questions included e.g., "Is Amber able to move and breathe properly?" and "Does the ascites influence her respiration at rest and during exercise?". When symptoms worsened over time, the content of the questions shifted from capacity-related questions towards more cost and benefits of training-related questions (e.g., "How do symptoms affect activities of daily living" and "Is Amber sufficiently fit to travel to the exercise facility?") (appendix I, vignette Amber).

In case of ascites, the experts tended to aim for continuation of exercise according to the protocol, but with enhanced monitoring of symptoms (e.g., respiratory rate, oxygen saturation, pain). They suggested making adaptations to the exercise protocol in case of discomfort, acute increase of abdominal swelling, decreased dietary intake or progressive loss of energy for activities of daily living. Adaptations to the exercise protocol included a change of exercise type, and/or reduction of exercise intensity and duration (appendix I, vignette Amber).

Expert Dietitians
The experts questioned the validity of the measured body weight as a representation of nutritional status (e.g., To what extent does ascites influence her body weight?", "Is the measured body weight valid due to the presence of ascites?", and "Could the weight be used for the assessment of nutritional status?"). They suggested closely monitoring clinical parameters such as Ambers' dietary intake, without using body weight as an indicator of sufficient dietary intake (e.g., using a 24-hour recall or 3-day dietary journal). Another question raised by the experts about this vignette focused on Ambers' ability to increase

dietary intake, during a period of insufficient dietary intake due to a low appetite caused by ascites. They would educate Amber about the importance of preventing malnutrition and its negative consequences during cancer, even if this meant that Amber would have to increase her dietary intake with "unhealthy products". To increase her dietary intake to a sufficient level, the experts would for example recommend to: 1) frequently consume small meals (e.g., six meals a day) instead of larger bigger meals less frequently (e.g., three meals a day), 2) consume her preferred products that are high in calories, instead of products which are usually considered "healthy", or 3) use oral nutritional supplements (appendix I, vignette Amber).

Fatigue

Expert Physical Therapists

For Fatima, fatigue was reported at the start of the intervention, in addition to joint pain and nausea. The presence of mild fatigue did not prompt additional questions at first. However, when Fatima explicitly provided information on the consequences of feeling fatigued at a later time point (e.g., when she indicated needing breaks), the experts were interested in more details about Fatima's capacity ("Does Fatima need breaks during ADL-activities or during the exercise training?"). Consequently, the experts suggested actions depending on the severity of the fatigue in hypothesized scenarios, but, in general, in all scenario's, they would educate Fatima about activity regulation (appendix I, vignette 2).

When Wendy reported to be very fatigued (Visual Analogue Scale 80/100), the experts raised several questions with the goal to determine which of the well-known causes of fatigue were most plausible in Wendy's case. This included emotional distress, disrupted sleep pattern, anemia (low hemoglobin), poor nutritional status, loss of muscle mass, or accelerated heart frequency in rest due to autonomic dysfunction. Not all possible reasons were verbalized by the physical therapists during the initial interviews; some were added after discussion with the experts in a group meeting. The different causes led to different actions, ranging from patient education and advice (e.g., acknowledge and normalize feelings of distress) to referral for further diagnosis or treatment (e.g., consider referral to physician/nurse/psychosocial care provider. In case emotional distress and a disrupted sleep pattern were considered as the likely cause of fatigue, physical therapists required more information on these symptoms to further guide their actions and considered referral to physician, nurse or psychosocial care provider (appendix I vignette 3).

Expert Dietitians

A combination of reported fatigue and previously mentioned fluctuations in dietary intake during different phases of the chemotherapy cycle led to the question whether Amber's dietary intake was sufficient on all days (appendix 1, vignette Amber). The experts stressed that it is important to assess the dietary intake repeatedly, at multiple time points during

one chemotherapy cycle. Furthermore, if her dietary intake fluctuates and is insufficient, Amber should be educated about possible consequences of an insufficient dietary intake (e.g., fatigue) and possibilities to increase dietary intake (appendix 1, Amber).

Wound problems

Expert Physical Therapists
In vignettes 2 and 3, Fatima and Wendy experienced wound problems due to surgery. In case of irritation of the abdominal scar, a stretchy feeling of the scar and/or pain in the abdomen when performing a pull-over exercise occurred, the experts raised questions about the etiology of the complaints, the patients' capacity to exercise and contra-indications. First, experts wanted to know whether there were signs of inflammation at the wound site. If the wound area was inflamed, the subsequent question was whether fever was present, as this is proposed as a contraindication for exercise [10]. If the wound was inflamed, but without fever, the experts proposed a more conservative (i.e., lower intensity) training, avoiding exacerbation of pain symptoms and inflammation of the wound. If the wound was not inflamed, but Fatima or Wendy only experienced a stretchy feeling of the scar, the experts would inform them that it is not harmful to experience tightness of the scar and that exercises to decrease this tightness (without exacerbation of pain) are indicated (e.g., pull-over without weights as homework exercise) (appendix I, both vignettes 2 and 3).

Expert Dietitians
The experts raised the question of whether dietary intake, and especially protein intake was sufficient to support wound healing after an interval debulking. In vignette 3, experts were particularly inquisitive about Wendy's protein intake because she maintained a strictly plant-based diet. They would inform Wendy about the higher protein requirement (of at least 1.5 gram of protein per kg body weight) due to a lower protein turnover of plant-based products. Besides patient education, the experts stress the importance of assessment of dietary intake and monitoring this over time (appendix 1, vignettes 2 and 3).

DISCUSSION

This paper provides an in-depth insight into the clinical reasoning of physical therapists and dietitians on how they would tailor exercise and dietary interventions to the adverse effects of ovarian cancer (treatment) and pre-existing comorbidities, based on clinical vignettes of ovarian cancer patients undergoing chemotherapy. During the process of clinical reasoning, within the EBP paradigm, expert physical therapists and dietitians raised questions about "clinical state and circumstances" but not about "patient preferences" or "evidence".

Within “clinical state and circumstances” the questions were mainly related to “capacity”, “etiology” and “safety”. Proposed actions of the physical therapists mostly consisted of “adaptations to the exercise protocol” and “extensive monitoring of symptoms”, while proposed actions of dietitians mostly consisted of “patient education and advice”, “extensive monitoring of symptoms” and “continuation of intervention according to the protocol”. In the proposed actions, physical therapists mainly suggested making changes in the exercise protocol or advised to perform additional monitoring of the patients, whereas dietitians proposed to counsel and motivate patients to acquire a different dietary intake.

This paper shed light on the relatively inscrutable process of tailoring exercise and dietary interventions, and has consequences for the content of intervention protocols, fidelity assessments and education of health care professionals. The delivery of exercise and dietary programs is not a one-size fits all approach but involves a complex clinical reasoning process. Therefore, protocols should not only describe the intervention content, but also the strategy on how to tailor the intervention to individual adverse effects and pre-existing comorbidities. For fidelity assessment, intervention protocols should specify, a priori, which adaptations are part of the tailored intervention, and which adaptations affect intervention fidelity. A detailed description of intervention fidelity is important to fully appreciate the results, and to replicate results of exercise and dietary interventions [18-21]. Education of healthcare professionals delivering the intervention is important as these professionals need to have good clinical reasoning skills to adequately tailor the intervention. As illustrated in the vignettes, patients are faced with multiple adverse effects during chemotherapy that may vary over time in type or severity. Consequently, the process of clinical reasoning needs to be executed in a recurrent pattern with raising questions (hypothesis-testing), performing actions (treatment) and reassessment. The clinical vignettes from this study can be used in the education of healthcare professionals to improve their clinical reasoning skills. Education on the delivery of more or less one-size fits all approaches of exercise and dietary interventions is rather straightforward, while education on clinical reasoning processes for integrating patient preferences and actions and clinical state and circumstances in treatment of patients is challenging. Improved integration of practicing clinical reasoning in education is warranted due to the importance of this construct to healthcare professionals [23-25].

Some points should be considered while interpreting these study results. There was no real-life interaction with the patient because this study captured clinical reasoning with the think aloud method during retrospective analyses of real-life reports by expert physical therapists and dietitians. Since clinical reasoning by healthcare professionals is generally contextual in nature involving both therapist and patient perspectives [27], real life interaction with the patients might have raised additional questions or alternative judgement and recommendations. While some of the proposed actions to be taken were unambiguous (e.g., refer to a physician, recommend consuming less

salt), other recommendations could vary by context, and therefore resulted in less detailed descriptions of the actions (e.g., monitor symptoms, monitor dietary intake). Knowledge on co-occurrence of symptoms and changes in symptom burden over time are conditional for some actions, which can only be clarified fully through patient interaction. Likewise, the absence of real-life interaction and the treatment within the context of a study protocol may explain our finding that most questions raised were labeled as being related to "clinical state and circumstances" rather than to patient preferences and values. However, in some cases, patient preferences were considered after the actions had been determined (e.g., if the patient needs more protein, they will be asked which kind of products they enjoy most).

Because this study focused on the tailoring of side-effects and pre-existing comorbidities in patients with ovarian cancer, we selected three vignettes based on the occurrence of significant adverse effects during their cancer treatments. Different questions and actions might have arisen from other casuistry and therefore, this paper does not provide a complete overview of all adverse effects and comorbidities and their interaction in patients with ovarian cancer.

With this paper, the inscrutable component of tailoring exercise and dietary interventions delivered during chemotherapy treatment for ovarian cancer is presented. Insight in the complex process of clinical reasoning on how to tailor these interventions provides useful starting points to improve the description of the content of interventions, fidelity assessments and education of health care professionals.

Table 1 - Exemplary questions raised by physical therapists and dietitians per vignette

Vignette 1, Amber (FIGO IIIC serous ovarian cancer, treated with neoadjuvant carboplatin and paclitaxel)
Timepoint 1 - at start of exercise and dietary intervention *Results retrieved from physical therapy examination* Amber visited the physical therapy practice for the first time ten days after the first chemotherapy administration. At that moment Amber felt fatigued and did not perform any sport due to abdominal swelling caused by ascites. Exercise history: running and playing tennis four times a week (until three months prior to the start of chemotherapy). *Results retrieved from dietetic examination* Amber visited the dietitian four days after the first chemotherapy administration. At that moment, the dietary intake was 70% of the caloric and 90% of the protein requirement. This insufficient dietary intake was caused by a decrease in appetite, rated as a 6.5/10. In the past month, ascites had increased, and Amber gained 4.3 kg in body weight. In addition, Amber experienced bowel movement problems.

Physical therapist	**Exemplary questions**	**Consequences**	
	Clinical state and circumstances - acuteness	**Actions – in case of gradual increase (interpretated as a non-acute situation)**	**Label**
	What was the course of the ascites over time?	First adjust to a comfortable posture and if not sufficient, adjust intensity	Adapt certain intervention elements
		Check if the physician is informed and check the medical policy	Inform referrer
		Exercise according to protocol, adjust in case of symptoms (e.g., dyspnea and/or pain)	Intensify monitoring symptoms
	Clinical state and circumstances - capacity	**Actions – in case respiration is hindered at rest**	**Label**
	Does the ascites influence the respiration at rest?	Strive for resistance exercises according to protocol, as long as this does not elicit a feeling of discomfort;	Intensify monitoring of symptoms
		Conduct low-intensity aerobic exercises, avoiding feelings of discomfort, if possible combined with balance exercises;	Adapt certain intervention elements
		Monitor heartbeat, respiratory rate, Borg Scale and oxygen saturation	Intensify monitoring of symptoms
		Advice and inform patient on proper activity levels (e.g., low intensity, being able to talk during exercise, Borg Scale <15).	Advise patient on intensity level
	Clinical state and circumstances - safety	**Actions – in case patient possibly suffer protein deficiencies**	**Label**
	Does the patient suffer protein deficiencies?	Contact the treating dietitian or refer to a dietitian if the patient did not yet receive any dietary counselling. In case of protein deficiencies, the appropriateness of resistance exercises should be reconsidered.	Refer to dietitian

Dietitian	Exemplary questions	Consequences	
	Clinical state - etiology	**Actions – in case ascites masks changes in body weight**	**Label**
	To what extent does ascites influence body weight?	Extra monitoring of other factors that gain insight in nutritional status	Extensive monitoring of parameters
	Clinical state - capacity	**Actions – in case the patient is not able to increase dietary intake**	**Label**
	Would it be possible to increase the patients' dietary intake in calories and protein?	Monitor dietary intake, body weight and body composition over time;	Extensive monitoring of parameters
		Discuss poor dietary intake and impossibility to increase the intake to an adequate level with the treating physician, discuss potential positive effect of the use of anti-sickness medication;	Inform and/or consult physician
		If other options fail to increase dietary intake, consider tube feeding.	Advice to start oral nutrition supplements or enteral feeding

Vignette 2, Fatima (FIGO IIIC serous ovarian cancer, treated with neoadjuvant carboplatin and paclitaxel; hypertension and history of barett-oesophagitis)

Timepoint 3 - a few days after interval debulking

Results retrieved from dietetic examination
The appetite and nutritional intake of Fatima increased a few days after the interval debulking. However, Fatima did not pass any stool yet and due to the interval debulking Fatima had a large abdominal wound.

Dietitian	Exemplary questions	Consequences	
	Clinical state - safety	**Actions**	**Labels**
	Specific consideration due to the surgical wound	Monitor dietary intake, especially protein intake;	Extensive monitoring of parameters
		Inform the patient that a sufficient dietary intake is needed to improve wound healing and recovery after surgery.	Educate patient

Timepoint 4 - 5 weeks after interval debulking

Results retrieved from physical therapy examination

A few days after surgery Fatima was walking in the hospital again. The first exercise training took place four weeks after interval debulking. The training was resumed with exercise testing to adequately determine the training load. Fatima experienced fatigue and irritation of the abdominal scar, therefore pull over was not possible. Besides symptoms related to surgery, Fatima was not able to walk on the treadmill due to foot problems.

Fatima was happy with the exercise training before surgery, as she felt that these exercises contributed to a quick recovery after surgery. Pull over was not possible due to pain and stretchy feeling in her abdomen.

Weight: 80.5 kg

Physical therapist	Exemplary questions	Consequences	
	Clinical state and circumstances - safety	**Actions – in case yes, but no fever**	**Label**
	Is the wound area inflamed?	Be sure to not further irritate the inflamed wound and consequently stagnate the healing process	Extensive monitoring of parameters
		Only offer exercises to such a level that they do not exacerbate pain symptoms, avoid exercises with a direct load on the wound area (e.g., isolated leg and arm exercises).	Educate patient
	Clinical state and circumstances – Exercise limitation	**Actions – in case the patient can perform a pullover without weights**	**Label**
	Is the patient able to perform a pullover without weights?	Advise the pull-over as a homework exercise to preserve shoulder mobility and a sense of movement	Add additional intervention elements

Vignette 3, Wendy (FIGO IC1 clear cell ovarian cancer, treated with adjuvant carboplatin; laparotomic staging 1.5 months prior to start of chemotherapy)

Timepoint 3 - after 13 weeks intervention

Results retrieved from physical therapy examination

Weight: 62.8 kg

Sense of muscle pain on the chest, feels less fit. The patient could not undergo chemotherapy as planned, while the amount of white blood cells was too low. Visual analogue score of 50/100.

Abdominal crunch and lateral pull were not possible. One training later: the visual analogue score rose to 80/100.

Results retrieved from dietetic examination

Current body weight: 63.5 kg

History of body weight: last month 60.5 kg, 58 kg in past 6 months

Nutritional intake meets nutritional recommendations. No nutrition-related complaints. Goal of dietary consultation: stable weight and focus on sufficient protein intake.

Physical therapist	**Exemplary questions**	**Consequences**	
	Clinical state and circumstances - etiology	**Actions - in case patient uses neupogen for low amount of white blood cells and experience a continuous feeling of muscle pain**	**Label**
	Does the patient experience pain on her chest at rest or during effort? Is the pain continuously present? Did the patient use medication to treat the low amount of white blood cells?	Adjust the specific strength training to a lower intensity where comfortable movement is possible	Adapt certain intervention elements
		Standard analgesics can be taken if necessary. No adjustment to exercise therapy needed	Advice on analgesics
		Advise the patient to contact a physician if symptoms worsen.	Advise patient to contact physician
	Clinical state and circumstances - capacity	**Actions - in case of increased heart rate in rest, possibly autonomic dysfunction; sinus tachycardia in rest or underlying arrhythmia**	**Label**
	What is the heart rate in rest?	Monitor heart rate at every exercise session during activity and rest; Heart rate in steady state exercise should remain stable. Use Borg score to adjust training intensity;	Intensify monitoring of symptoms
		Explain to patients that an increased heart rate without symptoms can be a result of chemotherapy.	Educate patient
		Monitor symptoms: in case of persistent co-existing symptoms (dyspnea, anxiety, fatigue): terminate exercise and refer to physician.	Contraindication for exercise Refer to physician
Dietitian	**Exemplary questions**	**Consequences**	
	Clinical state and circumstances - etiology	**Actions - in case ascites is the reason for increase in body weight**	**Label**
	What is the cause of the increase in body weight?	Monitor ascites by monitoring body weight, symptoms that indicate presence of ascites;	Monitor clinical parameters
		Keep in mind that ascites masks a decrease in body weight. Therefore, it is important to examine dietary intake.	

Table 2 - Categories and codes identified for proposed actions by physical therapists and dietitians

Physical therapists
Adaptations to exercise protocol (AE1)
Adapt certain intervention elements (AE1.1)
Consider home-based tailored exercise (AE1.2)
Add additional intervention elements (AE1.3)
Avoid certain exercises (AE1.4)
Strive for feeling of success (AE1.5)
Extensive monitoring of symptoms (AE2)
Intensify monitoring of symptoms (AE2.1)
Adjust exercise monitoring (AE2.2)
Adjust to symptom guided intensity (AE2.3)
Patient education and advice (AE3)
Inform patient to normalize feelings or symptoms (AE3.1)
Advice on hydration (AE3.2)
Advice on nutrition (AE3.3)
Discuss/inform on activity regulation (AE3.4)
Advice patient on intensity level (AE3.5)
Advise patient to contact physician (AE3.6)
Advice on analgesics (AE3.7)
Coach the patient on breathing technique (AE3.8)
Educate patient (AE3.9)
Refer for further diagnosis or treatment (AE4)
Refer to physician (AE4.1)
Refer to dietitian (AE4.2)
Refer to occupational therapist (AE4.3)
Refer to other health care professional (AE4.4)
Examine symptoms/exercise effects (AE5)
Inquire about effects of exercise (AE5.1)
Inquire about symptoms (AE5.2)
Inquire about activities of daily life (AE5.3)
Examine capacity (AE5.4)
Continuation of training according to protocol (AE6)
Consultation physician (AE7)
Inform refer (AE7.1)
Consult physician (AE7.2)
Discontinue exercise (AE8)
Interruption of exercise intervention (AE8.1)
Contraindication for exercise (AE8.2)
Discuss cost/benefits of training (AE9)
Application of extra hygiene of the environment (AE10)
Adaptation of posture (AE11)

Table 2 - Categories and codes identified for proposed actions by physical therapists and dietitians *(continued)*

Dietitians
Patient education and advice (AD1) Educate patient (AD1.1) Additional counseling and coaching of patient (AD1.2) Advice to discontinue oral nutrition supplements (AD1.3) Advice to start oral nutrition supplements or enteral feeding (AD1.4)
Extensive monitoring of parameters (AD2)
Continuation of intervention according to protocol (AD3)
Inform and/or consult physician (AD4)
Inquire on patients' motivation (AD5)

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APPENDIX I

Vignette 1 - Patient characteristics and side effects of the medical treatment

Vignette 1, Amber				
Age	Diagnosis	Chemotherapy	Medical history	Anthropometric measurements
55-60 years	FIGO IIIC serous ovarian cancer	Neoadjuvant carboplatin and paclitaxel	None	BMI: 23.1 kg/m^2 Fat free mass index: 14.2 kg/m^2 Fat mass index: 8.9 kg/m^2

Timepoint 1 - at start of exercise and dietary intervention

Results retrieved from physical therapy examination

Amber visited the physical therapy practice for the first time ten days after the first chemotherapy administration. She told the physical therapist that she felt fatigued and that her abdominal swelling due to ascites prevented her from exercising in the past few months.

Exercise history: running and playing tennis four times per week (until three months before starting chemotherapy)

Results retrieved from dietetic examination

Amber visited the dietitian four days after the first chemotherapy administration. Her dietary intake was 70% of her calorie need and 90% of her protein need. This decrease in dietary intake was caused by a decreased appetite (rated 6.5/10). Amber reported to gained 4.3 kg in the past month, the ascites had increased. Amber complained about experiencing problems with her bowel movement.

