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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.

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Keywords: Metastatic Breast Cancer, Physical Therapy, Goal Setting, Tailored exercise program

Declarations:

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Consent to participate All participants provided written informed consent prior to study participation.

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Code availability: Not applicable

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Wim Groen, Marieke ten Tusscher and Martijn Stuiver. The first draft of the manuscript was written by Wim Groen and Marieke ten Tusscher and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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: (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 was 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 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 eHealth (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 I.

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 eHealth 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 evaluated by 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 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 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, eHealth, 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 eHealth 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 work flow 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 0-100, 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 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 d_z) 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-minute 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] (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 cancelling/not attending appointments were related to illness, personal factors unrelated to the disease and hospitalization due to the cancer.

Outcome measures

Goal setting and -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

311 30 minutes"; (2) *activities of daily living* (n=31) (e.g., "walk two flights of stairs without
312 being short of breath"; (3) *maintaining posture* (n=10) (e.g., "standing upright for 30
313 minutes during cooking"); and (4) *Relaxation* (n=1).

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

320 *Satisfaction of patients*

321 Thirty-three participants provided feedback regarding their satisfaction with the
322 program. Of these, 28 (85%) indicated that they would "definitely recommend" (highest
323 response category) the *Veerkracht* program to other patients in a comparable situation,
324 1 (3%) was likely to recommend, 2 (6%) were unlikely to recommend the program and
325 2 patients (6%) did not know. Median satisfaction scores on all aspects were high and
326 patients, on average, believed that the intervention contributed to their physical fitness
327 and to their being able to perform their daily activities (Table 4).

328 *Satisfaction of physical therapists*

329 Twenty-one physical therapists (64%) completed the evaluation questionnaire. Of
330 these, ten (48%) reported using the written practice guide very often, two (10%) often,
331 eight (38%) occasionally, and one (5%) almost never (because she was already
332 familiar with the content). Almost all of the physical therapists (n=20, 95%) were (very)
333 satisfied with the written guidebook. Cited benefits of the education session were
334 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 eHealth 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 Minute walking test). Walking distance increased for 16 patients an average of 73.8 meters (95% CI: 37.1 ; 110.6) from 407 (SD 103) meters to 481 (102) meters (E.S. 0.72).

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 drop-out due to disease progression was 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.

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 was feasible in a hospital-based rehabilitation setting. Approximately 70% of the women achieved or exceeded their rehabilitation goals, which were not 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.

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 one-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* operationalisations 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 exactly what needs to be measured (i.e. a perceived change in [patient-specific] functioning). Thus, it may be a more direct reflection of performance, whereas standardized functional measures rather reflect capacity and as such is a valuable addition to functional testing. [26]. 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 accommodate for the complex nature of the intervention [27] .

Conflict of interest

We have no conflicts of interest to disclose. The corresponding author has full control of all data and agrees to allow the journal to review it if requested.

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528 the Multinational Association of Supportive Care in Cancer 22: 1537-1548

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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%)

532 Table 1. Patient characteristics. * N=53, ** N=54

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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	1.0 (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

534 Table 2. Intervention characteristics. *Data was available for 47 patients.

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	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

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

	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)

Table 4. Satisfaction with and perceived benefits of the intervention as rated by patients. *Net number of patients that contribute to the score, **Numbers are related

542 to total number of completed evaluation questionnaires. *** Score ranges from 0 (worst
543 possible score) to 10 (best possible score)