	Step 1: Questions raised	Step 2: Possible answers	Step 3: Actions to be taken	
Code	Exercise related			Code
QE1	What was the course of the ascites over time?	Acute increase of abdominal swelling.	Refer to a physician.	AE4.1
		Gradual increase of abdominal swelling.	• Check if the physician is informed and check the medical policy; • Exercise according to protocol, adjust in case of symptoms (e.g., dyspnea and/or pain); • First adjust to a comfortable posture and if not sufficient, adjust intensity.	AE7.1 AE2.1 AE1.1
QE3	What is the waist circumference? Is the patient able to move properly?	Certain exercises (like cycling and crunches) cause pain and abdominal swelling prevents the patient from doing these exercises.	• Adjust posture (e.g., adjust height of saddle and/or steer of cycle ergometer); • Adjust type of exercise (e.g., cross-trainer as alternative for cycle ergometer).	AE11 AE1.1
QE4	Is the patient able to breathe properly during resistance exercises?	The patient fixes her breath during the exercise which increases intra-abdominal pressure.	• First, coach the patient to exhale during the resistance exercises; • If the patient is not able to properly exhale during the exercise, reduce training load and increase the number of repetitions.	AE3.8 AE1.1
		The patient is able to breathe properly during the resistance exercises.	• Strive for resistance exercises according to protocol, without a feeling of discomfort.	AE2.1

QE4	Does the ascites influence the respiration at rest?	No influence on tidal volume at rest.	• Training according to the Borg Scale (<15).	AE6
		Proper respiration is hindered at rest.	• Strive for resistance exercises according to protocol, without a feeling of discomfort; • Conduct low-intensity aerobic exercises, if possible without a feeling of discomfort, if possible combined with balance exercises; • Monitor heartbeat, respiratory rate, Borg Scale and oxygen saturation; • Advice and inform patient on proper activity levels (e.g., low intensity, being able to talk during exercise, Borg Scale <15).	AE2.1 AE1.1 AE2.1 AE3.5
QE4	Does de ascites influence the patients' tidal volume during exercise?	Yes, monitored with: Disproportional increase of respiratory rate; Disproportional dyspnea; Decrease of oxygen saturation; Borg scale > 15.	• Identify whether low levels of intensity or interval training can be an appropriate alternative to reduce symptoms; • If not, terminate exercise session and refer to a physician.	AE1.1 AE8.2
		Tidal volume does not change during exercise.	• Training according to Borg Scale (<15).	AE6
QE5	Does the patient suffer protein deficiencies?	Possibly, while she does not eat a lot of food with proteins.	• Contact patients' dietitian or refer to a dietitian. In case of protein deficiencies, the effectiveness of resistance exercises should be considered.	AE4.2

Code	Nutrition related			Code
QD1	To what extent does ascites influence body weight?	Ascites masks changes in body weight and body composition.	• It is important to evaluate a patient's dietary intake using for example a 24-hour recall or 3-day dietary journal and not solely on body weight over time. NB: It is estimated that ascites is present in approximately 60% of patients with ovarian cancer [1]. It is important to keep in mind that ascites masks changes in body weight and body composition. A rapid increase in body weight is likely due to an increase in ascites. However, an increase in waist circumference and a stable body weight might indicate an increase in ascites and decrease in body weight. Body composition measurements using bioelectrical impedance vector analysis overestimate fat free mass and underestimate fat mass due to ascites	AD2.1
QD2	Would it be possible to increase the patients' dietary intake in calories and protein?	Yes, the patient is willing and able to change her dietary intake.	• Easy applicable dietary recommendations to prevent early satiety and/or nausea, e.g.: frequent consumption of small portions with products high in calories throughout the day, consumption of high calorie liquid products as liquid products are often less satiating, consider use of oral nutrition supplements.	AD1.2
		No, there is no opportunity to increase dietary intake as the patient has a poor appetite.	• Monitor dietary intake, body weight and body composition over time; • Discuss poor dietary intake and impossibility to increase the intake to an adequate level with the treating physician, discuss potential positive effect of the use of anti-sickness medication; • If other options fail to increase dietary intake, consider tube feeding.	AD2.1 AD4 AD1.4

QD3	What bowel movement related problems does the patient experience?	Constipation; Diarrhea; Bowel obstruction.	• Easy applicable dietary recommendations to improve bowel movement, e.g.: sufficient intake of dietary fiber, sufficient fluid intake, frequent consumption of small portions throughout the day; • Discuss bowel movement-related problems such as constipation or diarrhea and potential solutions with the treating physician (e.g., paracentesis, laxatives); • In case of bowel obstruction discuss with the treating physician the severity of the bowel obstruction and whether tube feeding or parenteral feeding is indicated.	AD1.2 AD4 AD4

Timepoint 2 - 1-2 weeks after start of training

Results retrieved from physical therapy examination

Amber reported to be feeling tired and that her waist circumference had increased which resulted in difficulties while exercising.

Step 1: Questions raised		Step 2: Probable answers	Step 3: Actions to be taken	
Code	Exercise related			Code
QE4	Which exercises can be performed without discomfort and dyspnea? Why can the exercises not be performed adequately? Is the load too heavy or is the posture uncomfortable? Is there sufficient possibility to catch her breath during exercises?	All exercises can be performed without dyspnea or discomfort.	• Aim for training according to protocol. With extra monitoring of respiratory rate, oxygen saturation, and heart rate.	AE2.1
		The patient experiences discomfort and dyspnea to some extent during resistance exercises.	Monitor how the patient responds to exercise; • Adjust or replace exercises in case of discomfort. First to a comfortable posture and if not sufficient, reduce the number of repetitions; • If a comfortable posture is regained, only apply small incremental steps in exercise intensity.	AE2.1 AE1.1
		The patient experiences discomfort and dyspnea to some extent during aerobic exercises.	Monitor how patients respond to exercise: • Monitoring HR, Borg Scale and respiratory rate; • Adjust or replace exercises in case of discomfort; First to a comfortable posture and if not sufficient, adjust intensity (before duration).	AE2.1 AE1.1

QE6	Are there objective signs that the patient has gained physical fitness since the start of the exercise training? Or does it require more effort than it gains results?	The patient has a disproportionate recovery time after activities and/or exercises. The patient does not feel the gain of the exercise program and fatigue has increased.	• Discuss with the treating physician if ascites can be expected to reduce on the short term; • Discuss effort and rewards of exercising at physical therapy practice and determine if exercise sessions should be pursued; if not: • Consider tailored home-based exercises and recommendations; • Advise the patient to seek contact if exercise sessions can be resumed. • Gain insight into activities of daily living and advice on intensity and frequency of activities. Additionally, an occupational therapist can be asked for consultation to advise on detailed activity regulation.	AE7.2 AE9 AE1.2 AE3.4 AE4.3
QE6	How do symptoms affect activities of daily living? Is the patient able to perform minimal activities of daily living? Are there signals that the exercise sessions make the patient functionally dependent for activities of daily living? Observation: has fitness increased over time? Has the patient gained functional independence in activities of daily living?	The level of independence to perform activities of daily living stays the same.	• Continue training according to protocol.	AE6
		The exercise sessions are costing the patient too much energy, as a consequence the patient becomes more functionally dependent on activities of daily living.	• Discuss with treating physician if ascites can be expected to reduce in the short term; • Discuss with the patient effort and rewards of exercising at physical therapy practice and determine if exercise sessions should be pursued; • Gain insight into activities of daily living and advise the patient on intensity and frequency of activities. Additionally, an occupational therapist can be asked for consultation to advise on detailed activity regulation; • Advise the patient to seek contact if exercise sessions can be resumed. Meanwhile, consider tailored home-based exercises and recommendations	AE7.2 AE9 AE4.3 AE1.2

QE6	Is the patient sufficiently fit to travel to the exercise facility?	Patient is independent in activities of daily living but is very fatigued or nauseous.	• Get an impression of the patients' response to exercise, if adequate: • Resume exercise session, but start with lower exercise intensity, but conserve exercise routine & skills and a sense of self-competence.	AE5.4 AE1.1
		Patient is independent in activities of daily living and experiences low symptom burden.	• Continue training according to protocol.	AE6

Timepoint 3 - week 7 of the intervention

Results retrieved from dietetic examination

Amber underwent paracentesis and lost more than six liters of ascites. As compared to the body weight measured at baseline, Amber lost five kg after paracentesis. Amber told the dietitian she felt better after paracentesis, leading to an increased appetite rated 8/10) feeling less satiated. Her dietary intake was ≥100% of her need. However, the first couple of days after a chemotherapy administration, Amber felt tired and her appetite decreased (rated 4 to 7 on a scale from 1-10) and so did her dietary intake (35-100% of her need).

Step 1: Questions raised		Step 2: Probable answers	Step 3: Actions to be taken	
Code	Nutrition related			Code
QD1	What is the body weight after paracentesis as compared to usual body weight (i.e., before ovarian cancer)?	Body weight has decreased.	• Increase dietary intake; • Monitor body weight and presence (of symptoms) of ascites; • Monitor body composition.	AD1.2 AD2.1 AD2.1
		Body weight is stable.	• Continue current dietary recommendations for patients with cancer; • Monitor body weight and presence (of symptoms) of ascites; • Monitor body composition.	AD3 AD2.1 AD2.1
QD2	Is the dietary intake sufficient? For example, use a 24-hour recall or 3-day dietary journal filled in by the patient to examine the nutritional intake.	Yes, dietary intake is sufficient.	• Continue current dietary recommendations for patients with cancer.	AD3
		No, in the days after chemotherapy dietary intake is insufficient.	• Dietary recommendations: frequent consumption of small portions with products high in calories throughout the day, consumption of high calorie liquid products as liquid products are often less satiating, consider use of oral nutrition supplements; • In case of nausea: discuss with the treating physician if any anti-sickness medication could be of use.	AD1.2 AD4

Timepoint 4 - week 12 of the intervention

Results retrieved from physical therapy examination

Amber is 6 weeks after her surgery and does not feel well. She reported to feel very fatigued and chemotherapy administration was postponed for one week.

NB: In the 2 weeks before surgery she was able to run for 10km

Step 1: Questions raised		Step 2: Probable answers	Step 3: Actions to be taken	
Code	Exercise related			Code
QE5	What are the blood values? Hemoglobin levels?	Anaemia (low hemoglobin)	• Lower exercise intensity based on symptoms (dyspnea and fatigue without performing strenuous activities, dizziness, headache, palpitations, perspiration, low body temperature). NB: extreme anemia (Hemoglobin <6) is a relative contra-indication for exercise. Consultation with physician is necessary.	AE2.1
		Trombopenia (low platelet count)	• Discuss reaction to previous exercise session; • Avoid high impact; • Avoid point pressure when using equipment; • Avoid strong elevation of blood pressure (high intensity exercise, Valsalva maneuver); • Hydrate during training session; • Monitor signs of bleeding. NB: Platelet count <20,000/µl is a contraindication for exercise.	AE5.4 AE1.4 AE1.4 AE1.4 AE3.2 AE2.1

QE7	Is the patient overtrained?	No, the previous exercises sessions and the days after these sessions went well.	• If the chemo is postponed, it is wise to start exercising at a low intensity and gradually increase if exercises are going well.	AE1.1
		Yes, she might be overtrained, while she gets more tired after every exercise session.	• Exercise at low intensity and properly monitor symptoms during training; • In case patient is still extra fatigued the day of the exercise session and the day after, discuss with the patient effort and rewards of exercising at physical therapy practice and determine if exercise sessions should be pursued; • Gain insight into activities of daily living and advise the patient on intensity and frequency of activities. Additionally, an occupational therapist can be asked for consultation to advise on detailed activity regulation; • Advise the patient to seek contact if exercise sessions can be resumed. Meanwhile, consider tailored home-based exercises and recommendations. In case patient reports back to be still extra fatigued after exercise session, consider.	AE1.1 AE9 AE4.3 AE1.2

Timepoint 5 - last chemotherapy gift - a few weeks after chemotherapy

Results retrieved from dietetic examination

Amber said that she felt fatigued, and that recovering from a chemotherapy administration took longer as compared to previous chemotherapy administrations. Amber filled out a food diary with the following outcomes; sufficient calorie and protein intake, many calories are derived from products high in fat, she consumed less carbohydrates than before, and her salt intake is higher than recommended. Anthropometric measurements:
Body weight 57.3 kg
Lean mass index: 14.7 kg/m2
Fat mass index: 7.4 kg/m2

	Step 1: Questions raised	Step 2: Probable answers	Step 3: Actions to be taken	
Code	Nutrition related			Code
QD2	Is dietary intake sufficient during the entire chemotherapy cycle? Specifically ask for nutrition-related symptoms (e.g., different taste perception or nausea) and dietary intake at different time points during a chemotherapy cycle (e.g., directly after chemotherapy, first, second or third week after chemotherapy). NB: In the food diary the dietary intake is sufficient. However, due to possible fluctuations in appetite and dietary intake during a chemotherapy cycle, it might be possible that the dietary intake is not always sufficient.	Yes, dietary intake is sufficient.	• Continue current dietary recommendations for patients with cancer.	AD3
		No, dietary intake is not sufficient due to nutrition-related problems such as a bad taste as a consequence of chemotherapy.	• Inform the patient that the bad taste is a common consequence of chemotherapy and cannot be solved with medication; • Advice the patient to try other food which they usually do not consume or did not prefer before their cancer diagnosis. Let them experience novel foods and flavors, to help them increase dietary intake; • Inform the patient that symptoms such as fatigue and loss of muscle mass could be caused by a reduced dietary intake, especially reduced protein intake, and that therefore it is important to increase dietary intake to a sufficient level.	AD1.1 AD1.2 AD1.1
		No, dietary intake is not sufficient as the protein intake is not sufficient and not equally distributed throughout the day.	• Recommend a diet rich in protein and explain it is important for an optimal protein synthesis to distribute the protein intake over 3 meals a day; • Inform the patient that symptoms such as fatigue and loss of muscle mass that fatigue and loss of muscle mass could be caused by a reduced dietary intake, especially reduced protein intake, and that therefore it is important to increase dietary intake to a sufficient level.	AD1.2 AD1.1

QD2	When is the right time to inform the patient about the WCRF guidelines?	Not now, as calorie and protein intake are still insufficient and consumed products which are high in fat are needed to reach a sufficient dietary intake.	• Accept that the patient consumes products which are considered "less healthy" because they are high in fat, as long as the patient needs these calories to achieve a sufficient dietary intake (i.e., dietary calorie intake meets the caloric needs of the patient); • Inform the patient that, during medical treatment for cancer, it is more important to consume enough calories and protein than to focus on the WCRF recommendations. This is because prevention of malnutrition during medical treatment for cancer is important and the WCRF guidelines focus on health outcomes in the long run.	AD3 AD1.1
		Now, as the patient can probably consume a sufficient amount of calories and protein without products high in fat and body weight is stable.	• Stop usage of oral nutrition supplements; • Decrease amount of dietary fat to recommended amount; • Explain other WCRF recommendations (e.g., do not consume more than 500 grams of red meat a week, try to avoid adding salt while cooking and products rich in salt (e.g., pizza, ready-to-eat meals).	AD1.4 AD1.2 AD1.1
QD1	Is the measured body weight reliable?	Possibly not, as a different scale to measure body weight and/or the presence of ascites could affect measured body weight.	• Monitor body weight over time by using the same, calibrated scale. NB: It is important to keep in mind that ascites masks changes in body weight and body composition and to evaluate a patients' dietary intake using for example a 24-hour recall or 3-day dietary journal and not solely on body weight over time.	AD3

Vignette 2 - Patient characteristics and side effects of the medical treatment

Vignette 2, Fatima				
Age	Diagnosis	Chemotherapy	Relevant medical history	Anthropometric measurements
55-60	Serous ovarian cancer FIGO IIIC	Neoadjuvant carboplatin and paclitaxel	Hypertension, history of Barett-oesophagitis, surgical removal cartilage malleolus	BMI: 29 kg/m^2 Fat free mass index: 17.8 kg/m^2 Fat mass index:11.2 kg/m^2

Timepoint 1 – at the start of the intervention

Information retrieved from physical therapy examination

Fatima reported to feel fatigued and she experienced pain in her joint. In addition, she felt slightly nauseous for which she uses medication.

Exercise history: Fitness.

1RM prior to start of physical therapy intervention:

- Upper Back 46.5kg
- Leg press 100 kg
- Bench press 14.4 kg
- Abd Crunch too easy with weights
- Pull Over 11.5 kg
- Lunge 13.9 kg

Results retrieved from dietetic examination

At the time of diagnosis, Fatima was referred to the dietitian by her treating physician due to risk of malnutrition. This was before the official start of the PADOVA exercise and dietary intervention. After consultation with the dietitian, Fatima started with an energy- and protein-enriched diet, including oral nutritional supplements (sip feeds). When Fatima received her first counseling session as part of the PADOVA study, which was a few weeks after diagnosis, her appetite was good, but she experienced an aversion for the consumption of dinner. Fatima replaced her dinner with soup.

	Step 1: Questions raised	Step 2: Probable answers	Step 3: Actions to be taken	
Code	Exercise related			Code
QE7	Does the patient use medication for hypertension?	Yes, the patient uses beta blockers.	• Heart rate cannot be used as a measure for exercise intensity; • Aerobic training according to protocol preferably with use of the intended Wattage from Steep Ramp Test and with use of the Borg-scale.	AE2.2
		No, the patient does not use medication.	• Training according to protocol.	AE6
QE4	How severe is the joint pain? Are daily activities hampered by joint pain? What is the nature of joint pain? Do the symptoms increase?	Much joint pain with an unclear nature.	Conservative start: • Cycle unloaded relatively long for a proper warming-up; • Start resistance training symptom guided with a tolerable load; • If the patient has energy left: start aerobic training, on the intended wattage*, but shorter in duration; • Strive for a feeling of success. * If wattage is not available, try to estimate intensity by using the Borg Scale	AE1.1 AE2.3 AE1.1 AE1.5
		Moderate joint pain with an unclear nature.	• Strive for training according to protocol but adjust weights and wattage if necessary (e.g., increase of pain or based on HF-zone and Borg Scale).	AE2.1
QE4	Does the patient suffer from nausea during the exercise training?	Nausea does not occur during the exercise draining.	• Training according to protocol.	AE6
		The patient suffers from nausea during training or symptoms worsen during exercise training.	• Start exercise program with a symptom guided intensity; • Start with resistance exercises and consider aborting training if the nausea increases.	AE2.3 AE2.1

Code	Nutrition related			Code
QD2	Is the dietary intake sufficient? For example, use a 24-hour recall or 3-day dietary journal filled in by the patient to examine the nutritional intake.	Yes, dietary intake is sufficient.	• Continue current dietary recommendations for patients with cancer.	AD3
		No, dietary intake is not sufficient.	• Be aware of a decreased dietary intake due to a poor appetite in the first few days after a chemotherapy cycle; assess appetite, symptoms of nausea or vomiting and dietary intake during various moments of chemotherapy treatment; • Advice the patient during days of a poor appetite and insufficient dietary intake to focus on small, frequent meals with products high in energy and if necessary, oral nutrition supplements (I.e., sip feeds). On days when the patient experiences an improved appetite and dietary intake oral nutrition supplements might not be necessary.	AD2.1 AD1.2
QD2	Does the patient (still) need additional oral nutritional supplements?	No, dietary intake is sufficient without oral nutritional supplements.	• Stop usage of oral nutritional supplements; • Provide recommendations to the patient on how to enrich calorie and protein intake with daily products if necessary.	AD1.3 AD1.2
		Yes, due to aversion for dinner and the high protein requirement the patient needs additional oral nutritional supplements to achieve a sufficient calorie and protein intake.	• Provide recommendations to the patient on how to enrich calorie and protein intake with regular products; • When energy and protein requirements cannot be met by a calorie- and protein-enriched diet then the use of oral nutrition supplements (I.e., sip feeds) are necessary. Preferably choose a sip feed which is high in protein, as the patients' protein requirement is high.	AD1.2 AD1.4
QD5	Does the patient need to adjust her dietary intake due to the frequent exercise training?	Yes.	• Inform the patient it is important to consume a sufficient amount of calories and protein during the day and to consume a snack or meal high in protein directly after exercise training.	AD1.2

QD3	Does the patient suffer from Barrett esophagitis?	No.	• No further action needed.	AD3
		Yes.	Provide information about Barrett esophagitis and nutrition-related recommendations, e.g.: • Stay upright seated after a meal consumption; • Try to avoid tight clothing, especially tight clothing around the waist.	AD1.1

Timepoint 2 - after 7 weeks of exercise

Results retrieved from physical therapy examination

Fatima experienced symptoms of fatigue, she indicated that she really needed her breaks, otherwise she cannot finish what she is doing. Other than feeling fatigued, Fatima reported to be “not feeling too bad”.

During the exercises, Fatima reported that the lunges are too heavy on her left knee, an old injury plays on. The physical therapist replaced the lunges with squats on a bosu ball. All 1 RM tests have shown improvements since the start of the exercise intervention.

Body weight: 80 kg

Step 1: Questions raised		Step 2: Probable answers	Step 3: Actions to be taken	
Code	Exercise related			Code
QE4	Does the patient need breaks during ADL-activities or during the exercise training?	Only during resistance exercises.	• The patient should be informed that it is appropriate to have breaks during resistance training; • Inquire about the course of the fatigue after the previous exercise training. Query if and how quickly fatigue reduced after exercise.	AE3.4 AE5.1
		Both during resistance and aerobic training.	• Adjust training load during aerobic training, monitor Borg Scale. Aim for an uninterrupted aerobic work-out; • The patient should be informed that it’s appropriate to have breaks during resistance exercises; • Inquire about the course of the fatigue after the previous exercise training, did it recover and how quickly.	AE1.1 AE3.4 AE5.1
		During ADL.	• Inquire about the number of breaks she needs, the course of the fatigue during the day and if this exacerbates after exercise training; • Educate the patient on activity regulation and the importance of alternating activity and rest; • Adjust protocol if patient suffers significantly from a lower energy level after training.	AE5.4 AE3.4 AE1.1

QE3	Does the patient experience pain in the left knee during other exercises besides lunges?	The patient cannot perform a leg press or leg extension without an increase in pain.	• Avoid exercise testing of the left knee; • Strive for functional exercises which do not cause an increase of pain.	AE1.4 AE1.1

Timepoint 3 - a few days after interval debulking

Results retrieved from dietetic examination

As a consequence of the interval debulking, Fatima had a large abdominal wound. A few days after interval debulking the appetite of Fatima and her nutritional intake increased. However, Fatima did not pass any stool yet.

Step 1: Questions raised		Step 2: Probable answers	Step 3: Actions to be taken	
Code	Nutrition related			Code
QD4	Is the patient at risk of constipation after surgery?	It is common that after surgery first stool passage might take a few days.	• Dietary recommendations to influence bowel movement are e.g., consumption of a diet rich in dietary fiber, sufficient fluid intake; • When the patient experiences discomfort because of constipation then discuss bowel movement problems and possible solutions with the treating physician.	AD1.2 AD4
QD4	Is the patient at risk of ileus after surgery?	Paralytic ileus might occur after surgery.	• When the patient suffers from a paralytic ileus then discuss possible feeding options (e.g., parental nutrition)	AD4
QD2	Does the patients' appetite and dietary intake increase in the days after surgery?	Yes.	• Continue monitoring appetite (e.g., with visual analogue scale) and dietary intake.	AD2.1
		No.	• Monitor appetite (e.g., with visual analogue scale) and dietary intake; • When appetite and dietary intake do not increase in a few days after surgery and dietary intake is not sufficient then consider supplementation of oral nutrition supplements or enteral feeding.	AD2.1 AD1.4

QD4	NB: Specific consideration due to the surgical wound		• Monitor dietary intake, especially protein intake; • Inform the patient that a sufficient dietary intake is needed to improve wound healing and recovery after surgery.	AD2.1 AD1.1

Timepoint 4 - 5 weeks after interval debulking

Results retrieved from physical therapy examination

At this timepoint, surgery was four weeks ago. Fatima told the physical therapist that she was able to walk again a few days after surgery. She thought that participating in the exercise intervention prior to surgery helped her to recover quickly after surgery.

Fatima resumed training 5 weeks after interval debulking. The training was resumed with exercise testing to adequately determine the training load. Fatima reported to experience fatigue and irritation of the abdominal wound/scar.

Weight: 80.5 kg

1RM:

- Upper Back 80 kg
- Bench Press 20.7 kg
- Leg Press 126.7 kg
- Leg extension 60 kg
- Leg curl 66.7 kg
- Pull over was not possible due to pain and stretchy feeling in her abdomen. Fatima was not able to walk on the treadmill because of symptoms of her feet.

Step 1: Questions raised		Step 2: Probable answers	Step 3: Actions to be taken	
Code	Exercise related			Code
QE2	What is the origin of the feet symptoms?	Neuropathy.	• Strive for training according to protocol. • Monitor symptoms of the feet.	AE6 AE2.1
		Not clear, possibly hand-feet syndrome.	• Redness and swelling would be a reason to avoid pressure and friction; • Use other equipment, which can be used without an increase of pain, like a hand bike or row ergometer; • Monitor symptoms of the feet.	AE1.4 AE1.1 AE2.1

QE4	To what extent does she suffer from pain in her abdomen and related symptoms?	Substantial pain symptoms.	Conservative training: • Reduce exercise intensity; • Only aerobic training to avoid strain on abdomen; • Inquire about the course of the pain after the previous exercise training, did it recover and how quickly?	 AE1.1 AE1.4 AE5.1
QE5	Is the wound area inflamed?	If yes, but no fever (<38,5°C).	• Be sure to not further irritate the inflamed wound and consequently stagnate the healing process; • Only offer exercises to such a level that they do not exacerbate pain symptoms, avoid exercises with a direct load on the wound area (e.g.: isolated leg and arm exercises).	AE2.1 AE1.1
		If yes and fever (>38,5°C).	• Contraindication for exercise, refer to a physician.	AE4.1
		If no, patient only feels a tight feeling standing up straight.	• Inform the patient that a stretchy feeling is acceptable and sometimes necessary to improve scar mobility; • Start with gentle core exercises (e.g., superman; bridge).	AE3.1 AE1.1
QE3	Is the patient able to perform a pull-over without weights	If yes,	• Advise the pull-over as a homework exercise to preserve shoulder mobility and a sense of movement; and if possible, add a light weight.	AE1.1
		If no,	• Do not start with homework exercises.	AE1.4

Vignette 3 - Patient characteristics and side effects of the medical treatment

Vignette 3, Wendy				
Age	Diagnosis	Chemotherapy	Medical history	Anthropometric measurements
35-40	FIGO IC1 clear cell ovarian cancer	Carboplatin, adjuvant	Laparoscopic adnex extirpation (2.5 months before start chemo), laparotomic staging (1.5 months before start chemo)	BMI: 18.9 kg/m^2 Fat free mass index: 13.5 kg/m^2 Fat mass index: 5.6 kg/m^2

Timepoint 1 – at the start of the intervention

Results retrieved from physical therapy examination

Wendy experienced a subcutaneous inflammation of the scar after surgery. Therefore, Wendy is not allowed to put pressure on her abdomen. Due to the wound inflammation, Wendy experienced pain (rated 4/10) and felt fatigued (rated 8/10).

Exercise history: 2-3 times per week, +/- 10 km running and two times per week yoga.

Results IRM and steep ramp test:

- 1RM: Leg Press: 66 kg
- Vertical row: 18 kg
- Bench press: 12 kg
- Lateral pull down: 12kg
  Steep ramp (MSEC): 250 watts

Results retrieved from dietetic examination

Directly after diagnosis Wendy radically removed meat/fish/bread out of her dietary intake. However, due to this change in dietary intake Wendy felt weak and reintroduced meat/fish and some carbohydrates. Wendy used to consume all kinds of dietary supplements, but at start of chemotherapy she only continued consumption of magnesium tablets. Currently, Wendy consumed a sufficient amount of calories and protein as she tried to consume all nutrients through regular food products.

Step 1: Questions raised		Step 2: Probable answers	Step 3: Actions to be taken	
Code	Exercise related			Code
QE2	What is the reason the patient cannot put pressure on her abdomen?	Prescription of the physician due to inflammation of the scar.	• Follow the instructions of the physician, avoid strength exercises of the abdomen or pressure on the abdomen until signs of inflammation disappear.	AE1.1 AE2.1
		Insecurity at the side of the patient.	• Explain that exercise can be safely performed by using a slow increment of exercises and monitoring symptoms.	AE3.1

QE5	Does the patient have fever due to the inflamed wound?	Yes (>38,5°C).	• Contraindication for exercise; • Refer to a physician.	AE8.2 AE4.1
		No (<38,5°C).	• Training as much according to protocol, but with adjustment of abdominal exercise to prevent exacerbation of wound problems; • Monitor pain symptoms (rated ≤4/10 is acceptable)	AE1.1 AE2.1
Code	Nutrition related			Code
QD1	Is the measured body composition reliable? Consider possible reasons for deviations in body composition results such as ascites, very lean body type, deviation in hydration status or errors in execution of body composition measurement.	Probably valid as the tumor is removed during surgery and ascites is not present.	• Continue monitoring body composition.	AD2.1
QD4	Specific consideration due to the surgical wound		• Monitor dietary intake, especially protein intake; • Inform the patient that a sufficient dietary intake is needed to improve wound healing and recovery after surgery.	AD2.1 AD1.1
QD5	Is the protein recommendation of 1.2-1.5 gram of protein per kg body weight sufficient?	Probably not due to the plant-based diet.	• Inform the patient that a higher protein intake (of at least 1.5 gram of protein per kg body weight a day) is recommended due to a lower protein turnover of plant-based products.	AD1.1

QD1	Why did the patient change her diet after diagnosis?	Personal reasons for lifestyle changes after diagnosis, e.g., to influence outcome of current disease, prevention of other diseases.	• Ask patient motivation for lifestyle changes; • Inform the patient about evidence-based dietary recommendations for healthy nutrition and use of supplements; • When a patient prefers or wants to avoid certain types of food, for example a plant-based dietary intake, then provide the patient with tips and tricks to meet nutrient requirements with respect towards nutritional preferences; • Explain to the patient that it is important to maintain a stable body weight during medical treatment (even when this weight is labelled as overweight) because due to metabolic processes that occur in cancer, weight loss is associated with relatively more muscle loss as compared to weight loss in healthy humans. High loss of muscle mass is associated with multiple negative consequences in patients with cancer, e.g., loss of physical functioning, higher risk of post-operative complications a poorer survival.	AD5 AD1.1 AD1.2 AD1.1

Timepoint 2 - after 6 weeks intervention

Results retrieved from physical therapy examination

Wendy is still not able to put pressure on her abdomen, as a consequence the pull over exercise is not possible. She experienced feelings of fatigue (rated 5/10) and muscle soreness in her legs.

Step 1: Questions raised		Step 2: Probable answers	Step 3: Actions to be taken	
Code	Exercise related			Code
QE4	Why isn't the patient performing abdominal muscle exercises?	Wound still not fully recovered.	• Alternative exercises, such as lunges, balance exercises; • Discuss patients' activities at home and advice in case patient needs to be more cautious.	AE1.1 AE3.4
QE4	To what extent does the patient have myalgia?	Extreme myalgia after exercise training.	• Perform strength training of the arms and aerobic training, but avoid strength training of the legs; • Consider low load high frequency exercises of the legs instead of high low load frequency.	AE1.4 AE1.1

QE2	What is the reason for the fatigue?	Emotional distress.	• Acknowledge and normalize feelings of distress; • Explore disruption of sleep pattern due to distress; • Consider referral to physician/nurse/psychosocial care provider.	AE3.1 AE5.2 AE4.4
		Disrupted sleep pattern.	• Explore causes of disrupted sleep pattern; • Discuss sleep-hygienic measures (exposure to blue light e.g., TV, tablets); • Provide relaxation exercises; • Consider referral to physician/nurse/psychosocial care provider.	AE5.2 AE3.9 AE1.3 AE4.4
		Anemia (low hemoglobin).	• Lower exercise intensity based on symptoms (dyspnea and fatigue without performing strenuous activities, dizziness, headache, palpitations, perspiration, low body temperature); • Extreme anemia (Hemoglobin <6) is a relative contra-indication for exercise. Consultation with physician is necessary.	AE1.1 AE2.1 AE8.2 AE7.2
		Poor nutritional status and loss of muscle mass.	• Discuss dietary patterns with the patient; • Refer to physician/nurse/dietitian in case of malnutrition (weight loss ≥5% in past month or ≥10% in past 6 months).	AE3.3 AE4.4
		Accelerated heart frequency in rest.	• Monitor heart rate during the training session, during activity and rest; • Maintain same intensity level as previous training.	AE2.1 AE1.1
QE2	When is fatigue most present?	Derives on the end of the day.	• Execute training as planned; • Educate the patient on activity regulation and the importance of alternating activity and rest.	AE6 AE3.4

Timepoint 3 - after 13 weeks intervention

Results retrieved from physical therapy examination

Wendy felt less fit and reported to experience a sense of muscle pain on her chest. In addition, she felt fatigued (rated 5/10) and she felt more fatigued during the second training in this week (rated 8/10). Wendy could not receive the scheduled chemotherapy as the white blood count was too low in her blood.

Results of 1RM and steep ramp testing:

- Leg press: 102 kg
- Vertical row: 27 kg
- Bench press: 21 kg
- Pull down: 11 kg
- Lunge: 36 kg
- Steep ramp test: 275 watts

Abdominal crunch and lat pull were not possible.

- Body weight: 62.8 kg

Results retrieved from dietetic examination

Current body weight: 63.5 kg

History of body weight: last month 60.5, 58 kg in past 6 months

The nutritional intake of Wendy met the nutritional recommendations. Wendy did not experience any nutrition-related complaints. In consultation with the dietitian Wendy agreed to continue focusing on a stable body weight and sufficient protein intake.

Step 1: Questions raised		Step 2: Probable answers	Step 3: Actions to be taken	
Code	Exercise related			Code
QE5	Does the patient experience pain on her chest at rest or during effort? Is the pain continuously present? Did the patient use medication to treat the low amount of white blood cells?	Chest pain is caused by exercise, either with or without dyspnea and change in heart rate.	• Relative contraindication for exercise; • Discuss with physician.	AE8.2 AE7.2
		Continuously present feeling of muscle pain after chest press strength training, provoked by movement.	• Adjust the specific strength training to a lower intensity where comfortable movement is possible.	AE1.1
		Patient uses neupogen for low amount of white blood cells and experience a continuous feeling of muscle pain. Granulocyte-colony stimulating factor injection (neulasta, neupogen); G-CSF injection is given 24h after the chemotherapy to stimulate white blood cell production. A common-side effect is musculoskeletal and bone pain (especially chest and back/pelvis area) within 2 days after the injection. This pain is present in rest and during movement.	• Adjust the specific strength training to a lower intensity where comfortable movement is possible; • Standard analgesics can be taken if necessary. No adjustment to exercise therapy needed; • Advise the patient to contact a physician if symptoms worsen.	AE1.1 AE3.7 AE3.6

QE2	Why did the patient get more fatigued?	Overtraining.	• Check if other signs of overtraining are present (e.g., increasing fatigue, insomnia, poor exercise performance, excessive muscle soreness, headaches); • If necessary, decrease intensity and duration (rather than session frequency); • Assess and discuss overall activity pattern; • Educate the patient on activity regulation and the importance of alternating activity and rest.	AE5.2 AE1.1 AE5.3, AE3.4 AE3.4
		Emotional distress.	• Acknowledge and normalize feelings of distress; • Explore disruption of sleep pattern due to distress; • Consider referral to physician/nurse/psychosocial care provider.	AE3.1 AE5.2 AE4.4
		Disrupted Sleep pattern.	• Explore causes of disrupted sleep pattern; • Discuss sleep-hygienic measures (exposure to blue light e.g., TV, tablets); • Provide relaxation exercises; • Consider referral to physician/nurse/psychosocial care provider.	AE5.2 AE3.9 AE1.3 AE4.4
		Poor nutritional status.	• Discuss dietary patterns with the patient; • Refer to physician/nurse/dietitian in case of malnutrition (weight loss ≥5% in past month or ≥10% in past 6 months).	AE3.3 AE4.4

QE5	The white blood cells were too low, what was the amount of other blood cells?	Leukopenia (low white blood cells).	• Apply appropriate hygiene (e.g., frequent hand washing and ensuring that exercise equipment is cleaned before and after use); • In general, for adults a count <4000µL (lower than 4000 white blood cells per microliter of blood) is considered a low white blood cell count; • Home exercises or individual supervision might be preferable to programs in public settings; avoid contact with others who may be infectious.	AE10 AE1.2
		Thrombopenia (low platelet count).	Avoid high impact exercise; • Avoid point pressure when using equipment; • Avoid strong elevation of blood pressure (high intensity exercise, Valsalva maneuver); • Hydrate during training session; • Monitor signs of bleeding; • Platelet count <20.000 µl is a contraindication for exercise.	 AE1.4 AE3.2 AE2.1
		Anemia (low hemoglobin)	• Lower exercise intensity based on symptoms (dyspnea and fatigue without performing strenuous activities, dizziness, headache, palpitations, perspiration, low body temperature); • Extreme anemia (Hemoglobin <6) is a relative contra-indication for exercise. Consultation with physician is necessary.	AE1.1, AE2.3 AE7.2

QE4	What is the heart rate in rest?	Increased heart rate in rest, possibly autonomic dysfunction; sinus tachycardia in rest or underlying arrhythmia.	• Monitor heart rate at every exercise session during activity and rest; Heart rate in steady state exercise should remain stable. Use Borg score to adjust training intensity; • Explain to patients that an increased heart rate without symptoms can be a result of chemotherapy; • Monitor symptoms: in case of persistent co-existing symptoms (dyspnea, anxiety, fatigue): terminate exercise and refer to physician.	AE2.1 AE3.1 AE2.1 AE8.2
Code	Nutrition related			Code
QD1	What is the cause of the increase in body weight?	Ascites.	• Monitor ascites by monitoring body weight, symptoms that indicate presence of ascites; • Keep in mind that ascites masks a decrease in body weight. Therefore, it is important to examine dietary intake.	AD2.1 AD2.1
		Increase in dietary intake.	• Continue monitoring dietary intake; • Explain the WCRF recommendations and inform the patient that a further increase in body weight is not necessary.	AD3 AD1.1

Abbreviations: BMI, body mass index; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; WCRF, World Cancer Research Fund; PADOVA, physical activity and dietary intervention in ovarian cancer; NB, Nota Bene, please note.
Code description questions and answers exercise related: QE1 Acuteness; QE2 Etiology; QE3 Exercise limitation; QE4 Capacity; QE5 Safety; QE6 Costs and benefits of training; QE7 Exercise prescription; AE1 Adaptations to exercise protocol; AE2 Extensive monitoring of symptoms; AE3 Patient education and advice; AE4 Referral to further diagnosis or treatment; AE5 Examination symptoms/exercise effects; AE6 Continuation of training according to protocol; AE7 Consultation physician; AE8 Discontinuation of exercise; AE9 Discuss costs/benefits of training; AE10 Extra hygiene of environment; AE11 Adaptation of posture. Code description questions and answers nutrition related: QD1 Etiology; QD2 Capacity; QD3 Dietary limitation; QD4 Safety; QD5 Dietary prescription; AD1 Patient education and advice; AD2 Extensive monitoring of symptoms; AD3 Continuation of intervention according to protocol; AD4 Consultation of physician; AD5 Inquire on patient' motivation.

1. Stelten, S., et al., Rationale and study protocol of the Physical Activity and Dietary intervention in women with OVArian cancer (PADOVA) study: a randomised controlled trial to evaluate effectiveness of a tailored exercise and dietary intervention on body composition, physical function and fatigue in women with ovarian cancer undergoing chemotherapy. BMJ Open, 2020. **10**(11): p. e036854.

6

TRANSLATING EVIDENCE FROM DUTCH EXERCISE ONCOLOGY-TRIALS IN PATIENTS WITH BREAST CANCER INTO CLINICAL PRACTICE USING THE RE-AIM FRAMEWORK

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Submitted

ABSTRACT

Purpose

We aimed to evaluate the potential for implementing exercise interventions for patients with breast cancer in the Netherlands, based on findings of the Dutch randomized controlled trials in this population.

Methods

We evaluated implementation of four Dutch exercise trials retrospectively, using the five dimensions of the RE-AIM framework: Reach (exercise participation rate), Effectiveness for physical fitness, fatigue and quality of life, Adoption (e.g., satisfaction of physical therapists guiding the exercise intervention), Implementation (cost-effectiveness and exercise adherence correlates thereof) and Maintenance (maintenance of exercise levels by individual patients and sustainability of exercise delivery at organization level). Thereby, we reflect on these results using (international) literature to gain better insight in overall barriers, facilitators and opportunities for further implementation of exercise interventions.

Results

Participation rates of 44–52% indicated acceptable Reach in the context of a trial, but also indicated room for improvement. Effectiveness of exercise during and after treatment was demonstrated in most trials showing benefits for aerobic fitness, physical fatigue and quality of life, and high patient satisfaction. Adoption of the exercise interventions by physical therapists was adequate (satisfaction score: 7.5 out of 10). Evaluation of Implementation indicated adequate adherence to supervised exercise, inconsistent findings on potential correlates of adherence, and promising results on cost-effectiveness. Currently, reimbursement for exercise programs is lacking. Maintenance of intervention effects at the patient level was limited and inconsistent. Maintenance of intervention availability at the organizational level was facilitated by an extensive network of specially trained physical therapists, but better communication and collaboration between different healthcare professionals is desired.

Conclusions

Improved implementation could particularly be achieved by increasing reach, and improved focus on exercise maintenance on both the patient and organizational level.

Implications for Cancer Survivors

To improve aerobic fitness, fatigue and quality of life, patients can participate in exercise programs. Hence, it is worth discussing participation with their physician. Due to limited healthcare coverage of exercise interventions, patients should expect out-of-pocket expenses when following a supervised exercise program.

INTRODUCTION

Evidence from randomized controlled trials (RCTs) indicates that exercise benefits aerobic fitness [1], fatigue [2] and health-related quality of life (HRQoL) [1, 3] during and after cancer treatment. This has led to the development of national and international guidelines [4-8] recommending exercise as an integral part of cancer care in a number of countries and professions, including sports medicine [9], medical oncology [10] and physical therapy [11, 12]. However, widespread implementation of exercise interventions is still limited. Translating research from RCTs into practice has shown to be difficult because of problems with population representativeness, limited (financial) resources and program availability and sustainability [13].

In 1999, the RE-AIM framework was developed to evaluate the potential for dissemination of research into clinical practice and to facilitate this process [14]. Since then, RE-AIM has been used to plan, evaluate and review health promotion and disease management interventions [14, 15]. In the RE-AIM framework, the overall impact of an intervention is described in five dimensions: Reach, Effectiveness, Adoption, Implementation, and Maintenance (Table 1).

Over the past years, four exercise RCTs have been conducted in the Netherlands that evaluate the effect of supervised exercise interventions on aerobic fitness or fatigue as primary endpoint in patients with breast cancer during treatment (Physical Activity during Cancer Treatment (PACT) [16-21] and Physical exercise during Adjuvant Chemotherapy Effectiveness Study (PACES) [22-26]) and after treatment (Resistance and Endurance exercise After ChemoTherapy (REACT) [27-30], and UMBRELLA Fit [31, 32]) (Table 2).

In this paper, we aimed to evaluate the potential for implementation of exercise interventions for people who have been treated for breast cancer with curative intent, based on these four RCTs, with use of the RE-AIM framework. We summarize the findings from the four Dutch trials only, since implementation of interventions is a dynamic, context-specific process [33], with (country)specific and more generalizable components. In addition, we reflect on these results using (international) literature (e.g., trials, reviews) to gain better insight in overall barriers and facilitators for implementation of exercise interventions. Finally, we describe opportunities for further optimization of implementation.

Table 1. Definitions of the RE-AIM framework and operationalization used in the current study

Reach	Refers to the number and characteristics of participants when compared to the target audience.
	Operationalization: Reach was evaluated by the number and characteristics of participants included in the exercise trials when compared to the target population.
Effectiveness	Refers to the positive and negative consequences of the intervention under optimal conditions or real-world circumstances, respectively.
	Operationalization: Effectiveness was evaluated by the impact of an intervention on aerobic fitness, fatigue, quality of life and patient satisfaction.
Adoption	Refers to the staff and settings that participate.
	Operationalization: Adoption was evaluated as the representativeness of settings and satisfaction of staff involved in the Dutch exercise trials.
Implementation	Refers to the extent to which the program was implemented as intended, i.e intervention fidelity and resources (e.g., cost and time).
	Operationalization: Implementation was evaluated by (i) the participants' adherence to an exercise program and ii) resources and intervention costs.
Maintenance	Refers to the long-term effects, both at the level of the individual patient, as well as the level of the organization in terms of the sustainability of the program delivery over time in the settings without added resources and leadership.
	Operationalization: We describe maintenance at both the patient (individual) and setting level. At the patient level, maintenance has been defined as the long-term effects (≥ 6 months) of the intervention. At the setting level we examined the extent to which the exercise programs are institutionalized or part of the routine organizational practices and policies.