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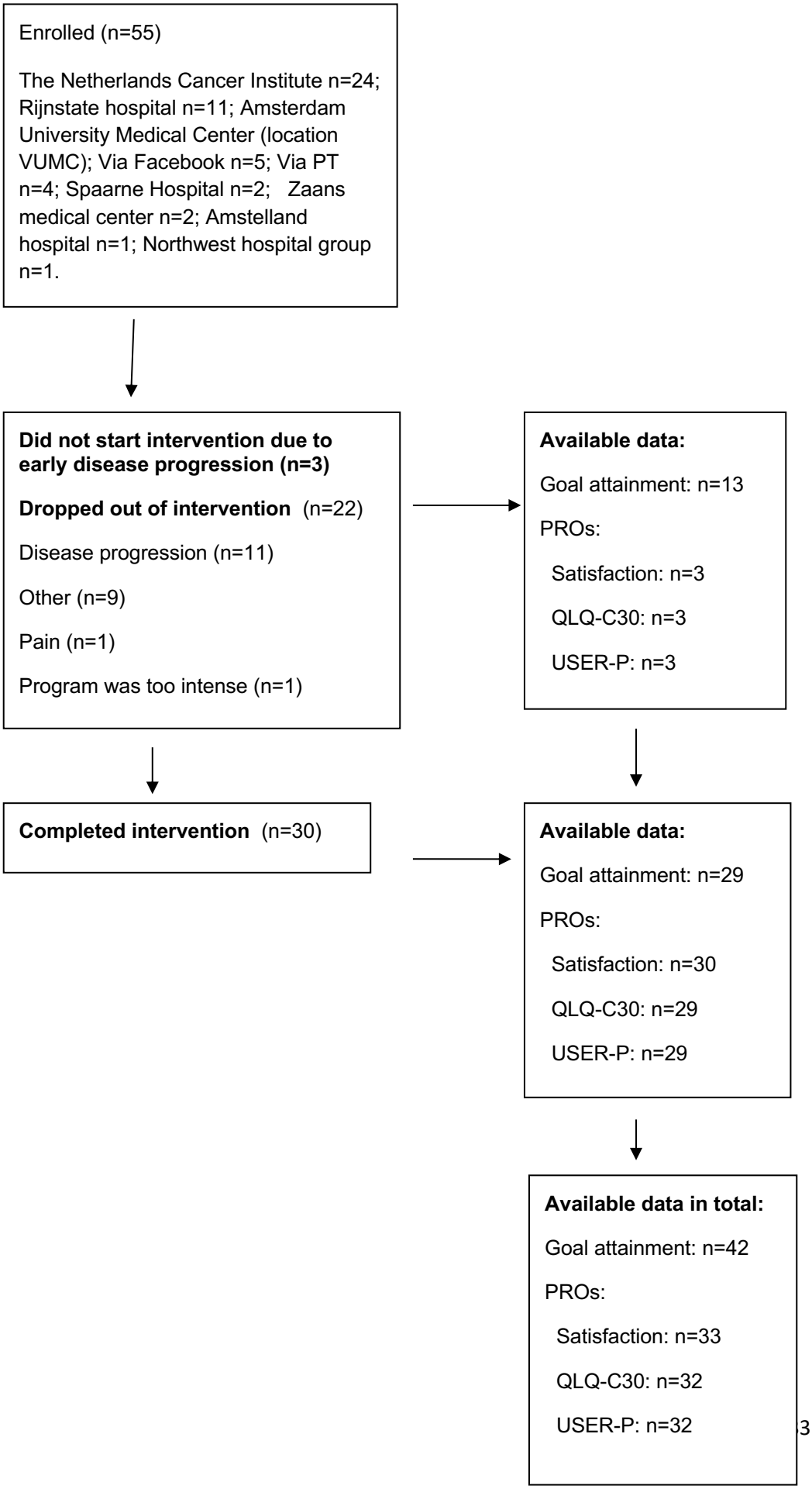
Variable	T0 for all patients (MEAN,SD)	T0 for which a T1 was available (MEAN,SD)	T1(MEAN, SD)	Mean change T0-T1 (effect size)	95%CI of change
USER-P*	N=55	N=32	N=32	N=32	
Satisfaction	55.6 (20.3)	59.1 (19.4)	65.3 (17.7)	6.2 (0.33)	0.3; 12.0
Restrictions	73.3 (16.5)	74.9 (16.8)	77.6 (16.8)	2.7 (0.16)	-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

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

Figure 1 Flow of participants and data



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 the following components:

Overview of program modules

<u>Exercise modules to target patient-specific functional goals</u>

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. PT's 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 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 Onco-Move. 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 minutes 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 minutes 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 minutes 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 increase and >16 for decrease of intensity. Participants who follow this program will also be encouraged to be physically active 5 days a week for 30 minutes. On-track 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 On-Track protocol have been adapted to the special needs of metastatic breast cancer patients (e.g. strength training of areas

615 with significant bone metastases are avoided according to the protocol of Cormie et al.
616 [32].

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

622 Generic module

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

628 **Origin of program modules**

629 The program modules were selected based on a needs assessment we performed
630 through focus groups and a survey among 114 patients with metastatic breast cancer
631 [6]. Intervention components 1-4 are, in fact, already part of daily practice of physical
632 therapists and only require some modification for the special needs of metastatic breast
633 cancer (points of attention include, for example, bone metastasis, impaired physical
634 fitness and/or diminished adaptive capacity due to the disease or its treatment).
635 Components 5 and 6 have been successfully evaluated in the curative setting by van
636 Waart et al. [31] and were consequently adapted for patients with metastatic disease.
637 Component 7 is a component that is written specifically for the target population to
638 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 are 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, there is no uniform recommendation with regard to frequency, intensity and amount of supervision. 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. travelling distance, physical functioning level).

Appendix 2: Detailed information on the Onconet-network

Onconet is a nation-wide network of physical therapists. These physiotherapists 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 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. Both the initial courses as the refresher courses are offered via a not for profit post-graduate education institute, in close collaboration with the Onconet board. For initial registration, several other Dutch institutes also provide accredited trainings (including MSc-level oncology physical therapy specializations). 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. This policy ensures that only physical therapists who are willing to do the extra effort needed and who possess sufficient skills and knowledge remain in the network, and that those who remain in the network are up to date with the latest evidence and best practices. 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 formal parnter of the Oncology section of the Royal Dutch Society of Physical Therapy (KNGF).

685 **Appendix 3.** Full list of physical tests or questionnaires used

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

686 Legend: TUGT: timed up and go test. SWT: shuttle walk test. 6MWT: 6 minute walk
687 test. 5TSTST: 5 times sit to stand test. SPPB: Short physical performance battery.

688 1RM-LE: 1 repetition maximum – lower extremities. 1RM-UE: 1 repetition maximum –
689 upper extremities. 1minRM NPRS: numerical pain rating scale. BBS: Berg Balance
690 Scale. SRT: Steep ramp test. Astrand: Astrand test. MFI: Multidemensional fatigue
691 inventory. VAS fatigue: visual analogue scale for fatige. AFQ: abbreviated fatigue
692 questionnaire.