Table 2. Characteristics of the studies

	N°	Study-arms	Mean age (SD)	Timing of the Intervention & Duration	Description of the intervention (FITT)[a]
PACT - breast cancer [17, 18]	204	Intervention (n=102) Control (usual care) (n=102)	Intervention: 49.7 (8.2) Control: 49.5 (7.9)	During chemotherapy and/ or radiotherapy Duration = 18 weeks	**F**: 2x/week **I:** AE: HR at or below VT RE: 65% of 1RM (2x10) towards 45% of 1RM (2x20) **T**: 60 min **T**: AE: interval training of alternating intensity (25min) RE: major muscle groups (25 min)
PACES - breast cancer [23, 24]	230	OnTrack (n=76) *Supervised exercise program* Onco-Move (n=77) *Home-based, individualized, self-managed PA program* Control (usual care) (n=77)	OnTrack: 49.8 (8.4) Onco-Move: 50.5 (10.1) Usual Care: 51.6 (8.8)	During chemotherapy Duration = Start in week of first chemotherapy cycle until 3 weeks after the last cycle of chemotherapy (mean = 118.6 days of length of chemotherapy)	<u>OnTrack</u> **F**: 2x/week **I:** AE: 50-80% of Wmax as estimated by SRT. RE: 70% of 1RM (2x12) towards 80% of 1 RM (2x8) **T**: 60 min **T**: AE: min. duration of 10min per exercise (total 30min) RE: ≥ 6 exercises of major muscle groups (20 min) <u>Onco-Move</u> **F**: 1x/3weeks + 2 weeks after start (per telephone) **I**: moderate intensity – Borg 12-14 **T**: 30min per day **T**: activities depend on patient preference

Table 2. Characteristics of the studies *(continued)*

	N°	Study-arms	Mean age (SD)	Timing of the Intervention & Duration	Description of the intervention (FITT)[a]
UMBRELLA FIT [31, 32]	260 (TWICs design; n=68 accepted the intervention)	Intervention (n=130) Control (usual care) (n=130)	Intervention: 58.0 (9.8) Control: 58.3 (9.5)	After cancer treatment (except for hormonal therapy) Duration = 12 weeks	**F**: 2x/week **I**: AE: week 1-3: 40-6-%% HRR+HRrest; week 4-8: 60-70% HRR+HRrest; week 9-12: 60-75% HRR+HRrest + interval-training RE: week 1-3: 1x 20-25rep (20RM) 9 exercises; week 4-12: 2x 15-20 rep (15RM) 7 exercises. **T**: 60 min **T:** AE: gradually increase, week 1-3: 15-20min; week 4-8: 15-20min MI & 5-10min HI. week 9-12: 10min moderate intensity & 10min HIIT, 10x30sec, 1min active rest. RE: major muscle groups
REACT [27, 28]	181 Breast	HI (n = 62) LMI (n = 62) WLC (n = 57)	HI: 51.7 (9.5) LMI: 51.8 (10.5) WLC: 51.9 (8.2)	After chemotherapy Duration = 12 weeks	HI **F**: 2x/week **I:** AE: first 4 weeks 2x8 min with alternating workloads (30/65% MSEC) after 4 weeks 1x 8min interval supplemented with 3x5min constant workload (≥80% HRR) RE: 70% 1RM (2x10) to 85% 1RM (2x10) **T:** 60min **T:** AE: two types of endurance interval exercises (week 1-4: 16min week ≥ week 5: 25 min) RE: 6 exercises of major muscle groups (25min)

Table 2. Characteristics of the studies *(continued)*

	N°	Study-arms	Mean age (SD)	Timing of the Intervention & Duration	Description of the intervention (FITT)[a]
					LMI: **F**: 2x/week **I**: AE: first 4 weeks 2x8 min with alternating workloads (40/55% MSEC) after 4 weeks 1x 8min interval supplemented with 3x5min constant workload (40-50% HRR) RE: 40% 1RM (2x10) to 55% 1RM (2x10) **T**: 60min **T**: AE: two types of endurance interval exercises (week 1-4: 16min week ≥ week 5: 25 min) RE: 6 exercises of major muscle groups (25min)

[a]Complementary to the supervised interventions, participants were stimulated to be physically active at moderate intensity for at least 30 minutes, 3-5 times per week in all trials.

Abbreviations 1RM One-repetition-maximum; *AE* Aerobic exercise; *FITT* Frequency intensity time type; *HI* High intensity; *HIIT* High intensity interval training; *HR* Heart rate; *HRR* Heart rate reserve; *HRrest* Resting heart rate; *LMI* Low-to-moderate intensity; *PACES* Physical exercise during Adjuvant Chemotherapy Effectiveness Study; *PACT* Physical Activity during Cancer Treatment; *MI* Moderate Intensity; *MSEC* Maximal short exercise capacity; *RE* Resistance exercise; *REACT* Resistance and Endurance exercise After ChemoTherapy; *SD* Standard deviation; *UMBRELLA Fit* Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation; *VT* ventilatory threshold; *WLC* Wait list control; *Wmax* Maximal Wattage

METHODS

For each dimension of the RE-AIM model, we summarized the findings from the four Dutch trials, as published before August 2022, using the operationalizations described in Table 1. Most results have been published previously [17, 19, 20, 22, 23, 25, 26, 32], except for information on patient satisfaction (PACT and UMBRELLA Fit trial). As the REACT trial also included patients with other types of cancer, we performed subgroup analyses on the subpopulation of patients with breast cancer, except for the cost-effectiveness analyses of which results are presented from the original papers. For better comparisons, we calculated Cohen's d effect sizes (ES) of the intervention effects, where significant effects ($p \leq 0.05$) were considered small for ES ≤ 0.2, medium for ES 0.2-0.5, and large for ES ≥ 0.8 [34].

RESULTS

Reach

Summary of results of Dutch RCTs

Across the four RCTs, 44-52% of eligible patients were willing to participate in the trials and the exercise intervention. Main reasons for non-participation were lack of time, mental burden, travel distance to the hospital, not wanting to be randomized, or wanting to exercise on their own (Table 3).

Comparison of participants and non-participants indicated that patients with a higher educational level were more likely to participate in exercise trials both during and after treatment (Table 3). Additionally, behavioral motivational factors were associated with participation during chemotherapy. Patients with more expected benefits of exercise, higher self-efficacy, fewer negative attitudes, more social support, and fewer perceived barriers to exercise were more likely to participate. Conversely, for exercise interventions following completion of anti-cancer treatment, patients who perceived more barriers were more likely to participate (Table 3).

Reflections and opportunities to improve implementation

The reported participation rate of 44-52% in the Dutch exercise trials is somewhat higher than the pooled estimate of 30% reported in a meta analyses of 23 exercise trials in patients with breast cancer [35]. The highest participation rate of 52%, reported by the UMBRELLA Fit trial, is likely related to the Trials within Cohorts (TwiCs) design, in which patients participating in an observational cohort were randomly invited to participate in an exercise intervention, thereby limiting intervention non-participation due to unwillingness to be randomized [31, 36]. In other trials, this proportion was shown to be approximately 10-15% [17, 26] (Table 3). Additionally, participation rates were influenced to some extent by the eligibility criteria employed, as they most often excluded patients with severe

comorbidities, and those with cognitive disorders or not fluent in Dutch. These patients may benefit even more from exercise guidance, as they may need specific exercise prescriptions, and may be less aware of health benefits and less able to find adequate health information, respectively. Patients with insufficient mastery of the language may benefit from additional health communication strategies, such as including visual aids to improve reach [37, 38].

The finding that travel time to the hospital was a commonly reported barrier to exercise participation is in line with other studies reporting that cancer survivors rated long travel time to exercise facilities as an important barrier to participation, particularly when supervised sessions were scheduled for 2 or 3 times per week [39, 40]. Travel time can be reduced by offering exercise interventions in local physical therapy practices or in the community settings close to patients' homes. In the Netherlands, regional networks of physical therapists working with patients with cancer are expanding, facilitating the accessibility to supervised exercise sessions. In addition, a network of fitness instructors with additional oncology education is developing, which might ease the transition from healthcare to community settings.

Experiencing less 'barriers to exercise' was associated with higher participation during chemotherapy, while after treatment, patients with more barriers were more likely to participate. These findings might indicate that at start of treatment patients might be too occupied with the burden of diagnosis and treatment to overcome existing barriers to exercise, while after treatment, patients' declined fitness levels and difficulties overcoming these might make them more prone to accept exercise guidance.

Two other commonly reported barriers are time and mental burden (e.g., 'having too many things on one's mind') [41]. In studies with patients under active treatment, the timing of trial inclusion before the start of chemotherapy is challenging because of the short time window and because patients who were diagnosed recently can be overwhelmed [26]. These barriers might be reduced by improving knowledge on the content and benefits of exercise during and after chemotherapy and by optimizing the timing of discussing exercise with patients. Shaping knowledge is among the most commonly used behavioral change techniques [42]. Specifically, instructions on how to perform the exercise behavior and information on the health consequences thereof were often part of interventions that were effective in improving exercise behavior in breast cancer survivors [43]. Hence, increasing knowledge of health benefits may help patients to restructure priorities. This may also be the case for patients with lower educational levels, who were less willing to participate in exercise trials both during and after chemotherapy [26, 30]. However, for the latter patients, the educational techniques applied might need to be adapted; for example, by breaking down information into small concrete steps and/or by including visual aids [37].

In the Netherlands, an e-learning module is available for nurse (practitioners) which, in addition to addressing common effects of exercise in patients with cancer, also pays attention to how to coach and motivate patients towards improving and maintaining adequate exercise levels [44]. The optimal timing of discussing exercise with patients is unknown. While results from the Dutch trials indicated that thinking about exercise shortly after diagnosis may be an additional burden for some patients, for other patients the diagnosis may be a teachable moment [45], and the right time to discuss exercise at the time of diagnosis [46]. It is also likely that patients' information needs and receptivity change over the course of their treatment and recovery, although this is currently an understudied subject. The ACSM Exercise Is Medicine (EIM) initiative proposes assessing, advising, and referring to physical activity in a recurrent pattern to take into account the different preferences and changing needs of patients for referral to exercise programs [47]. For trial purposes, with small windows of opportunities for including patients at start of chemotherapy, an improvement of research infrastructure and a proactive approach of patients would be helpful (e.g., a research outpatient department, a broad consent of patients for being approached for research participation).

Physicians play an important role in referring patients to exercise, and thus in increasing the reach, as patients are more likely to participate in exercise after it has been recommended by a physician [40, 48, 49]. However, while most oncologists, including those in the Netherlands, report understanding the importance of exercise, only one in three actually refers patients [50-52]. Reported barriers for this poor referral rate are lack of time, insufficient knowledge and safety concerns [53]. It has been suggested that the development of a roadmap for oncology clinicians with detailed pathways for exercise programming, in which discussing exercise participation becomes part of routine care, would facilitate referral [47]. However, empirical evidence on the effectiveness of such a roadmap and feasibility in Dutch clinical practice is lacking. Additionally, physicians' referral may also be improved by increasing patient awareness of exercise benefits, empowering patients to raise the issue of referral themselves during consultation [54] and improving insurance reimbursement and thereby accessibility [52].

Table 3. Results of the Dutch exercise trials summarized using the dimensions of the RE-AIM framework

Reach		
	During chemotherapy [17, 26]	**After treatment** [30, 32][a]
Recruitment setting:	Both academic and general hospitals	Both academic and general hospitals
In- and exclusion criteria:	Histologically diagnosed breast cancer < 6-10 weeks before recruitment; Stage M0; Scheduled for chemotherapy; Aged 25-75 years (PACT)/ Aged > 18 years (PACES) ; Karnofsky Performance status ≥60; No contraindications for physical activity; No cardiovascular, serious orthopedic, or cardiopulmonary conditions; No malnutrition; Basic fluency Dutch language; No psychiatric or cognitive problems	Histologically diagnosed breast cancer; Completed (neo)adjuvant chemotherapy; No contraindications for exercise; Able to perform basic activities; No psychiatric or cognitive problems; Basic fluency of Dutch language
Participation rate:	44 and 48%	47% and 52%[b]
Barriers to participation:	Time/mental burden (34-40%); Travel distance to hospital (12-22%); Problem with random assignment (11-15%); Want to exercise by him-/ herself (24%); Poor timing (22%); Does not want to exercise (18%); Unknown (1-23%)	Mental burden (26-55%); Not interested/did not want to exercise (8 -19%); Already exercising (17-23%); Problem with randomization (10%); Unknown (8-21%)
Characteristics participants versus non-participants[c]	Higher educational level, More likely to be employed, Less fatigue, Higher HRQoL, Higher self-efficacy, Fewer negative attitudes, More social support, More benefits and fewer barriers, Lower self-reported activity level; lower cancer stage (I-II); less likely to have had a mastectomy	[e]Higher educational level, Younger, Lower BMI, Higher outcome expectations, Lower distress, More barriers
Characteristics participants versus non-participants[d]	More likely to be employed, Lower self-reported activity level, lower exercise stage (maintenance); more social support; fewer negative attitudes	

Table 3. Results of the Dutch exercise trials summarized using the dimensions of the RE-AIM framework *(continued)*

Effectiveness					
	During chemotherapy [17, 23]		**After treatment** [28, 32][a]		
		Effect sizes[f]	**Effect sizes**		
General fatigue	*Supervised*	0.23 and 0.29	*MHI vs control*	*LMI vs WLC*	*HI vs WLC*
	Unsupervised	0.17	0.09	0.40	0.43
Physical fatigue	*Supervised*	0.30 and 0.63	*MHI vs control*	*LMI vs WLC*	*HI vs WLC*
	Unsupervised	0.28	0.24	0.40	0.64
Aerobic fitness[g]	*Supervised*	0.11 and 0.45	*NA*	*LMI vs WLC*	*HI vs WLC*
	Unsupervised	0.14		0.21	0.35
Left knee extensor peak torque[h]	*Supervised*	0.33	*NA*		
HHD (knee extensor)[i]	*Supervised*	0.38	*NA*		
	Unsupervised	0.10			
HHD (elbow flexion)[i]	*Supervised*	0.54	*NA*		
	Unsupervised	0.21			
HRQoL – Quality of life	*Supervised*	0.11	*MHI vs control*	*LMI vs WLC*	*HI vs WLC*
			0.05	0.27	0.54
HRQoL – Physical functioning	*Supervised*	0.16 and 0.81	*MHI vs control*	*LMI vs WLC*	*HI vs WLC*
	Unsupervised	0.68	0.02*	0.28	0.27

Table 3. Results of the Dutch exercise trials summarized using the dimensions of the RE-AIM framework *(continued)*

	Patient satisfaction during chemotherapy [22][j]	**Patient satisfaction after treatment**[a,k]
Patient satisfaction with supervised exercise program[l]	*Average scores:* 8.5 out of 10 on overall satisfaction with the exercise program 9.4 out of 10 on "Would you recommend this program to fellow patients?"	*Average score:* 8.4 out of 10 on overall satisfaction with the exercise program
	Experiences (positive): • benefits (better physical fitness, positive feelings, more energy, fulfillment, better appetite and confidence in and positivity about the body) (44%) • good timing of the exercise intervention (63-91%) • intensity and load of the program overall (90%)	*Experiences (positive):* • improvement in physical fitness (LMI: 20%, MHI: 28%, HI: 26%) • guidance by the physical therapist with regard to the supervised exercises (LMI:21%, MHI:23%, HI: 21%) • exercising with peers (LMI:12%, MHI:3%, HI:9%)
	Experiences (negative or suggestions): • intervention was burdensome (burdensome directly after chemotherapy or when ill) (4-25%), • inadequate supervision (e.g. no discussion of the diary, lack of continuity of supervision) (20%) • difficulty with scheduling (16-18%) • more variation in training (by adding for example yoga or aerobics and more personalized supervision) (45%) • total duration of intervention period too short (32%)	*Experiences (negative or suggestions):* • training (too) heavy or (too) exhausting (LMI:2%, MHI:12%, HI:17%), • difficulty with scheduling (LMI:8%, MHI:10%, HI:10%) • the program as not being tailored enough (LMI:6%, MHI:16%, HI:10%) • improved variation in exercises and/or less arm exercises (LMI:7%, MHI:26%, HI:5%)

Table 3. Results of the Dutch exercise trials summarized using the dimensions of the RE-AIM framework *(continued)*

Patient satisfaction with unsupervised exercise program[l]	*Average scores:* 7.4 out of 10 on overall satisfaction 8.2 out of 10 on "Would you recommend this program to fellow patients?"	*NA*
	Experience (positive): • structure on how to be physically active (38%) • benefits (physical fitness, gave less stress and fatigue and made them feel better and happier) (29%)	
	Experiences (negative): • limited counseling (42%) • the diary is burdensome (19%)	
Adoption		
Guidance of the exercise programs	Patients in the Dutch RCT's were referred to a trained PT close to their home to guide the exercise intervention. The PTs were trained on the specific exercise protocols by a visit of the coordinating researcher before the start of the intervention. In the Netherlands, PTs are the exercise professionals whom are dedicated to supervise the exercise programs for patients during chemotherapy.	
Satisfaction of physical therapists[l]	• 20 PTs rated the exercise intervention after chemotherapy with a 7.5 out of 10. • Preference for HI over LMI, but with the suggestion to start with LMI in patients with reduced physical fitness. • Preference for a more flexible exercise protocol to be able to improve variation of exercises. • Counseling techniques were rated with a 7 out of 10, with remarks that the counseling was not always possible in the available time (20%) and PTs expressed a need for education with regard to counseling techniques (10%)l.	

Implementation – participants adherence

	During chemotherapy [17, 22]		**After treatment** [30, 32][a]		
Attendance[n] median% (IQR%)	*Supervised*	77 (65-90) and 83 (69-91)	*MHI*	*LMI*	HI
	Unsupervised	71 (49-83)	96 (88-100)	88 (67-96)	92 (80-96)

Table 3. Results of the Dutch exercise trials summarized using the dimensions of the RE-AIM framework *(continued)*

Compliance[o] median% (IQR%)	*Aerobic*	*Duration*[q]	*Intensity*[r]	*Advice*	*NA*	*LMI*	*HI*
		88 (63-97)	50 (22-82)	61 (33-79)		81 (68-92)	88 (73-95)
	Resistance	84 (65-94)			*NA*	*LMI*	*HI*
						92 (85-96)	94 (88-98)
Predictors of high attendance[a,n,p]	*Supervised*	Higher educational level, Low BMI, Higher disease stage, Having a partner			*NA*	*LMI*	*HI*
	Unsupervised	Higher baseline endurance time, Attitude				Treatment with hormonal therapy	Sport history, Higher exercise stage, Radiotherapy, Higher self-efficacy, Positive attitude, Less barriers
	Exercise advice	Higher baseline fitness (endurance time)					
Predictors of high compliance[a,o,p]	*Aerobic*	Duration	Intensity		*NA*	*LMI*	*HI*
		No significant predictors	Low levels of baseline physical fatigue; No addition of radiotherapy to chemotherapy			No employment at baseline	Higher self-efficacy and Positive attitude
	Resistance	Her2+ and ER or PR+ tumor type (vs triple negative); Lower BMI; Lower baseline PA			*NA*	*LMI*	*HI*
						No employment at baseline and Lower education	Having a more positive attitude towards exercise
	Exercise advice	Beliefs about PA; Higher baseline PA; Peak O_2 consumption					

Table 3. Results of the Dutch exercise trials summarized using the dimensions of the RE-AIM framework *(continued)*

Implementation – cost-effectiveness		
Currently, physical therapy is not reimbursed through basic healthcare insurance in the Netherlands. For patients who have been hospitalized prior to their chemotherapy or had radiotherapy sessions in the past 6 months, physical therapy is covered starting from the 21st session. Hence, patients who receive neoadjuvant chemotherapy are not entitled to any reimbursement from basic coverage, and patients who receive adjuvant chemotherapy face out-of-pocket expenses for the first 20 sessions, unless they have additional coverage packages.		
During chemotherapy [21, 25]		**After treatment** [29]
Supervised	The OnTrack intervention (PACES-trial) was found to be cost-effective for QALYs. Mean interventions costs for the supervised intervention was 756.67euros per participant. The probability of OnTrack being cost-effective compared with UC was 45% at a willingness-to-pay of 20.000€/QALY and 79% at a willingness-to-pay of €80.000/QALY. The probability that the PACT intervention is cost-effective for patients with breast cancer is 2% for a willingness-to-pay 20.000/QALY and 6% for a willingness-to-pay €80.000/QALY.	The probability that HI was cost-effective compared to LMI exercise was 0.91 at 20.000€/QALY and 0.95 at 52.000€/QALY.
Unsupervised	The unsupervised OncoMove intervention (PACES-trial) was found not to be cost-effective. Mean interventions costs for the unsupervised intervention was 46euros per participant. The probability of cost-effectiveness was 25% at a willingness-to-pay of 20.000€/QALY, and 55% at a willingness-to-pay of €80.000/QALY.	

Table 3. Results of the Dutch exercise trials summarized using the dimensions of the RE-AIM framework *(continued)*

Maintenance – patient level					
	During chemotherapy [19, 23]				**After treatment** [29][a]
		6 months	**8 months**	**48 months**	**15 months** (HI vs LMI)
	Effect sizes				*Effect sizes*
General fatigue	Supervised	0.28	0.22	0.04	0.06
	Unsupervised	0.16	*NA*	*NA*	
Physical fatigue	Supervised	0.18	0.11	0.17	0.17
	Unsupervised	0.01*	*NA*	*NA*	
Aerobic fitness[g]	Supervised	0.13	0.10*	*NA*	0.21
	Unsupervised	0.08	*NA*		
Left knee extensor peak torque[h]	Supervised	*NA*	0.20	*NA*	*NA*
HDD (knee extensor)[i]	Supervised	0.06	*NA*	*NA*	*NA*
	Unsupervised	0.02			
HHD (elbow flexion)[i]	Supervised	0.12	*NA*	*NA*	*NA*
	Unsupervised	0.08			
HRQoL - Quality of life	Supervised	*NA*	0.03	*NA*	0.27
HRQoL - Physical functioning	Supervised	0.13	0.00	*NA*	0.16
	Unsupervised	0.23	*NA*		

Table 3. Results of the Dutch exercise trials summarized using the dimensions of the RE-AIM framework *(continued)*

Maintenance – setting level	
Physical therapy network	Existence of a broad network of PTs trained to guide patients with cancer with exercise during and after chemotherapy. All PTs within the network follow mandatory refresher courses and have to pass summative tests related to these courses. The network covers most of the populated areas in the Netherlands and an specialized PT is available within a 15 min commute for most people.
Oncology specializations for physical therapists	*2 types of specializations:* • Around 127 physical therapists have a *master degree in Oncology Physical Therapy*, a three-year (60-96ECs) part-time study which covers both hands-on treatment of oncology patients and guidance of patients in exercise programs. • Over 550 PTs working at over 700 locations in the Netherlands have been specifically educated on exercise treatment during and after treatment, via the Onconet courses executed by the Dutch Institute of Allied Healthcare. These PTs have received 67 hours or more of additional training in subjects such as basic oncology, exercise oncology, behavioral support, dealing with cancer-specific side effects, dealing with comorbidities, using clinimetrics and clinical reasoning in an oncology context.

[*] Indicate effects in favor of the control group

EC European credits; *HI* High intensity; *IQR* Interquartile range; *LMI* Low-to-moderate intensity; *MHI* Moderate-to-high intensity; *PT* physical therapist; *QALY* Quality-adjusted life year; *WLC* Wait list control

[a]Unpublished results of the REACT trial (additional analysis on data from patients with breast cancer only); analysis on predictors for participation with multivariable logistic regression; analysis on predictors for adherence performed with univariate logistic regression; [b]Relatively high participation rate of 52% due to the Trials within Cohorts (TwiCs) design; [c]A comparison of characteristics between participants and a subgroup of non-participants (patients who did not want to exercise) [26]; [d]A comparison of characteristics between participants and a subgroup of non-participants (who want to exercise by themselves); [e]Combined characteristics of 2 separate studies as reported in Gal, 2021 [32] combined with unpublished results REACT[a]; [f]In case effect sizes of 2 studies were available for the same outcome, this is reported for instance as 0.23 and 0.29; [g]Evaluated using cardiopulmonary exercise testing (peak power output, Watt) [18, 27] and Steep Ramp Test (Maximal short exercise capacity, watts) [24]; [h]Evaluated using a Cybex dynamometer at angular velocities of 60°/s; [i]Evaluated with a handheld dynamometer; [j]Unpublished results of the PACT trial ; [k]Unpublished results of the UMBRELLA Fit trial; [l]The percentages presented are calculated by the number of specific suggestions divided by the total number of suggestions; [m]The percentages are calculated by the number of specific suggestions divided by the number of PTs that rated their satisfaction (n=20); [n]Attendance: number of supervised exercise sessions attended/number of supervised sessions offered; [o]Compliance: achieved intensity and volume/prescribed intensity and volume of both resistance and endurance exercises; [p]Predictors are reported if p≤0.05; [q]performing the total prescribed number of minutes; [r]performing the prescribed number of minutes at or above the VT

Effectiveness

Summary of results of Dutch RCTs
Supervised exercise interventions *during* chemotherapy had a significant positive effect on aerobic fitness in one study [23], but it was not statistically significant in the other [17]. Supervised exercise limited physical fatigue significantly, while an unsupervised exercise program did not (Table 3). Both supervised and unsupervised exercise had a significant beneficial effect on physical functioning in one trial [23] but not in the other [17] (Table 3). Exercise *after* completion of treatment significantly improved aerobic fitness, physical functioning, global QoL and general fatigue in one trial (Table 3) and physical fatigue in both trials [32] (Table 3).

Average patient satisfaction was 8.5 (on a 1-10 scale) for supervised exercise *during* chemotherapy, 8.4 for supervised exercise after treatment, and 7.4 for an unsupervised exercise program *during* chemotherapy. Up to 25% of patients reported that the exercise program *during* chemotherapy was "too burdensome". After treatment, up to 16% of patients reported the program as 'not being tailored enough', up to 10% reported difficulties with scheduling exercise sessions and some patients reported the exercise program as "(too) heavy or exhausting" (12% up to 17% for patients in the High Intensity (HI) exercise group) (Table 3).

Reflections and opportunities for further implementation
The beneficial effects of exercise on aerobic fitness, fatigue and HRQoL found in the Dutch trials correspond with findings from other studies [9]. Of note, the stringent eligibility criteria of RCTs (e.g., excluding patients with serious orthopedic and cardiovascular- or pulmonary comorbidities) may hamper generalizability of the beneficial effects to all patients with breast cancer treated with curative intent. Although it may be expected that these patients could also benefit from exercise, more extensive tailoring of the exercise protocols is likely necessary to take specific co-morbidities into consideration [55].

The beneficial effects on aerobic fitness, fatigue and HRQoL, both during and after treatment, were also reported by several meta-analyses on aggregated and individual patient data (IPD) meta-analyses [1-3] that also reported larger benefits for supervised interventions and patients with lower baseline HRQoL [56]. High baseline values of HRQoL may explain the lack of effects on HRQoL in the UMBRELLA Fit trial, as the HRQoL in this cohort of patients was already comparable to the Dutch general female population at the start of the intervention, leaving little room for improvement [32].

The average effects of exercise on aerobic fitness observed in the Dutch trials correspond to the mean peakVO_2 improvements of 1.80 and 2.13 ml/kg/min reported in the literature [57]. Strikingly, previous studies with IPD-analyses reported that exercise interventions during treatment did not yield benefits for aerobic fitness in patients with a low fitness

level (peakVO_2 below 15.4 ml/kg/min, which is the threshold for functional independence in women [58]) at baseline [56]. Also, effects on aerobic fitness were smaller in older patients [1]. The limited effects in these subgroups may be related to low adherence or inability to complete exercises as intended and highlight the need for exercise interventions that are specifically tailored to older and unfit cancer patients to further improve implementation.

The Dutch trial results suggest a dose-response effect for exercise intensity on aerobic fitness (low-to-moderate (LMI) versus HI) (Table 3). Internationally, in the past 5 years, an increasing number of studies successfully examined the effects of high intensity interval training (HIIT) in patients with cancer and found positive results on cardiorespiratory fitness and cancer-related fatigue [59, 60]. However, results of the Dutch trials suggest that HIIT may not be the best choice for all patients, as up to one quarter of the patients indicated that the exercise intervention conducted during cancer treatment was too burdensome directly after their chemotherapy administration, and 17% of those who participated in HI exercise after cancer treatment found it (too) heavy or exhausting (Table 3). Also, depending on the goal of the intervention, higher exercise intensity may not always be necessary. For example, relatively low volumes of resistance exercises, at moderate-to-high intensity, have been found to yield significant benefits in terms of fatigue levels and HRQoL in patients with prostate cancer [61].

Despite the finding that some patients found the intervention to be too strenuous or burdensome, the vast majority of the patients in the four Dutch trials indicated being very satisfied with the exercise interventions in which they participated. This has also been the case in other exercise trials in patients with breast cancer [62-64]. Patients in the Dutch trials suggested that they would appreciate being able to reschedule missed exercise sessions, add more variety to the prescribed exercises, and combine the exercise sessions with yoga [22]. This was also found in a study of women with ovarian cancer [65]. Taking patient preferences into account can increase enjoyment, which in turn can have a beneficial effect on exercise maintenance [66]. At the same time to achieve their goals and the desired health benefits, it is important that patients are informed on the exercise frequency, intensity, type and time (FITT) required. Patient satisfaction, and thereby potentially exercise maintenance, can be further improved by taking sufficient time for exercise familiarisation, optimizing exercise scheduling in relation to chemotherapy administrations [67], and adequate tailoring of exercise intensity to the individual's fitness level.

The generally lower level of satisfaction reported for the home-based exercise counselling compared to supervised exercise may be related to the limited time devoted by healthcare professionals (e.g., physical therapists or nurse practitioners) (HCPs) to instructing and motivating patients, and to individualizing the home-based exercises. Motivational interviewing appeared to be an effective technique to improve exercise behaviour of patients with cancer in some studies [68, 69], but not all [70]. Dedicated time, and better

training in exercise counselling, and development of supportive tools may improve the counselling skills of HCPs delivering exercise programs.

Adoption

Summary of results of Dutch RCTs
Most patients in the Dutch RCTs were recruited from both community and university hospitals and were referred to a physical therapist specifically trained to work with patients with cancer, located close to the patients' homes. The physical therapists who delivered the intervention after completion of cancer treatment were generally satisfied with the content of the trial intervention (supervised aerobic and resistance exercise two days per week, supplemented by counseling on unsupervised exercise for three other days). The average satisfaction score was 7.5 (on a 1-10 scale, Table 3). While overall, the physical therapists were satisfied with the exercise intervention, some reported that they would have preferred to prescribe more variation in the resistance exercises (20%), that the exercise counseling was too time consuming (20%) and that physical therapists could benefit from some additional training in this regard (10%) (Table 3).

Reflections and opportunities to improve adoption
Few studies have described experiences of professionals delivering exercise interventions to patients with cancer treated with curative intent in the context of a trial. More variation in exercises has also been suggested by other studies, in order to prevent boredom, better tailor exercises to patients' preferences, needs (e.g., functional training), or capabilities, and to add exercise types other than resistance or aerobic exercises, such as balance exercises [65, 71]. In addition, physical therapists and personal trainers have reported that guidance of a group of patients can be challenging (e.g., dealing with different types of group dynamics; providing sufficient attention to individual patients' abilities and needs) [72, 73]. This indicates the importance of qualified trainers and preferably small group sizes, although the latter needs to be balanced with affordability.

Results of focus groups in various HCPs working in primary or secondary care in the Netherlands (e.g. physicians, nurses, physical therapists) reported that insufficient evidence about benefits of exercise programs was a barrier for their use [71]. This can be a reason for not referring patients to exercise programs. Hence, efforts to disseminate the evidence on the effects of exercise on cancer outcomes will likely accelerate the implementation of exercise as part of standard cancer care [74]. Additionally, these exercise programs should be adequately tailored to the individual patients' needs, capabilities and preferences [71], while taking evidence-based exercise frequency, intensity, type and time (FITT) into account.

Implementation

Implementation was evaluated based on (a) exercise adherence and (b) resources and intervention costs [75].

Exercise adherence

Summary of results of Dutch RCTs

The median attendance rates of supervised exercise in the Dutch trials varied between 77% and 98% and was 71% for unsupervised exercise (Table 3). Median compliance rates ranged between 81% and 88% for moderate intensity aerobic exercises, between 50% and 87% for HI aerobic exercises, and between 84% and 94% for resistance exercises (Table 3). The most frequently reported reasons for not attending the sessions during chemotherapy were feeling too ill (53%) and logistical reasons (30%). During chemotherapy, higher disease stage, having a partner, higher educational level, and a lower Body Mass Index (BMI) were associated significantly associated with better attendance [20, 22]. Results on predictors of compliance to the prescribed exercises during and after treatment suggested a difference between exercise type (resistance versus aerobic), intensity (LMI versus HI), and delivery mode (supervised versus unsupervised) [20]. In general, after cancer treatment, psychosocial factors, such as higher self-efficacy and having a more positive attitude towards exercise were associated with a higher attendance and compliance to HI but not to LMI exercise (Table 3).

Reflections and opportunities to improve implementation

The exercise adherence rates and the diversity in predictors thereof of the Dutch studies are in line with previous findings from other studies [76-78]. This diversity can be explained by differences in exercise prescriptions between studies and in the predictors studied. The finding that treatment related adverse effects ('feeling too ill') accounted for over half of the total missed sessions is also in line with other exercise studies in patients with breast cancer receiving chemotherapy [79, 80]. Consideration of side-effects as part of exercise program design has been proposed, for example by using 'chemotherapy-periodized' exercise prescriptions that take chemotherapy side-effects into account [67]. The finding that patients with lower exercise self-efficacy and more negative attitudes towards exercise had more difficulties with adhering to HI exercise suggests that realistic goal setting and starting at a lower intensity, to gain confidence before progressing to HI exercise, may be useful to improve adherence of these patients.

Previous systematic literature reviews found exercise history to be associated with better exercise adherence [77, 78]. This was not supported by the results from the Dutch trials, which suggests that other factors may be more important. It should be noted that the overall adherence reported in the Dutch trials was relatively high. This may not, however, turn out to be the case in clinical practice, due to variation in motivation and less emphasis on required adherence [73, 81]. Future studies in daily clinical practice that yield real-

world data on exercise adherence, collected via electronic medical records, might help elucidate which factors are associated significantly with adherence to exercise outside the trial context, and to identify subgroups of patients and cancer survivors that might require adjustments to the exercise intervention or psychosocial and behavioral support for improving adherence.

Resources and intervention costs

Summary of results of Dutch RCTs

Two of the Dutch trials assessed the cost-effectiveness of the exercise interventions during treatment. In one trial, the supervised exercise intervention during chemotherapy was found to be cost-effective with a probability of 45% at a willingness-to-pay of 20.000€/quality-adjusted life year (QALY) [25]. The other trial reported that, at a willingness-to-pay of 20.000€/QALY, the probability that the intervention would be cost-effective was very low (2%) [21]. The unsupervised exercise intervention was not cost-effective (25% probability for cost-effectiveness at a willingness-to-pay of 20.000€/QALY). After completion of chemotherapy, a HI-exercise program was more cost effective than a LMI exercise program [29], with a probability of 91% at a willingness-to-pay of 20.000€/QALY.

Reflections and opportunities for further implementation

Results on the cost-effectiveness of exercise interventions in Dutch trials were mixed, possibly explained by contamination or differences in follow-up time [21, 25]. Previous systematic reviews showed that supervised exercise interventions and multimodal interventions were cost-effective when they yielded significant beneficial effects on health outcomes such as energy, fear of recurrence, mood and pain [82, 83].

In the Netherlands, exercise supervision from a physical therapist is currently not reimbursed by basic healthcare insurance. However, exercise sessions for patients who have had surgery prior to their chemotherapy or received radiotherapy treatment in the past 6 months, can be reimbursed from the 21st session onwards until 1 to 2 years (depending on the treatment and insurance). Additionally, biweekly one-hour supervised exercise sessions can only be provided in group sessions of 2-10 persons because physical therapists are allowed to invoice for a maximum of 30 minutes per day per person. Fortunately, group sessions are often appreciated by cancer survivors and facilitate peer support [22, 62, 65], and may consequently improve adherence rates. On the other hand, group sessions are often less flexible with regard to exercise times, which has been reported as barrier to (adhering to) exercise programs [22]. Also, group sessions are not suitable for every patient as some patients feel uncomfortable with group exercise and/or may require more intensive coaching than possible in group settings.

More information on the cost-effectiveness of exercise interventions and consideration of other healthcare reimbursement strategies (e.g., bundled-payment models) could

be helpful to better inform discussions among health policy makers and insurers about appropriate reimbursement policy and insurance coverage for exercise interventions during and after chemotherapy. Future cost-effectiveness evaluations need to take into account that higher chemotherapy completion rates resulting from exercise interventions may result in higher costs of medication and secondary healthcare, but also higher survival rates [84], and that work absenteeism may be underestimated when absence, beyond the percentage sick leave that is agreed upon by patients and employers, is not reported as absenteeism days [25].

Maintenance

In this section, we evaluated maintenance at the *patient level*, describing long-term effects of the intervention, and at the *organizational level,* describing the extent to which the exercise programs have been institutionalized and integrated into routine practice, as well as the policies enabling program sustainability.

Patient level

Summary of results of Dutch RCTs

Exercise *during* chemotherapy did not yield significant effects on aerobic fitness, self-reported fatigue, or HRQoL at follow-up (i.e. 6, 8 and 48 months)[19, 23]. However, patients who participated in an exercise program *after* completing their oncological treatment successfully maintained their improved levels of cardiorespiratory fitness and HRQoL at one-year post-intervention (Table 3). The positive intervention effects on HRQoL observed at one-year follow-up were significantly larger for HI compared to LMI exercise (Table 3).

Reflections and opportunities for improving maintenance at the patient level

The limited maintenance of intervention effects on most outcomes might be explained by the uptake of exercise by control group participants after the completion of chemotherapy, or the specific focus on improving outcomes during the intervention period without sufficient incorporation of behavioral change techniques to maintain healthy behaviors in the long-term.

Sustained benefits on aerobic fitness were found one year after completion of exercise interventions after cancer treatment. Nevertheless, peakVO_2 levels were still 'poor', as compared to healthy adults [29]. This might indicate that a 12-week program might be too short for patients to fully return to normative values, and patients may not have received sufficient guidance to continue exercising at home at sufficient intensities after completion of the trial to continue improving their peakVO_2. This is in line with the previously mentioned feedback of physical therapists that they had insufficient time for counseling and expressed a need for additional education (Table 3). Further development of tools to improve the quality of counseling and efficient integration into daily practice might improve maintenance of adequate exercise levels to further improve peakVO_2.

This could be achieved by improved incorporation of behavioral change techniques, such as 'instruction on how to perform the behavior', 'feedback and self-monitoring of behavior' and 'goal setting (behavior)' [43]. Education on how to use behavior change techniques may help to overcome some perceived barriers of exercise maintenance that have been reported by patients with breast cancer, including *psychological barriers* (e.g., lack of motivation, fears, dislike of gym, or not being the 'sporty type'), *physical barriers* (e.g., ageing, side-effects of cancer treatment and other co-morbidities, weight gain) and *contextual* and *environmental barriers* (related to employment, traditional female care-giving roles, access to facilities, seasonal weather) [85].

Organizational level

Summary of results of Dutch RCTs

For the conduct of the Dutch trials, physical therapists were trained to supervise patients with cancer in exercising during chemotherapy and after treatment, within the initiated Onconet network. After trial completion, the Onconet foundation further educated physical therapists on the content and delivery of exercise programs for patients with cancer, and thereby consolidated and expanded a physical therapist network. The education also includes mandatory refresher courses where physical therapists are updated on results from recent studies. Currently, the network of physical therapists specialized in guiding patients with cancer is nationwide, with over 700 locations mostly within a 15-minute travel distance from any address. Additionally, MSc-level programs are available to educate physical therapists in oncology.

Reflections and opportunities for improving maintenance at the organizational level

In the Netherlands, currently, most supervised exercise interventions are offered by allied healthcare professionals. In primary care, this is primarily via physical therapists working in private clinics. Exercise can also be offered as part of a multidisciplinary rehabilitation program in secondary (hospitals) or tertiary (rehabilitation clinics) care. Outside of the healthcare system, fitness trainers with oncology specialization are increasingly available. These fitness professionals mainly deliver exercise interventions to patients who have completed treatment at least 3 months earlier [71].

Results from a qualitative study in the Netherlands indicate that HCPs working in primary care (e.g., general practitioners, physical therapists) perceive collaboration, communication, and referral between primary and secondary HCPs to be suboptimal [71], whereas HCPs working in secondary care (e.g., physicians, nurses, paramedics) raised general concerns about inadequate cooperation and networks between healthcare institutes [71]. The HCPs suggested that more use of health information technology, improved access to electronic health records, improved rehabilitation guidelines with recommendations about roles and responsibilities of each HCP, and better networks would improve the implementation of exercise in cancer care [71].

Internationally, the most reported barriers to integrating exercise in oncology settings are at the organizational level [86]. These barriers are related to the limited capacity and resources of staff, including insufficient time to prescribe and refer patients to exercise programs, and to the organization of care processes (e.g., absence of an established care pathway or structure) [86]. To reduce organizational barriers in the Netherlands, the 'Taskforce Cancer Survivorship Care' has been established since 2017. In this taskforce, HCPs, policymakers, researchers and patient organizations join forces aiming to improve attention for and optimization of quality of care over the whole cancer continuum and to improve organizational structures by better coordination between HCPs [87]. The taskforce also pursues an increase of physical therapist participation in multidisciplinary and oncology care networks, enabling further knowledge exchange and improved communication with other HCPs.

DISCUSSION

In this paper we have used the RE-AIM framework to describe the potential for implementation of exercise interventions for patients with breast cancer, based on four RCTs previously conducted in the Netherlands. Results from these RCTs demonstrated that exercise during and after treatment has beneficial effects on aerobic fitness, fatigue and HRQoL in patients with breast cancer. Additionally, both patients and physical therapists were generally satisfied with the intervention, but there were challenges to exercise maintenance.

The current network of physical therapists specialized in oncology that was initiated at the start of the trials continues to expand and represents a fruitful interaction between research and clinical practice. The current evaluation revealed key opportunities to further optimize implementation of exercise programs in the oncology setting. First, there is room to further increase knowledge and awareness among HCPs of the potential benefits of exercise and to improve organizational structures to increase referral to supervised programs. Improving awareness and referral requires more insight into perspectives of organizational stakeholders and policymakers and optimal dissemination of patient information between HCPs for which a whole system-approach is needed [71, 86].

Second, although the interventions in the Dutch exercise trials were tailored to individuals' fitness level and treatment side effects, specific subgroups of patients, such as the elderly and those who are in poor physical condition, are more prone to non-participation and appear not to benefit as much [1, 56]. These patients may benefit from an even more personalized and goal-directed functional exercise training program. Such programs have been shown to be feasible and promising in patients with metastatic breast cancer [88]. Similarly, a patient-centred, goal-directed, self-management enhancing functional exercise program that is based on a biopsychosocial model, Coach2move, has shown

to be (cost-)effective in improving physical activity and function in community dwelling older adults with mobility problems [89]. A personalized program that is tailored to the individual's needs and preferences, including behavioral change techniques such as 'goal-setting' and 'feedback and self-monitoring of behavior' may also facilitate sustained benefits over time. Successful inclusion of behavioral change techniques as part of exercise supervision may require additional schooling for physical therapists.

Finally, implementation of exercise programs for all patients with cancer is currently hampered by the lack of reimbursement of physical therapist guided exercise programs during and after treatment. The Taskforce Cancer Survivorship aims to improve healthcare during and after cancer treatment and one of the pillars of the Taskforce is to improve reimbursement of allied healthcare [87].

Some limitations of our study should be noted. Because it has been suggested that implementation strategies must be tailored to its context to improve effectiveness [90], we summarized exercise trials with a homogeneity in settings, circumstances and conditions, thereby specifically focusing on patients with breast cancer in the Netherlands. Hence, caution is needed when generalizing our findings to other countries with different healthcare systems, and to patients with other cancer types or advanced cancer [91, 92]. On the other hand, the findings from Dutch trials seem to echo those of studies conducted in other countries. Additionally, we based our assessments on a retrospective evaluation of the potential impact of exercise intervention trials. Our findings might have been different if data from the clinical practice setting had been collected prospectively (e.g., information on treatment referral and treatment fidelity outside of the context of a trial). Future studies should therefore prospectively evaluate the implementation of exercise interventions using the RE-AIM framework, for example, by collecting real-world data to describe characteristics of patients who are referred to exercise interventions, to register the delivered exercise prescription in terms of FITT-factors, and the resulting changes in aerobic fitness, physical functioning, HRQoL, and achievement of physical therapy goals. This would also facilitate obtaining information about and from patients with comorbidities or those who otherwise would be excluded from trials or referred to less extent to trials [93, 94]. Such collection of real-world data would be facilitated by an adequate registration system to structurally monitor clinical practice, in order to learn from every patient, and subsequently optimize healthcare [95]. Moreover, future research could benefit from hybrid designs, in which elements of clinical effectiveness and implementation research are combined [73, 96]. This might speed up the translation of research's finding into clinical practice [97].

In conclusion, the RE-AIM framework facilitated a retrospective evaluation of the impact of exercise interventions and their potential for implementation in clinical practice. We found acceptable RE-AIM outcomes in terms of participation rates, intervention effects, satisfaction of patients and physical therapists, and adherences rates within the trial

context. Additionally, an established network of physical therapists educated in oncology facilitates the maintenance of exercise interventions outside of clinical trials. We have recommended several steps that could be taken to further improve implementation of exercise programs for cancer patients and survivors, including improved referral (*reach*), improved tailoring of exercise interventions to individual needs and preferences, improved attention to maintenance of exercise behavior (*effectiveness, adoption, implementation and maintenance*) and improved reimbursement (*reach and maintenance*).

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7

GENERAL DISCUSSION

There is substantial evidence showing beneficial effects of exercise for patients with cancer that are treated with curative intent, including on physical fitness, health-related quality of life (HRQoL) and fatigue [1-4]. However, the feasibility and efficacy of exercise interventions in patients with advanced cancer is less clear [5, 6]. Also, despite the growing body of evidence in patients treated with curative intent, exercise is currently not an integral part of cancer treatment [7]. The aim to include attention and referral to exercise into standard care is supported by multiple initiatives and guidelines [8-10]. In these guidelines, the need for individualized exercise prescriptions (e.g. towards patients' capacity, needs and goals) is propagated. A close alignment of exercise prescriptions to patients' exercise goals is also important to achieve maintenance of these benefits [11]. In order to aid the development of such tailored exercise interventions for patients with cancer and to facilitate their implementation, the studies described in this thesis aimed to: 1) improve physical therapist-guided tailored exercise programs for patients with metastatic breast cancer; 2) capture the process of clinical reasoning of health professionals towards tailoring exercise prescriptions, and 3) identify the lessons learned from Dutch exercise trials that examined state-of-the-art exercise interventions and describe opportunities for future implementation in cancer care. This chapter starts with a summary of the main findings, followed by methodological considerations, educational and clinical implications, and suggestions for future research.

MAIN FINDINGS

Physical therapist-guided tailored exercise-based interventions for patients with metastatic breast cancer

From 2016-2019, the *Veerkracht* project was conducted, which aimed to develop and evaluate a physical therapist-guided exercise intervention approach for patients with metastatic breast cancer. Results from a mixed-methods study, comprising a cross-sectional survey and focus groups, conducted as part of this project (**Chapter 2**), showed that many patients with metastatic breast cancer reported at least some level of physical problems limiting their ability to be physically active. These problems included, for example, fatigue, painful joints, painful muscles and shortness of breath. Additionally, patients indicated that they valued guidance by specialized physical therapists for a prolonged period of time (> 8 weeks), while their preferred exercise type varied. In a second mixed methods study, we examined physical therapists' educational needs towards guidance of patients with metastatic cancer. This study revealed educational needs for establishing effective interprofessional collaboration with referring physicians or oncology nurses; knowledge on adverse effects of medical treatment, current evidence on effectiveness, and safety of physical therapy interventions in patients with metastatic cancer or bone metastases; and setting realistic treatment goals (**Chapter 3**). The results of **Chapters 2** and **3**, combined with aggregated evidence from previous exercise trials in patients with metastatic cancer, as well as evidence regarding the validity and reliability

of measurement instruments for evaluating physical fitness and health problems in this population, were used to develop a written guidebook for physical therapists working with patients with metastatic breast cancer. For the development of this guidebook, multiple consensus meetings with clinical experts and a patient advocate were used to translate the research findings into practical recommendations. These recommendations describe how physical therapists can select, deliver and evaluate exercise-based interventions that are tailored to individual goals, abilities, and preferences. The written guidebook was then introduced in a one-day educational session for selected physical therapists. These physical therapists delivered the physical therapy intervention to patients participating in an uncontrolled feasibility study **(Chapter 4)**. The aim of the feasibility study was to examine participation rate, safety, adherence and goal-attainment. The program appeared to be feasible in terms of uptake, safety, and goal-attainment. However, substantial dropout occurred, mostly due to disease progression. Both patients and physical therapists were satisfied with the intervention and physical therapists valued the written guidebook and felt empowered by it. The exercise prescriptions were highly tailored to the patient goals and preferences, and therefore optimally aligned to the exercise principle of task specificity [12]. Additionally, the intervention approach used in this pragmatic feasibility study closely matched physical therapists' method of working. This facilitates implementation in clinical practice. On the other hand, due to the inherent heterogeneity of the applied intervention components, it is difficult to draw conclusions on which exercise components contributed most to the outcomes.

The personalized and flexible approach of our study is presumably more feasible in this patient population than a highly structured predefined approach, which is likely to require multiple adjustments for individual patients during the course of the intervention [13]. Although the outcomes of our study were encouraging, robust evidence on the effectiveness of exercise in patients with metastatic breast cancer is still lacking. Further elucidating the efficacy of exercise programs in patients with metastatic breast cancer is therefore desirable. An international randomized controlled trial among 350 patients with metastatic breast cancer evaluating the effect of a 9-month supervised aerobic and strength exercise intervention [14] has recently completed patient enrolment. Although the intervention in that study was not tailored to individual goals, it will yield further knowledge on the effectiveness of a specific exercise prescription to combat fatigue and improve quality of life in patients with metastasized breast cancer.

The process of clinical reasoning to tailor exercise prescription for patients with cancer

Physical therapists use a complex process of clinical reasoning when adapting an exercise intervention to adverse effects and comorbidities of individual patients. We aimed to capture this process using the "think aloud method" on three vignettes presenting patients with ovarian cancer, who experienced specific adverse effects of cancer and its treatment (e.g., ascites, fatigue, wound problems) (**Chapter 5**). This study showed

that expert physical therapists posed various questions for additional information, particularly related to patients' capacity and safety, and/or to etiology of the adverse events. Via hypothetical scenario's, these questions resulted in various actions to tailor the intervention to the patients' adverse effects and comorbidities, including adaptations to the exercise protocol, (more) extensive monitoring of symptoms, patient education, and advice and referral for further diagnosis. The insights gained in this study provide useful leads to improve the description of the content of interventions, fidelity assessments, and physical therapists' education. Besides that, knowledge on which information is necessary for physical therapists to be able to adequately tailor exercise programs, could prompt the provision of such information when referring patients to exercise interventions. To adequately tailor exercise interventions within the context of a trial, expert physical therapists proposed several adaptions to the prescribed exercise protocol. Since not all adverse events and subsequent adaptations can be anticipated when writing study protocols, this raises the question which adaptations should be considered as part of the intervention (i.e., representing adequate personalized care), and which ones affect treatment fidelity. A detailed and *a priori* operationalization of intervention fidelity is important to fully appreciate the results of exercise interventions and to replicate the results [15-18].

Lessons learned and opportunities for future implementation of exercise interventions in Dutch cancer care

Chapter 6 described an evaluation of the impact of Dutch exercise trials on implementation of exercise in clinical practice for patients with breast cancer, in the Netherlands, with use of RE-AIM framework. RE-AIM is a commonly used framework used to plan, evaluate, and review health promotion and disease management, and serves as a good theoretical model able to identify both individual, as well as population impact [19].

The *Reach* appeared to be acceptable for the interventions compared with other exercise trials. Because some subgroups of patients were excluded from participation in exercise oncology trials (such as patients with severe comorbidities) or more prone to non-participation (e.g., lower educational level), the reach can be improved by making exercise participation more attractive for patients not willing to participate and by minimizing exclusion criteria. The exercise trials were predominantly ***E****ffective* for improving aerobic fitness, physical fatigue, and quality of life. Both patients and physical therapists were satisfied with the exercise interventions, but the ***A****doption* of other healthcare professionals (HCPs), was not examined in the Dutch trials. A qualitative study examining perspectives on the implementation of exercise interventions in Dutch HCPs (e.g. physicians, nurses, physical therapists) working in primary or secondary care, indicated that non-tailored exercise programs and an experienced lack of knowledge on exercise effects hampered the use of exercise programs [20]. ***I****mplementation* is facilitated by the adequate adherence to supervised exercise and promising results on cost-effectiveness, but hampered by a lack of reimbursement. Beneficial effects of the

exercise intervention on a patient level were not ***M**aintained* on the long term [21-23], except for maintenance of intervention induced improvements in physical fitness and HRQoL in one post-treatment exercise trial [24]. At the organizational level, maintenance is facilitated by the availability of an extensive network of physical therapists with enhanced qualifications for working with cancer patients.

The results of this study indicate a need to further increase knowledge and awareness of the potential benefits of exercise in HCPs, and improve organizational structures to increase referral to supervised programs. It has been suggested that a nationwide approach is needed to overcome the reimbursement barrier and other barriers for referral in the Netherlands [20]. In the Netherlands, the Taskforce Cancer Survivorship (TCS) was established in 2017. In this taskforce, HCPs, researchers, policymakers and patient organizations joined forces to improve survivorship care [25]. The Taskforce aims to improve attention for and optimization of quality of care over the whole cancer continuum and to improve organizational structures by better coordination between HCPs. One of the Taskforce's core efforts is aimed at improving structural embedding and financing of exercise as part of cancer care. Recently, the National Health Care Institute of the Netherlands published an interim advice report supporting admission of physical therapy (under certain conditions) to basic health insurance. If this advice is implemented, it could be a major facilitator for further implementation of exercise in cancer care [26].

METHODOLOGICAL CONSIDERATIONS

When interpreting the findings from this thesis, some methodological considerations related to study design, outcome measures and generalizability should be taken into account. We selected study designs and methods that fitted best with our research objectives, but some of them may also have limitations. These limitations will be discussed here.

Study design

In this thesis, we used both quantitative and qualitative study designs. The needs regarding exercise programs of both patients with metastatic breast cancer and physical therapists treating these patients were identified using mixed methods studies (**Chapters 2** and **3**). Via focus groups, we gathered insights into the type and severity of limitations, exercise preferences of patients, and educational needs of physical therapists. Parallel to that, quantitative data were collected on the most prevalent limitations, preferences and educational needs, via surveys. Given the time constraints of the project, we decided -a priori- to conduct two focus groups. Consequently, our qualitative data collection might not have reached saturation. We may therefore have missed relevant themes. However, we assumed that the most prevalent and urgent limitations and preferences would be mentioned in focus groups. In support of this assumption, our results are in

line with a recent survey among 141 patients with advanced cancer, showing that 70% reported physical barriers limiting physical activity [27], and with an international focus group and survey study reporting patients with metastatic breast cancer to express mixed preferences for exercise programs and a desire for personalized advice by a physical therapist [28, 29].

The qualitative think aloud approach that we used to capture processes of clinical reasoning (**Chapter 5)**, has been recommended for making the predominantly implicit processes, such as clinical reasoning, more explicit [30, 31]. Because the participating physical therapists had > 10 years' experience in training patients with cancer, and most were also experienced teachers, we considered them as experts and assumed that they would be competent in verbalizing their reasoning [32]. We did however, not test this assumption by comparisons with non-experts (i.e. novice physical therapists). Because the strategies of clinical reasoning differ between novice and expert physical therapists [33, 34], adding insights from novice physical therapists might further improve the education on tailoring exercise intervention in patients with cancer for (novice) physical therapists.

As part of the think aloud procedure, the experts were asked to reflect retrospectively on vignettes containing information from real-life reports of physical therapists that delivered exercise to patients that participated in the PADOVA study [30]. Consequently, the vignettes may have lacked details as compared to knowledge available during clinical practice. Additionally, interaction with patients could have raised additional questions, alternative judgements, and recommendations [35].

In **Chapter 4**, which describes the results of a study on exercise-based physical therapy interventions for patients with metastatic breast cancer, we used an uncontrolled trial design. When compared to a randomized controlled trial (RCT), this one-group design has the disadvantage of giving little information on the causality of the outcomes of an intervention [36]. When evaluating feasibility of exercise however, this design enables including more patients in the evaluation and gives more accurate information on the uptake, while reasons for non-participation such as "not wanting to be randomized" are eliminated [37]. This reason for non-participation could also be overcome by the use of a "trial within cohorts design (TwiCs)", as used in one of the trials incorporated in **Chapter 6**, in which patients participating in an observational cohort are randomly invited to participate in an exercise intervention [38]. Even though this TwiCs design generally improves recruitment logistics and prevents contamination, the complexity of such a design did not match the primary aim of our study in **Chapter 4**, to examine the feasibility of an exercise program in women with metastatic breast cancer [39].

In **Chapter 6,** we used the RE-AIM framework to *retrospectively* evaluate the potential for implementation of exercise interventions during and after cancer treatment in clinical practice [40], and were able to generate an overview of key opportunities for

future implementation. Because the Dutch exercise trials [22, 23, 38, 41] did not report extensively on treatment fidelity and we examined implementation retrospectively within a trial context, we were unable to capture information on actual rate of referral, referring HCPs, and exercise fidelity. It has been shown that exercise interventions in clinical practice will differ to some extent compared to the trials in which they were evaluated [42], due to the more patient centered and tailored approach applied in clinical practice [43, 44]. Future cohort studies examining real world data from clinical databases should reveal whether such protocol variations will yield *smaller* effects than those observed in RCTs due to less optimal exercise prescription, or to *larger* effects due to better alignment with patients' goals and preferences [45]. In the Netherlands, such a database containing real-world data is operative, namely the "National database Physical therapy" managed by the Royal Dutch Society for Physiotherapy (KNGF). Around 2.300 physical therapy practices share their data on diagnostic processes and treatment outcomes, currently containing around 6 million treatment episodes [46]. It is unclear to what extent this database can (already) be used for research purposes regarding patients with cancer.

Outcome measures

In the feasibility study described in **Chapter 4**, the outcomes *adherence*, *safety* and *goal attainment* were evaluated via session report checklists filled out by physical therapists as part of their physical therapy care. Such data collection is challenging because it imposes an extra time burden on physical therapists who are already pressed for time. Consequently, collection of data was not always complete, which resulted in several missing values and/or a need for retrospective evaluation by physical therapists. We evaluated adherence by the number of sessions attended relative to the number of scheduled sessions. Consequently, we missed information about the extent of achieving predetermined FITT-factors (i.e. Frequency, Intensity, Time and Type) per session, and consequently information on compliance. More detailed session report checklists would be helpful to gain better insight into compliance as well as exercise prescription behavior of physical therapists, but would increase the time burden even more. Finding ways to improve efficiency and completeness of data collection, in co-creation with physical therapists, might be helpful to some extent (e.g., preferences for online versus paper checklists). Additionally, to improve the quality of assessing intervention fidelity and reproducibility additional administration time for physical therapists should be incorporated in the budget in grant applications.

Safety was evaluated based on the occurrence of (serious) adverse events directly related to the Veerkracht-intervention with use of the Common Terminology Criteria for Adverse Events (CTCAE) and evaluation was limited to grade 2-5 complications. Goal attainment was assessed using a 4-point adjective scale to evaluate the treatment goals that were formulated with use of the Patient Specific Goalsetting method (PSG) [47]. Goal-attainment evaluation is a key method used in clinical practice to measure a perceived change in patient-specific functioning, rather than more standardized functional

measures evaluating a patient's capacity. Besides that, goal setting enables the physical therapist to tailor the exercise program to the patients' goals and consequently improves adherence to the exercise principle of (task) specificity. It is therefore remarkable that goal attainment evaluation has rarely been used as a primary outcome of exercise and/or rehabilitation trials in patients with cancer [48, 49]. A methodological disadvantage of this goal attainment scaling is a dependency on the ability of the therapist to guide the process of goal setting. [50] Goal-setting by physical therapists is not always executed as intended [44]. We also experienced this in our study (**Chapter 4**), where treatment goals were sometimes formulated on a level of function (e.g. improve strength or balance) instead of activity and participation level (e.g., walking to the supermarket), despite explicit instructions in the treatment manual and educational sessions to focus on the latter domain. In the future it would be desirable to further educate physical therapists on goal-setting as is described in the latter section of this discussion on implications for educational practice.

Another possible disadvantage of goal attainment scoring is the risk of social desirability bias, in particular when goal attainment is scored by patients in the presence of their own physical therapist, as is the case in regular clinical practice. To diminish social desirability bias towards the trial coordinator or their treating physical therapist evaluating the goals, it could be expedient to let patients evaluate their own goals via (digital) questionnaires using a clear description on the evaluation method.

Generalizability

In this thesis, we specifically focused on patients with breast or ovarian cancer. Cautiousness is therefore warranted when translating these results to other cancer populations, for example with regard to the implementation evaluation (**Chapter 6**). The effectiveness of exercise programs described in **Chapter 6** is less demonstrated in patients with other types of cancer or with advanced disease and, it is assumed that as a consequence, the Reach, Adoption, Implementation and Maintenance on an organization level is less established in patients with other types of cancer.

The focus group and survey study presented in **Chapter 2** may have been prone to selection bias towards patients who are more interested in physical activity and exercise. This is reflected by the large proportion of focus group participants indicating to be fairly or very fit (77%), and the high physical activity levels of survey responders (PASE-score [51]: 96.7, IQR: 50.7-156.2) as compared to for example a heterogeneous sample of patients with lung cancer (65.7)[51]. Consequently, we potentially missed useful information on exercise barriers and exercise preferences of less active patients, which may have been useful to further improve reach and adherence to the Veerkracht-program. Barriers for research participation in patients less interested in exercise might be reduced by making patients feel more addressed and by improving accessibility (e.g., digital focus groups).

A comparable selection bias may also have occurred in the feasibility trial described in **Chapter 4**. This may have been introduced by recruiting patients for trial participation by physical therapists familiar with the trial (16%) and by physicians who, despite clear in- and exclusion criteria, may only have presented the study to patients that they found sufficiently fit for exercise based intervention at a physical therapy practice. Hesitations and lack of referral to exercise programs by physicians have been reported in other studies and might be related to lack of time and insecurity on safety of exercise programs [52, 53]. Unfortunately, we did not gather more detailed information on reasons for non-referral. As hesitations towards referral may be a barrier to implementation, this should be further addressed in future studies.

Chapters 2 to 4 specifically focused on patients with metastatic cancer, while the studies in **Chapter 5 and 6** included patients treated with curative intent. Findings in patients treated with curative intent may not be fully generalizable to those receiving palliative treatment and vice versa. Specifically, during the clinical reasoning process described in **Chapter 5**, physical therapists may have raised additional questions on "clinical state and circumstances" when tailoring their intervention to patients with advanced cancer, due to additional exercise limitations (e.g. bone metastases)[54], faster declines in physical fitness, suspicion of disease progression as a cause for (new or increasing) symptoms, and potentially different priority setting towards exercise [55].

IMPLICATIONS FOR CLINICAL AND EDUCATIONAL PRACTICE

Physical-therapy guided tailored exercise programs for patients with metastatic breast cancer

The findings from the Veerkracht project described in **Chapters 2, 3** and **4** indicate (1) a need for tailored exercise programs guided by a physical therapist for patients with metastatic breast cancer; (2) educational needs in physical therapists working with patients with advanced cancer and; (3) that tailored exercise prescriptions for patients with metastatic breast cancer are safe, feasible and can help patients achieve their goals, also in case of bone metastases. The safety of exercise programs in patients with metastatic cancer has also been demonstrated in other trials [56, 57]. This knowledge can improve the confidence of patients, physical therapists and referrers when considering exercise safety. In 2022, the International Bone Metastases Exercise Working Group (IBMEWG) released the world's first clinical exercise recommendations for HCPs and exercise professionals for adequate exercise programming and recommends that the perceived risk of skeletal complications should be weighed against potential health benefits on the basis of consultation between the patient, the healthcare team, and the exercise professional [54]. Similar recommendations are provided by the guidelines of the Royal Dutch Society of Physical Therapy (KNGF), released in 2022 [58]. These relatively new insights in the safety of exercise for people with bone metastases constitute a paragdigm

shift, which should have consequences for education of physical therapists. Results and casuistry from the *Veerkracht* project have been incorporated in a two-day course on "Physical therapy during palliative treatment of patients with cancer" of the Dutch Institute of Allied Health Care (NPI) together with the recommendations of the IBMEWG [54], and the updated guideline oncology for physical therapists [58]. This semi-annual course aims to fulfill the educational needs of physical therapists reported in **Chapter 3** and **4**, such as knowledge of medical treatment, current evidence of exercise interventions, treatment of patients with bone metastases, setting realistic goals, strategies to end a treatment episode and appropriate use of clinimetrics.

The process of decision making of exercise prescription in the context of a trial to tailor interventions

Results from **Chapter 5** give insight into the clinical reasoning process that physical therapists use to tailor exercise and dietary interventions to the adverse effects of cancer and cancer treatment. Tailoring exercise interventions appears to be a complex process of clinical reasoning, because patients are faced with multiple adverse effects, especially during chemotherapy, which may vary over time in type or severity. This suggests a need for extensive clinical expertise for physical therapists and consequent clinical reasoning towards tailoring regarding "clinical state and circumstances", but also "patient preferences and actions" and "research evidence" (Figure 1).

Clinical reasoning with the use of casuistry is strongly integrated in the educational program of the Dutch Institute for Allied Health Care (NPI), to teach physical therapists how they can tailor exercise programs to patients with cancer. Previously published results on strategies to tailor exercise interventions to comorbidities and treatment side-effects during chemotherapy for breast cancer have already been implemented in specialized oncology education for physical therapists [59]. This can be further expanded based on the framework presented in **Chapter 5** (Appendix I), which gives an overview of the process of clinical reasoning with hypothetical scenario's, considerations and consequential actions. This framework can serve as a blueprint in discussing the casuistry with the physical therapists.

Figure 1. An updated model for evidence based clinical decisions [60].

Lessons learned and opportunities for future implementation of exercise interventions in Dutch oncology clinical practice.

Chapter 1 highlights that exercise during and after treatment has beneficial effects on physical fitness, fatigue, and QoL [1]. Additionally, **Chapter 6** highlights the most important steps to be taken to further increase impact of exercise programs in the Netherlands by improving implementation. To make exercise programs accessible to all patients with cancer and to improve referral to exercise interventions, an increased awareness and knowledge on the benefits in referrers and patients is required. This calls for educational efforts directed at physicians and nurse specialists. This increased knowledge is facilitated by improved attention for exercise in basic education for physicians [61]. Also the "Beter Gezond" initiative of the Radboudumc, Nijmegen, The Netherlands, offers educational courses and tools for HCPs to discuss lifestyle with patients. Moreover lifestyle front offices (in Dutch: leefstijlloketten) are more commonly available in hospitals.

The lack of maintenance of exercise effects reported in patients with cancer (**Chapter 6**), might be addressed by an improved focus on behavioral counseling techniques as part of the exercise intervention [11]. Based on our experiences in the studies included in this thesis, studies published before [62, 63], and observations in clinical practice, this will require educational efforts in both the initial bachelor programs as well as in post-bachelor education of physical therapists.

FUTURE RESEARCH

Over the past decades, the body of evidence on exercise efficacy towards improving physical fitness, fatigue and HRQoL has increased, leading to the development of several national and international guidelines that recommend exercise as an integral part of cancer care [1, 8, 54, 58, 64-67]. However, the implementation of these results into clinical practice lingers behind. Therefore, future research should focus on how to improve implementation [68]. Additionally, to gain better insight into the level to which exercise interventions as shown effective in research settings are effectively implemented in clinical practice (e.g., information on treatment fidelity, reach), study designs using real world data (collected from electronic patient files) are warranted. Finally, knowledge on the relative effectiveness of highly tailored exercise interventions (i.e., tailored towards patients' characteristics, goals, preferences, adverse-effects and comorbidities), compared to the more usual "one size" exercise prescriptions, is lacking. Improved tailoring of exercise interventions is desirable to increase *reach*, by making interventions better accessible for certain subgroups of patients [23, 37, 38, 63], improve *effectiveness* for subgroups of patients [69], improve *adoption* by responding to healthcare professionals' desire for increased tailoring [20, 70], and improve *maintenance* due to a better alignment with patient preferences [11, 71]. An example of an intervention that is highly tailored to patient characteristics, goals and preferences, is the Coach2Move program [72, 73]. This program is delivered by a geriatric physical therapist specifically educated on the Coach2Move strategy, which includes the use of motivational interviewing, an algorithm to support clinical reasoning, shared decision making, coaching on self-management, counseling towards home-based activities and a predefined number of sessions related to patient-tailored intervention profiles. A previous RCT has shown that the Coach2Move program is (cost)effective for improving long-term physical activity and function in older adults with mobility problems as compared with exercise guidance by a physical therapist without additional education in geriatrics. Considering the relatively low effectiveness of exercise interventions in older patients with cancer observed to date [3] and the small number of trials evaluating exercise interventions in older patients [74], such an intervention might improve reach, adherence of these patients and consequently effectiveness. Future research should elucidate whether the approach used in Coach2Move could be adapted to make it applicable for older patients with cancer, and whether this results in equal effectiveness.

Proven efficacy of exercise during and after treatment of cancer on physical fitness, fatigue and HRQoL [2-4, 69], supported by guidelines [1] and promising results on cost-effectiveness [75] may not be sufficient to change clinical oncology practice and to make exercise programs an essential component of cancer care [76]. This might require additional evidence, on the effects of exercise on what are considered to be "widely recognized established clinical cancer outcomes", e.g. recurrence, progression and survival [76]. Observational studies have shown that higher levels of physical activity

are positively associated with cancer-specific and overall survival (OS) [77, 78], but to date evidence on a causal relation between exercise and survival is limited. Few studies are currently being conducted internationally. These include the CHALLENGE-trial in patients with colon cancer who completed adjuvant therapy [79], the INTERVAL-GAP4 trials in patients with metastatic castrate-resistant prostate cancer [80] and the ECHO-trial in patients with ovarian cancer receiving first-line chemotherapy [81]. Additionally, in 2020, we launched the Aerobic fitness or Muscle mass to Improve Colorectal cancer Outcomes trial (AMICO) trial. This study evaluates the efficacy of resistance exercise training and high intensity interval training versus usual care during first line palliative chemotherapy in patients with metastatic colorectal cancer on chemotherapy dose modifications and progression free survival (PFS) (NCT04754672). Next to knowledge on the exercise effects on clinical outcomes, a better understanding of underlying mechanisms of action is also essential to further understand the potential of exercise as integral part of cancer treatment [7]. One of the hypothesized mechanisms linking exercise to clinical outcome is the improved functioning of the immune system. Studies in rodents have shown that exercise (voluntary wheel running) can directly affect tumor growth [82]. Further analyses of the mechanisms showed that exercise induced an increase in epinephrine which resulted in mobilization of NK-cells into the circulation which were then activated and redistributed to the tumor as a result of the production of IL-6 released by contracting muscles [82]. This finally resulted in an increase in intratumoral Natural Killer (NK) and T-cells and a 50-60% reduction in tumor growth [82]. Importantly, studies in healthy people showed that epinephrine also results in NK-cell mobilization into the circulation within minutes of initiating exercise [83]. Findings from a pilot RCT, evaluating effects of exercise during chemotherapy in a small sample of patients with breast and colon cancer, suggests that exercise may preserve NK cell activity [84]. Whether this mechanism of action of exercise can also increase NK-cell infiltration into the human tumor is unknown. Currently, we are evaluating the outcomes of the Supervised exercise to Promote Infiltration of NK-cells into the Tumor (SPRINT)-pilot trial (NCT04704856). This trial aims to examine the feasibility of a study designed to assess the effect of exercise on Natural Killer (NK)-cell infiltration into the tumor in patients with breast cancer undergoing neoadjuvant chemotherapy. Twenty patients were randomized before start of neoadjuvant chemotherapy to 1) the intervention study arm in which patients received supervised moderate-to-high intensity aerobic and resistance exercises (6 weeks, 2 times a week) or 2) a wait-list control group in which patients were offered the same exercise intervention 6 weeks after start of chemotherapy. We aim to explore immune cell infiltration in tumor biopsies taken after 6 weeks of chemotherapy. To date, inclusion of the study is finished, and results are expected to be published in the foreseeable future.

CONCLUSION

This thesis reveals specific exercise needs and uncertainties in both patients with advanced cancer, as well as in physical therapists guiding these patients, and indicates that tailored exercise interventions in patients with metastatic breast cancer are both feasible and safe. Future studies should evaluate effectiveness of such tailored exercise programs. Additionally, this thesis provides insight into the complex processes of clinical reasoning underlying the tailoring of exercise interventions to patients' adverse effects and comorbidities. Finally, key opportunities to further improve implementation of exercise interventions in clinical practice include efforts to increase the awareness of healthcare providers and patients alike, interventions to improve referral, and improving the maintenance of exercise effects on the long-term. Future research should focus on gaining more knowledge on implementation outcomes (reach, adoption, implementation) by better prospective evaluation in future exercise trials on the one hand and by evaluating data that better resemble clinical practice on the other hand (e.g. real-world data).

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APPENDICES

English summary

The general aim of this thesis was to improve the development and facilitate implementation of tailored exercise interventions for patients with cancer.

Chapter 1 provides a general introduction to physical-therapist guided exercise programs for patients with cancer and its implementation. It describes the adverse-effects of cancer treatment in patients with breast and ovarian cancer, the potential of exercise to counteract both short- and long-term effects, the importance for tailoring physical-therapist guided exercise programs in cancer patients and the current status on implementation of exercise programs in clinical practice. Additionally, this chapter provides the outline of this thesis by identifying the knowledge gaps of evidence that are addressed in the subsequent chapters, including 1) feasibility of physical therapist-guided, tailored exercise programs for patients with metastatic breast cancer; 2) insight into clinical reasoning towards tailoring exercise prescription and 3) insight into the current state of implementation of exercise interventions, following four Dutch trials.

Chapter 2 presents the results of a mixed methods study consisting of a cross-sectional survey and focus group sessions on the views about exercise of patients with metastatic breast cancer. The aim of the study was to identify physical problems and functional limitations that limit patients to be physically active and to explore preferences for physical therapist-guided exercise programs. A total of 114 women completed the survey of which the majority reported to have at least some level of physical problems, with fatigue and painful joints as the most commonly reported problems. Preferences for physical therapist-guided exercise programs were heterogeneous. The majority of patients preferred regular contact with and supervision by a qualified physical therapist, rather than exercising on their own at home. This might be a consequence of feelings of insecurity about their ability to self-manage physical functioning, as was clarified by focus group participants.

Chapter 3 presents findings of a study assessing educational needs and clinical uncertainties of physical therapists related to the treatment of patients with advanced cancer. For this study, we conducted a survey to which 162 physical therapists responded, and two focus groups with in total 17 therapists. The most frequently reported educational needs were related to effective interprofessional collaboration, and knowledge of medical treatment and current evidence for exercise interventions in these populations. Physical therapists in the focus groups expressed several uncertainties related to treating patients with bone metastases, setting realistic goals, when and how to end a treatment episode, and interprofessional collaboration. The findings of this study underscore the need for educational programs for physical therapists working with patients with advanced cancer in the Netherlands.

Chapter 4 presents the results of an observational, uncontrolled feasibility study in patients with metastatic breast cancer. This study aimed to evaluate the feasibility and outcomes of a goal-directed, physical therapist-guided exercise program. The content of the exercise program was highly tailored to the individual goals, abilities, and preferences of patients, and could include different combinations of functional, resistance, aerobic, and relaxation exercises. Fifty-five patients were enrolled, representing a participation rate of 34%. We encountered a large drop-out rate of 45%, mainly due to disease progression. Median adherence was 90% among patients who completed the intervention and no serious adverse events occurred. Fifty-two percent of all patients with an available goal attainment score (n=42) achieved their main goal fully or largely, and another thirty-six percent partially achieved their main goal. Reasons for non-achievement were not reported. Both patients and physical therapists highly valued the program and the supporting materials. Our findings should be replicated and tested for efficacy, in future randomized controlled trials.

Chapter 5 describes a study enlightening the clinical reasoning process of expert physical therapists and dietitians on the tailoring to adverse effects and pre-existing comorbidities, of an exercise and dietary intervention during chemotherapy for patients with ovarian cancer. Experts were asked to verbalize their clinical reasoning with the think aloud method. Findings were categorized in: 1) questions raised to gain additional information, 2) anticipated answers to these questions, and 3) actions to be taken. Physical therapists and dieticians posed various questions, especially about patients' capacities, safety, and etiology of symptoms. Reported actions in physical therapists concerned mostly 'adaptations to the exercise protocol' and both physical therapists and dieticians reported actions such as 'extensive monitoring of symptoms', 'patient education and advice' and 'continuation of intervention according to protocol'. The information about the clinical reasoning process as described in this study is relevant for designing, adapting, and evaluating interventions, and to educate healthcare professionals involved in delivering the interventions.

Chapter 6 describes a retrospective evaluation of the implementation of exercise interventions in the Netherlands, following four Dutch randomized controlled exercise trials in patients with breast cancer. We used the RE-AIM framework, which consists of 5 key outcomes: Reach, Effectiveness, Adoption, Implementation and Maintenance. We found acceptable RE-AIM outcomes on participation rates, intervention effects, satisfaction of patients and physical therapists, and adherence rates, within the context of the trials. Additionally, an established network of physical therapists educated in oncology facilitates the maintenance of exercise interventions outside clinical trials. On the other hand, several steps should be taken to further improve implementation. This includes raising more awareness of the benefits of exercise and improving referral (*reach*); tailoring of exercise interventions to individual needs and preferences, and attention towards

maintenance of exercise behavior as part of exercise supervision (*effectiveness, adoption, implementation and maintenance*); and financial reimbursement (*reach and maintenance*).

Chapter 7 presents the main findings of this thesis, methodological considerations, clinical and educational implications, and suggestions for future research. Overall, the findings of this thesis reveal specific needs and uncertainties in patients with advanced cancer and uncertainties in physical therapists guiding these patients. Tailored exercise interventions in patients with metastatic breast cancer appear to be feasible and safe, and findings and casuistry from this so called *Veerkracht* project (**Chapter 2, 3** and **4**) have been incorporated in a semi-annual course for physical therapists offered by the Dutch Institute for Allied Health Care.

Future studies should further evaluate effectiveness of exercise interventions in patients with metastatic breast cancer. Additionally, this thesis provides insight into the complex processes of clinical reasoning underlying the tailoring of exercise interventions to patients' adverse effects and comorbidities. These findings can be useful for fidelity assessment and reporting of interventions, and for training of healthcare professionals.

Finally, we discuss how the implementation of exercise interventions into clinical practice can be improved by sustainable changes in organizational and reimbursement structures to make exercise interventions accessible for all patients. Future research should focus on an improved translation from research findings into clinical practice by accompanying study designs with implementation outcomes and/or closely aligning to clinical practice. This could potentially be achieved by the use of real-world data and effectiveness studies using complex interventions that allow for a high level of individual tailoring.

Nederlandse samenvatting

De studies beschreven in dit proefschrift hadden als doel om op maat gemaakte, fysiotherapeutisch-begeleide trainingsprogramma's te ontwikkelen voor patiënten met kanker en de implementatie hiervan in de klinische praktijk te faciliteren. In **Hoofdstuk 1** wordt de aanleiding van dit proefschrift beschreven. Het beschrijft de nadelige effecten van behandelingen van borst- en eierstokkanker en de in de literatuur bekende positieve effecten van lichamelijke inspanning op het tegengaan van deze korte en langetermijneffecten van de behandelingen. Tevens wordt in hoofdstuk 1 het belang beschreven van het op maat maken van fysiotherapeutisch-begeleide trainingsprogramma's voor patiënten met kanker en inzicht gegeven in de huidige stand van zaken met betrekking tot het implementeren van trainingsinterventies in de klinische praktijk. Daarnaast worden in dit hoofdstuk de hoofdlijnen van dit proefschrift weergegeven door de hiaten in kennis te identificeren die in de daaropvolgende hoofdstukken worden behandeld, waaronder: 1) de haalbaarheid van fysiotherapeutisch-begeleide trainingsprogramma's op maat voor patiënten met uitgezaaide borstkanker; 2) inzicht in het klinisch redeneren van fysiotherapeuten om trainingsinterventies op maat te maken, en 3) inzicht in de huidige stand van zaken met betrekking tot de implementatie van fysieke trainingsprogramma's, naar aanleiding van vier Nederlandse trainingsstudies.

In **Hoofdstuk 2** worden de resultaten beschreven van een gecombineerd onderzoek, met kwalitatieve (focusgroepen) en kwantitatieve (vragenlijsten) methoden, naar de opvattingen van patiënten met uitgezaaide borstkanker over fysieke training. Het doel van de studie was om te identificeren welke fysieke klachten en functionele beperkingen lichamelijke inspanning negatief beïnvloeden en om de voorkeuren voor fysiotherapeutisch-begeleide trainingsinterventies in kaart te brengen. In totaal vulden 114 patiënten de vragenlijst in, waarvan de meerderheid aangaf op zijn minst enige lichamelijke klachten te hebben, met vermoeidheid en pijnlijke gewrichten als meest genoemde klachten. De voorkeuren voor fysiotherapeutisch-begeleide trainingsprogramma's waren heterogeen, maar de meerderheid van de patiënten verkoos regelmatig contact met, en begeleiding door een gediplomeerd fysiotherapeut boven zelfstandig thuis sporten. Deze bevindingen zouden een gevolg kunnen zijn van gevoelens van onzekerheid over het zelf kunnen managen van het fysiek functioneren, zoals bleek uit de resultaten van de focusgroepen.

Hoofdstuk 3 beschrijft de bevindingen van een studie waarin de scholingsbehoeften en klinische onzekerheden van fysiotherapeuten met betrekking tot de behandeling van patiënten met uitgezaaide kanker werden onderzocht. Voor dit onderzoek hebben we een vragenlijst afgenomen bij 162 fysiotherapeuten en twee focusgroepen gehouden met in totaal 17 fysiotherapeuten. De meest genoemde scholingsbehoeften hadden betrekking op een effectieve interprofessionele samenwerking, kennis van de medische behandeling en van het huidige bewijs ten aanzien van fysieke trainingsprogramma's bij patiënten

met uitgezaaide kanker. In de focusgroepen werden verschillende onzekerheden geuit met betrekking tot de behandeling van patiënten met botmetastasen, het stellen van realistische doelen, wanneer en hoe een behandelingsepisode moet worden beëindigd en over interprofessionele samenwerking. De bevindingen van deze studie onderstrepen het belang van specifieke scholingsprogramma's voor fysiotherapeuten die werken met patiënten met uitgezaaide kanker in Nederland.

Hoofdstuk 4 beschrijft de resultaten van een observationele, ongecontroleerde haalbaarheidsstudie bij patiënten met uitgezaaide borstkanker. Deze studie was gericht op het evalueren van de haalbaarheid en resultaten van een doelgericht, op maat gemaakt, fysiotherapeutisch-begeleid trainingsprogramma. De inhoud van het trainingsprogramma werd voor elke patiënt afgestemd op diens individuele doelen, fysieke belastbaarheid en voorkeuren. De interventie kon verschillende combinaties van functionele training, kracht-, aerobe- en ontspanningsoefeningen omvatten. Uiteindelijk konden 55 patiënten deelnemen, wat 34% was van alle benaderde patiënten. Een groot deel van de deelnemers (45%) stopte voortijdig met het programma en/ of de studie, voornamelijk door ziekteprogressie. Van alle patiënten die de trainingsinterventie hadden voltooid, was de mediane aanwezigheid op de vooraf ingeplande trainingssessies 90%. Er werden geen ernstige bijwerkingen van de training gerapporteerd. Tweeënvijftig procent van alle patiënten in de studie had een beschikbare score op de patiënt-specifieke goal attainment scale (PSG) (n=42) en bereikte het persoonlijke hoofddoel volledig of grotendeels, en nog eens 36% van de patiënten bereikte het persoonlijke hoofddoel gedeeltelijk. Redenen voor het niet bereiken van doelen werden niet vermeld. Zowel patiënten als fysiotherapeuten waardeerden het programma zeer, evenals de ontwikkelde handreiking voor fysiotherapeuten. Idealiter worden onze bevindingen in de toekomst gereproduceerd en wordt het programma geëvalueerd op effectiviteit door gerandomiseerde trials.

Bevindingen en casuïstiek uit dit zogenaamde Veerkracht-project (**hoofdstuk 2, 3** en **4**) zijn verwerkt in een halfjaarlijkse cursus voor fysiotherapeuten aangeboden door het Nederlands Paramedisch Instituut (NPI).

Hoofdstuk 5 beschrijft een studie die inzicht geeft in het klinisch redeneerproces van deskundige fysiotherapeuten en diëtisten over het aanpassen van een trainings- en voedingsinterventie op basis van chemotherapie-gerelateerde bijwerkingen en reeds bestaande co-morbiditeit bij patiënten met eierstokkanker. Experts werd gevraagd hun klinisch redeneren te verwoorden met de "hardop-denkmethode". De bevindingen van het klinisch redeneren werden onderverdeeld in: 1) vragen die werden gesteld om aanvullende informatie te verkrijgen, 2) verwachte antwoorden op deze vragen, en 3) te ondernemen acties. Fysiotherapeuten en diëtisten stelden verschillende vragen, met name over de belastbaarheid van patiënten, veiligheid van training, en etiologie van symptomen. De meest voorkomende beschreven acties van fysiotherapeuten betroffen

aanpassingen aan het trainingsprotocol. Overige acties van de fysiotherapeuten en diëtisten betroffen uitgebreidere monitoring van symptomen, voorlichting en advies aan de patiënt en het vervolgen van de behandeling volgens protocol. Informatie over het klinisch redeneerproces uit deze studie is relevant voor het ontwerpen, aanpassen en evalueren van interventies, en voor het opleiden van fysiotherapeuten en diëtisten die patiënten met kanker begeleiden bij fysieke inspanning en een passende voedingsinname.

Hoofdstuk 6 beschrijft een retrospectieve evaluatie van de implementatie van trainingsinterventies aan de hand van vier Nederlandse gerandomiseerde gecontroleerde trainingsstudies bij patiënten met borstkanker. We gebruikten hiervoor het RE-AIM framework, dat bestaat uit 5 belangrijke uitkomsten: *Reach (bereik)*, *Effectiveness (effectiviteit)*, *Adoption (interesse van betrokken zorgprofessionals)*, *Implementation (eigenlijke uitvoering)* en *Maintenance (verankering en behoud van effecten)*. We vonden acceptabele uitkomsten met betrekking tot de deelnemingspercentages (44-52%), significante interventie-effecten op verschillende uitkomsten (fysieke fitheid, vermoeidheid, kwaliteit van leven), hoge mate van tevredenheid van patiënten en fysiotherapeuten en therapietrouw van deelnemende patiënten. Naar aanleiding van deze trials is in Nederland een netwerk opgezet van fysiotherapeuten die zijn opgeleid in de oncologie. Desalniettemin moeten er nog wel stappen genomen worden om de implementatie verder te verbeteren, waaronder het realiseren van een beter bewustzijn bij verwijzers en patiënten over de voordelen van lichaamsbeweging tijdens en na de behandeling voor kanker en daardoor een betere doorverwijzing (*reach*); betere aansluiting van trainingsinterventies op individuele behoeften en voorkeuren; aandacht voor het volhouden van beweeggedrag als onderdeel van de trainingsinterventie (*effectiveness, reach, implementation* en *maintenance*); en financiële vergoeding (*reach* en *maintenance*).

In **Hoofdstuk 7** worden de belangrijkste bevindingen uit dit proefschrift bediscussieerd, wordt er verder ingegaan op de gebruikte methodologieën in dit proefschrift, worden de implicaties voor de klinische en de onderwijspraktijk benoemd en worden suggesties gedaan voor toekomstig onderzoek. De bevindingen in dit proefschrift hebben betrekking op specifieke behoeften en onzekerheden bij patiënten met uitgezaaide kanker en onzekerheden bij fysiotherapeuten die deze patiënten begeleiden. Op maat gemaakte trainingsinterventies voor patiënten met uitgezaaide borstkanker blijken haalbaar en veilig. Het is wenselijk dat toekomstige studies de effectiviteit van trainingsinterventies bij patiënten met uitgezaaide borstkanker evalueren.

De inzichten in de complexe processen van klinisch redeneren die ten grondslag liggen aan het aanpassen van trainingsinterventies op basis van bijwerkingen van een oncologische behandeling en de co-morbiditeit van patiënten. Kennis hierover kan helpen om in toekomstige trainingsprotocollen op voorhand beter te kunnen omschrijven welke

aanpassingen binnen of buiten het voorgeschreven trainingsprotocol vallen, zodat ook het onderzoek beter kan worden gereproduceerd. Daarnaast kunnen de verzamelde data met verscheidene hypothetische scenario's en bijbehorende protocolaanpassingen gebruikt worden voor het trainen van fysiotherapeuten.

Ten slotte bediscussiëren we hoe de implementatie van trainingsinterventies in de klinische praktijk kan worden verbeterd door duurzame veranderingen in organisatie- en vergoedingsstructuren om daarmee de toegankelijkheid voor alle patiënten te vergroten. Toekomstig onderzoek zou zich idealiter moeten richten op een verbeterde vertaling van onderzoeksresultaten naar de klinische praktijk door implementatie van uitkomsten te integreren in het studie design en door nauw aan te sluiten bij de klinische praktijk. Dit zou bijvoorbeeld gedaan kunnen worden door gebruik te maken van zogenaamde real-world data en effectiviteitsstudies die complexe interventies evalueren die in hoge mate gepersonaliseerd zijn.

Research Data Management

Ethics and privacy

This thesis is based on the results of human studies or existing data from published papers, which were conducted in accordance with the principles of the Declaration of Helsinki. The medical ethical committee of the Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital approved the study described in Chapter 4 (file numbers: NL60151.031.16) and determined the study described in Chapter 2 as Research non subject to the Medical Research Involving Human Subjects Act (WMO) (METC dossier number: 16.0127). The medical ethical committee of the Amsterdam University Medical Center, location AMC approved the Physical Activity and Dietary intervention in women with OVArian cancer **(**PADOVA) trial (METC dossier number: 2017-149) of which data was used for Chapter 5. Informed consent was obtained from all patients participating in the studies (Chapters 2, 4 and 5). Technical and organizational measures were followed to safeguard the availability, integrity and confidentiality of the data (these measures include the use of pseudonymization, access authorization and secure data storage).

Data collection and storage

Data described in Chapters 2 and 4 was extracted from (electronic) health records, paper questionnaires, Case Report Forms (CRF) and data described in Chapter 2, 3 and 4 was extracted from secured online questionnaire programs (SurveyMonkey and Explora). Electronic data has been stored on the department server of the Antoni van Leeuwenhoek and is only accessible by project members working at the Antoni van Leeuwenhoek. Data used for Chapter 5 is stored on the department server of the Amsterdam UMC. These secure servers safeguard the availability, integrity and confidentiality of the data. Paper (hardcopy) data is stored in cabinets on the department.

Availability of data

Chapter 3 is published open access and Chapter 5 and 6 are submitted to open access journals. The data will be archived for 15 years after termination of the study. Using the patient data in future research is only possible after a renewed permission by the patient. The anonymous datasets that were used for the analyses presented in these studies are available from the corresponding author upon reasonable request

Curriculum Vitae

Marieke ten Tusscher was born on February 2th 1985 in Raalte, the Netherlands. After graduating from secondary school at Carmel College Salland in Raalte in 2002, she studied physical therapy at Saxion University of Applied Sciences in Enschede and received her degree as a physical therapist in 2006. Subsequently, she enrolled in a (pre) master Human Movement Sciences at the VU University in Amsterdam and completed her Master's degree in 2008.

After working as a physical therapist in a nursing home and a general hospital she started working in the Antoni van Leeuwenhoek hospital in 2010. During her time there, she worked with patients with various cancer diagnoses and treatments on the wards, outpatient clinic and rehabilitation center. After several years, she combined working in clinical physical therapy practice with a junior researcher position on the 'Veerkracht project' in the Antoni van Leeuwenhoek in 2015. This project aimed to improve physical-therapist guided exercise care for patients with metastatic breast cancer. The results of this project are included in a semi-annual course for physical therapists from the Dutch Institute of Allied Health Care of which Marieke is one of the teachers. After completing the 'Veerkracht' project, Marieke started a position as junior researcher at the Medical Oncology department of the Amsterdam UMC, location VUmc in December 2019. She initiated and coordinated the Supervised Exercise to Promote Infiltration of NK-cells into the Tumor 'SPRINT' pilot-trial and the Aerobic fitness or muscle mass training to Improve Colorectal cancer Outcomes 'AMICO' trial. During that period she formally started as a PhD student, under supervision of dr. Laurien Buffart who obtained a position at Radboudumc Nijmegen. Consequently, Marieke registered as an external PhD student at Radboudumc.

Currently, Marieke continues her work as a researcher at the department of Medical BioSciences at Radboudumc Nijmegen. In this position, she focuses on research regarding goal-directed and personalized exercise interventions for patients with cancer, including rare cancer. Additionally, she co-develops a website with information on exercise and cancer, for both patients and health-care professionals, funded by the World Cancer Research Fund.

Dankwoord

De afgelopen jaren heb ik met veel plezier aan mijn proefschrift gewerkt. Eerst vanuit het Antoni van Leeuwenhoek ziekenhuis en later vanuit het Amsterdam UMC en het Radboudumc. In die jaren heb ik met veel mensen mogen samenwerken en daar veel van opgestoken. Hierdoor heb ik mij als onderzoeker kunnen verbeteren, maar zeker ook als persoon. Graag wil ik een aantal mensen in het bijzonder bedanken.

Allereerst een grote dank aan alle **patiënten** die hebben deelgenomen aan de studies van het Veerkracht-project. Zonder jullie belangrijke input hadden wij nooit zoveel kennis kunnen vergaren. In het bijzonder wil ik graag Adrienne Veraart noemen, zij was als patiëntvertegenwoordiger (met een achtergrond als fysiotherapeut) betrokken bij ons Veerkracht-project. Haar motivatie om bewegen beter op de kaart te zetten voor patiënten met uitgezaaide borstkanker, heeft mij zeer gesterkt in het belang van dit onderzoek.

Daarnaast zou ik ook graag de deelnemende **fysiotherapeuten** bedanken voor jullie enthousiasme om deel te nemen aan focusgroepen en het begeleiden van patiënten in de Veerkracht-studie. Dit leverde interessante gesprekken op over allerlei casussen in de eerstelijns praktijk waar ik als klinisch werkend fysiotherapeut zelf niet mee te maken had.

Lieve **Laurien** en **Martijn**, mede dankzij jullie aanstekelijke enthousiasme en energie heb ik met veel plezier aan dit proefschrift gewerkt. Jullie zullen mijn langdurige getwijfel over het ingaan van een promotietraject vast niet altijd makkelijk hebben gevonden, maar dat ik heb nooit aan jullie gemerkt. Dank voor het geduld en vertrouwen.

Laurien, ik vind het heel fijn om met je samen te werken. Door jouw kritische blik heb ik mij in de afgelopen jaren verder kunnen ontwikkelen als onderzoeker. Je deur staat altijd open en ik ervaar veel ruimte voor eigen ideeën bij nieuw op te zetten projecten en aanvragen. Gelukkig kunnen we onze samenwerking voortzetten, hopelijk volgen er nog veel interessante projecten!

Martijn, dankzij jou heb ik naast mijn werk als fysiotherapeut ervaring op kunnen doen met wetenschappelijk onderzoek, eerst binnen jouw promotietraject en later ook binnen de Veerkracht-studie. Ik ben je ontzettend dankbaar voor de kansen die ik gekregen heb. Ondanks al je verschillende werkzaamheden, ben je altijd bereid om mee te denken als het nodig is en doe je dat met een hele sterke analytische blik. Bovenal waardeerde ik de samenwerking door je humor en relativeringsvermogen.

Beste **Maria**, wij hebben elkaar pas later in mijn promotietraject leren kennen, eerst via Teams en later gelukkig ook in het ‘echt’. Met jouw kordate manier van aanpakken en

het scheppen van overzicht heb je me goed kunnen helpen bij het maken en overzien van een planning. Dank daarvoor.

Beste **Hans**, zonder jouw overredingskracht was er misschien geen boekje gekomen. Dank voor het inzicht dat je me gegeven hebt. Daarnaast ben je een fijne projectleider op het SPRINT-project, dit project is weliswaar geen onderdeel geworden van mijn proefschrift, maar mijn lab vaardigheden hebben wel een enorme vlucht genomen.

Graag wil ik de leden van de manuscriptcommissie, **prof. dr. van der Wees, prof. dr. van Herpen en prof. dr. van de Poll,** heel erg bedanken voor het lezen en beoordelen van mijn proefschrift.

De artikelen in dit proefschrift heb ik niet alleen geschreven. Ik wil dan ook graag alle co-auteurs hartelijk bedanken voor het meedenken en meeschrijven aan de artikelen. Jullie kritische blik en feedback waren erg waardevol.

Lieve **Loes**, vanaf de eerste dag op de opleiding fysiotherapie zijn we elkaar niet meer uit het oog verloren. Eerst samen in Enschede op kamers en later bij elkaar om de hoek in Amsterdam. Ik kon en kan je nog steeds altijd bellen om even te luchten en met jouw humor en onze zelfspot zorgt dit altijd voor ontspanning. Dank dat je er altijd voor me bent!

Lieve **Carla**, met jouw rust, warmte en vertrouwen heb je me in de afgelopen jaren enorm geholpen op zijn tijd alles weer even in perspectief te zien. Bedankt voor alles. Heel fijn om jou als paranimf bij mijn promotie te hebben.

Graag wil ik ook mijn collega's op het Veerkracht-project bedanken. Ik kijk heel fijn terug op die periode waarin we met deze leuke groep zoveel, voor mij nieuwe, dingen hebben gedaan. Van het organiseren van focusgroepen, het overleggen met app-ontwikkelaars en het maken van filmpjes tot het ontwikkelen van een handreiking en scholing voor fysiotherapeuten. Allereerst **Wim**, bedankt voor de fijne samenwerking. Jij had al meer ervaring in het onderzoek en met mijn patiënten ervaring vulden we elkaar goed aan. Daarnaast hebben we veel leuke momenten gehad in het CPET-lab met alle verschillende patiënten die we hebben gezien. **Neil**, wat fijn dat je, ondanks al je andere werkzaamheden, zo betrokken was bij de uitvoer van het Veerkracht project. Dat heb ik erg gewaardeerd. **Edwin**, ik vond jouw verfrissende ideeën en 'out of the box' denken altijd erg leuk en leerzaam! **Rachel** en **Dagmar** ook jullie wil ik graag bedanken voor jullie betrokkenheid en enthousiasme bij het Veerkracht-project en wat leuk dat we met elkaar de cursus Fysiotherapie in de palliatieve zorg bij kanker geven.

Daarnaast wil ik ook mijn collega's bedanken in de 3 ziekenhuizen waar ik de afgelopen jaren heb gewerkt. In het **Antoni van Leeuwenhoek ziekenhuis** heb ik mijn

onderzoekswerk een tijd kunnen combineren het werken op de poli en in het ziekenhuis. Ik kijk met een heel warm gevoel terug op mijn tijd bij jullie. Dank voor alle mooie ervaringen **Ronald, Miranda, Paulien, Anne-Marie, Kim, Sarah, Carolien, Anne, Marjon, Danique, Andy, Esther en Corine.**

Lieve collega's van de medische oncologie van het **Amsterdam UMC**, zo fijn dat de corona-maatregelen voorbij waren en we weer in het ziekenhuis konden werken, dank voor de gezellige momenten! In het bijzonder, lieve **Hanneke**, ik had graag nog eens vaker in de avond doorgewerkt met een kerstpakket binnen handbereik en lieve **Sofie**, dank voor je aanstekelijke enthousiasme en luisterend oor.

En last but not least wil ik graag mijn collega's van de afdeling fysiologie van het **Radboudumc** bedanken. Heel leuk dat ik nog wat langer kan blijven en nu wat meer aanwezig ben op deze gezellige afdeling. Graag wil ik nog een aantal mensen in het bijzonder noemen. **Calvin** en **Isa**, ik werk erg fijn met jullie samen. Jullie geven back-up als het nodig is, zijn altijd te porren voor een goede bak koffie en ik heb jullie nog nooit met een slecht humeur getroffen. **Anna** en **Marlou-Floor**, wat leuk dat jullie de 'Exercise Oncology' groep verder hebben aangevuld. Anna, van jouw kennis van het immuunsysteem kan ik erg veel leren, wat een bevlogenheid. En Marlou-Floor, mijn nieuwe kamergenoot, heel fijn om om over jouw ervaringen met het promovoren te horen en het ook af en toe over toekomstplannen te hebben. **Stephanie**, ik heb bij het opzetten van de studies heel veel gebruik kunnen maken van jouw ervaring. Daarnaast vond ik het fijn om samen te werken met iemand die ook uit de praktijk komt, helaas door corona en verschillende werkplekken wat minder vaak dan ik had gewild. En dank aan alle andere (oud) 'Exercise Oncology' leden, **Milan, Yvonne, Anna, Niek** en **Koen**, voor jullie interessante en leuke bijdragen aan de overleggen.

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in Enschede of Amsterdam was of mijn reizen naar het buitenland, jullie gaven mij altijd vertrouwen.

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List of publications

Stuiver MM, **ten Tusscher MR**, Agasi-Idenburg CS, Lucas C, Aaronson NK, Bossuyt PM. Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy. Cochrane Database Syst Rev. 2015 Feb 13;(2):CD009765.

Stuiver MM, **ten Tusscher MR**, van Opzeeland A, Brendeke W, Lindeboom R, Dijkstra PU, Aaronson NK. Psychometric properties of 3 patient-reported outcome measures for the assessment of shoulder disability after neck dissection. Head Neck. 2016 Jan;38(1):102-10. doi: 10.1002/hed.23859. Epub 2015 Jun 15. PMID: 25224150.

Stuiver MM, **Ten Tusscher MR**, McNeely ML. Which are the best conservative interventions for lymphoedema after breast cancer surgery? BMJ. 2017 Jun 1;357:j2330.

Ten Tusscher MR*, Groen WG*, Geleijn E, Sonke GS, Konings IR, Van der Vorst MJ, van Zweeden A, Aaronson NK, Stuiver MM. Physical problems, functional limitations, and preferences for physical therapist-guided exercise programs among Dutch patients with metastatic breast cancer: a mixed methods study. **Shared first authorship.* Support Care Cancer. 2019 Aug;27(8):3061-3070.

Ten Tusscher MR, Groen WG, Geleijn E, Berkelaar D, Aaronson NK, Stuiver MM. Education Needs of Dutch Physical Therapists for the Treatment of Patients With Advanced Cancer: A Mixed Methods Study. Phys Ther. 2020 Mar 10;100(3):477-486.

Groen WG*, **Ten Tusscher MR***, Verbeek R, Geleijn E, Sonke GS, Konings IR, Van der Vorst MJ, van Zweeden AA, Schrama JG, Vrijaldenhoven S, Bakker SD, Aaronson NK, Stuiver MM. Feasibility and outcomes of a goal-directed physical therapy program for patients with metastatic breast cancer. **Shared first authorship.* Support Care Cancer. 2021 Jun;29(6):3287-3298.

Veerkracht: een fysiotherapeutisch begeleid, doelgericht beweegprogramma voor mensen met uitgezaaide borstkanker. Oedeem & Oncologie 2022 maart: volume 1. Marieke ten Tusscher, Wim Groen, Martijn Stuiver.

Marieke R. ten Tusscher, Martijn M. Stuiver, Caroline S. Kampshoff, Rosalie J. Huijsmans, Neil K. Aaronson, Miranda Velthuis, Roxanne Gal, Hanna van Waart, Anne M. May, Laurien M. Buffart. Translating evidence from Dutch exercise oncology-trials in patients with breast cancer into clinical practice using the RE-AIM framework. *Submitted*

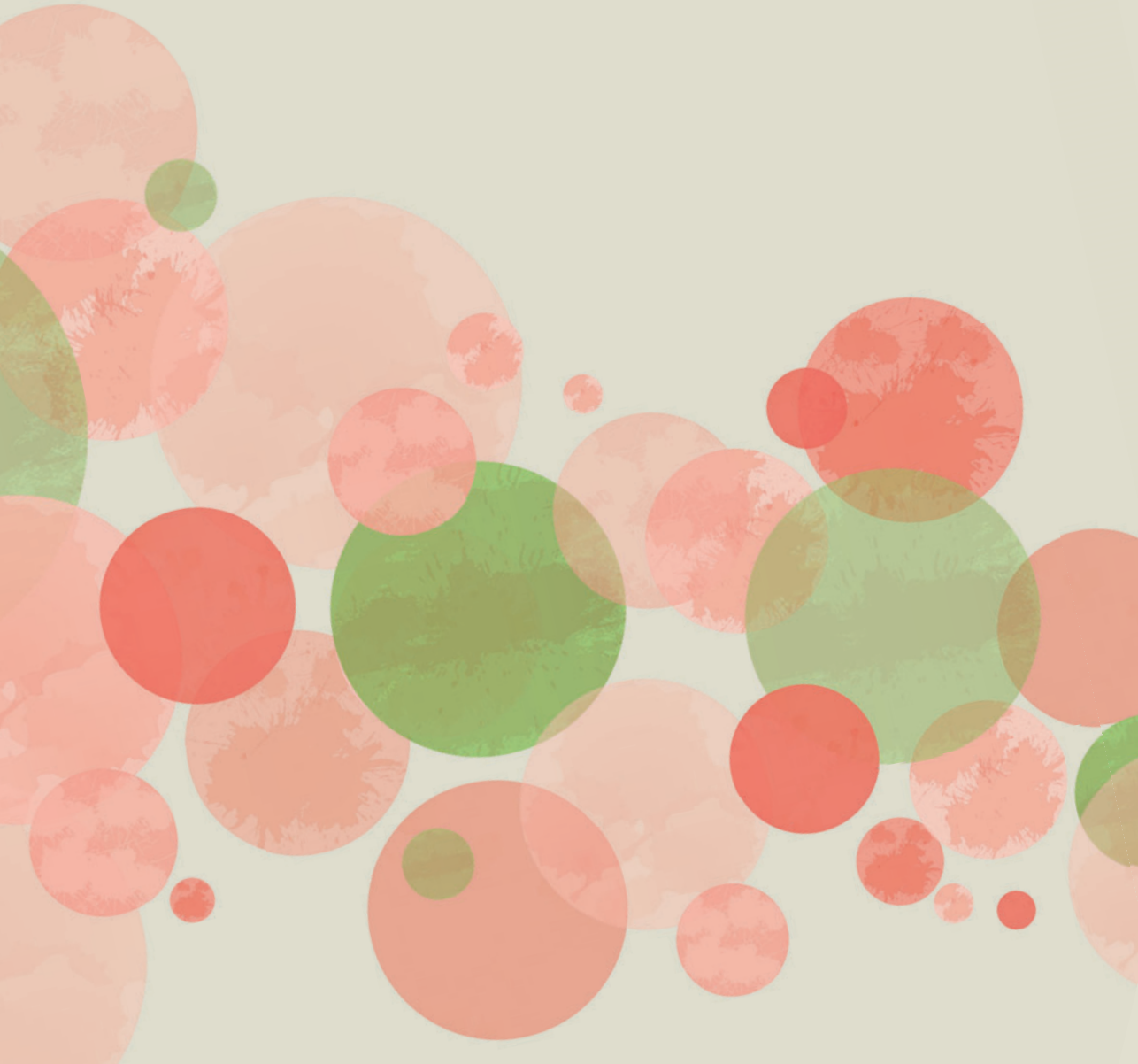
Stephanie Stelten MSc.*, **Marieke R. ten Tusscher MSc.***, Martijn M. Stuiver Ph.D., Yvonne A.W. Hartman Ph.D., Luc R.C.W. van Lonkhuijzen MD Ph.D., Gemma G. Kenter MD Ph.D.,

Marike van der Leeden Ph.D., Meeke Hoedjes Ph.D., Laurien M. Buffart Ph.D. Tailoring of Exercise and Dietary Interventions to Adverse Effects and Existing Comorbidities in Patients with Cancer Receiving Chemotherapy: a clinical vignettes study among expert physical therapists and dietitians. * *Shared first authorship. Submitted*

PhD portfolio of Marieke ten Tusscher

Department: **Medical BioSciences**
PhD period: **01/09/2015 – 01/01/2023**
PhD Supervisor(s): **Prof. dr. M.T.E. Hopman, prof. dr. J.J. van der Vliet**
PhD Co-supervisor(s): **Dr L.M. Buffart, dr. M.M. Stuiver**

Training activities	Hours
Courses	
Presenting with impact (2016)	12.00
Qualitative research in health care (2016)	38.00
English scientific writing (2017)	16.00
Motivational Interviewing (2018)	12.00
Maximal Exercise testing (2019)	20.00
Regression techniques (2019)	48.00
Good Clinical Practice (basic) (2020)	6.00
BROK course (basic course regulations and organization for clinical researchers) (2021)	20.00
Career orientation (2021)	26.00
Scientific integrity (2022)	20.00
Implementation research (2022)	36.00
Overtuigen, Spreken en Presenteren (2022)	18.00
Seminars & lectures	
Exercise oncology meetings (since 2021)	20.00
Research meetings physiology group (since 2020)	30.00
Conferences	
Annual Meeting of Supportive Care in Cancer (MASCC) (poster and brief oral presentation) (2017)	32.00
Voeding, Bewegen en Kanker (oral presentation) (2017)	14.00
International Conference on Physical Therapy in Oncology (ICPTO) (oral presentation) (2021)	24.00
Fitfair (oral presentation) (2022)	14.00
Radboud Oncology Retreat (poster) (2022)	24.00
Teaching activities	
Lecturing	
Lecturer on the minor Rehabilitation, Movement and Sports at the Erasmus MC (2021)	5.00
Assisting in lectures and workshops for Biomedical sciences on exercise oncology (2022)	22.00
Lecturer on the semi-annual course of physical therapy in patients with palliative cancer (NPI) (since 2018)	14.00
Supervision of internships / other	
Thesis supervision Master Oncologic Physical Therapy (2017)	24.00
Thesis supervision Master Oncologic Physical Therapy (2018)	24.00
Literature study supervision Master Oncology (2022)	10.00
Total	**529.00**



Pink Ribbon

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