

Feasibility and outcomes of a goal-directed physical therapy program for patients with metastatic breast cancer

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1 **Feasibility and outcomes of a goal-directed physical therapy program for**
2 **patients with metastatic breast cancer**

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41

42 **ABSTRACT**

43 **Purpose**

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

46 **Methods**

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

54 **Results**

55 Fifty-five patients (estimated participation rate: 34%) were enrolled. Three patients did
56 not start the intervention due to early disease progression. An additional 22 patients
57 discontinued the program prematurely, mainly due to disease progression. Median
58 intervention adherence was 90% and no major intervention-related adverse events
59 occurred. A goal-attainment score was available for 42 patients (of whom 29 had
60 completed the program and 13 had prematurely dropped out). Twenty-two (52%) of
61 these patients achieved their main goal fully or largely and an additional 15 patients
62 (36%) partially. Eighty-five percent would "definitely recommend" the program to other
63 patients with MBC. We observed a modest improvement in patient satisfaction with
64 physical activities (Cohen's d_z 0.33).

65 **Conclusion**

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

69

70 **Trial registration:** NTR register, NTR6475, date of registration: 2017-03-09

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

73

74

75 **Declarations:**

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77 **Conflicts of interest/Competing interests:** There are no conflicts of interests to
78 disclose.

79 **Ethics approval:** The institutional review board of the Netherlands Cancer Institute
80 approved the study. All participants provided informed consent, and were treated in
81 accordance with the Declaration of Helsinki.

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

84 **Consent for publication** n.a.

85 **Availability of data and material:** Data can be obtained from the corresponding
86 author

87 **Code availability:** Not applicable

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

94

95

96 **INTRODUCTION**

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

104

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

113

114 In advanced breast cancer, the empirical support for the feasibility and effectiveness
115 of exercise and rehabilitation is limited[13, 14]. To date, the studies performed in
116 advanced cancer are to a large extent “intervention centered”; although exercise
117 parameters are tailored to patients' capacity, the intervention itself is rather uniform
118 [13, 14]. We would argue that tailoring the program to individual patients' unique goals
119 and preferences needs special consideration in the palliative phase. The aim is to
120 precisely target those aspects of functioning in daily life that are most valuable to the

121 individual, and thus most likely to improve their quality of life. Such a goal-directed
122 program does not yet exist, and in general the range of exercise- and rehabilitation
123 interventions available for this patient population is currently limited and fragmented.
124 At the same time, patients with MBC have expressed an interest in exercise-based
125 rehabilitation programs[5].

126

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

137

138

139 **METHODS**

140 **Design and patients**

141 In this single-arm feasibility study we recruited patients from seven Dutch hospitals:
142 The Netherlands Cancer Institute, Amsterdam University Medical Center (location
143 VUMC), Amstelland hospital, Rijnstate hospital, Northwest Hospital Group (location
144 Alkmaar), Zaans Medical Center and Spaarne hospital. The recruitment strategies

145 differed between these hospitals. In The Netherlands Cancer Institute and Rijnstate
146 hospital, all eligible patients who were under current care of the hospital were
147 evaluated for eligibility for inclusion by their treating physician and then approached by
148 a letter. In the other hospitals the treating physician approached eligible patients during
149 their regular outpatient appointments. Patients were also recruited via a closed-group
150 Facebook page for patients with advanced breast cancer and via the website of the
151 Dutch Breast Cancer Association. Finally, physical therapists involved in the study
152 could refer potentially eligible patients.

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

164 **Intervention**

165 During a comprehensive intake performed by the physical therapist, program goals
166 were set using a stepwise approach, "Patient-specific goal setting (PSG)", as proposed
167 by Stevens et al. [16]. The steps included: (1) identifying health-related problems in
168 activities in daily life; (2) prioritizing the most important activities to be targeted by the

169 intervention; (3) scoring the perceived ability to perform these activities on a Numeric
170 Rating Scale (0 = impossible to perform to 10 = easy to perform); (4) translating the
171 selected activities into specific treatment goals; and (5) planning treatment. A tailored,
172 exercise-based physical therapy program was then provided that best targeted the
173 patients' goal(s).

174 Tests of physical fitness and functioning were used to measure baseline capacity,
175 identify targets for therapy, and to evaluate the treatment outcome at the functional
176 level. The physical therapist selected from a core set of tests those tests that were
177 most relevant to the patient's goals. Thus, the tests could differ from patient to patient.
178 Also, the frequency, duration and specific content of the program was determined for
179 each patient individually, again depending on the patient's goals and clinical status.
180 Program content could include resistance and/or aerobic exercises, functional
181 exercises (e.g. stair climbing) and/or or relaxation exercises. Also, the program could
182 be offered with differing degrees of supervision, ranging from fully supervised/in-
183 person to fully home-based, and included the optional use of eHealth (Physitrack,
184 Physitrack Ltd, London, UK). Specific exercise libraries were prepared within
185 Physitrack using both readily available exercises and exercises that were added
186 specifically for this patient population. Detailed information about the program modules
187 and their rationale are presented in Appendix I.

188 **Education of physiotherapists**

189 All participating physical therapists had previous training in working with oncology
190 patients via the Onconet network (Appendix 2). They received an additional, full day
191 training session specifically targeted at providing the *Veerkracht* program. This training
192 session included medical background information on MBC, goal setting in the context

193 of MBC, physical testing procedures, and the use of the Physitrack eHealth platform.
194 Additionally, the physical therapists were instructed on study procedures, received a
195 *Veerkracht* practice guide, and a subscription to *Physitrack*, with access to the
196 *Veerkracht* library of exercises.

197 **Assessments**

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

202

203 Process related outcomes

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

213

214 **Safety** was evaluated based on the occurrence of any serious adverse events (SAEs)
215 or of adverse events (AEs) that were directly related to the *Veerkracht* intervention,
216 and that occurred during or shortly after the sessions (e.g., cardiovascular events or

217 falls resulting in fractures, but also muscle pain or joint pain). We used a selection of
218 the Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 v.4.03,
219 including muscle pain, joint pain, back pain, bone pain, pain in extremities, hypotension
220 and lymphedema. We only registered grade 2 complications (moderate symptoms and
221 limited in instrumental ADL) or worse.

222

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

226

227 Outcomes related to satisfaction with and preliminary results of the intervention

228 **Satisfaction** of patients was measured by a short, study-specific questionnaire that
229 covered the intake procedure and the applicable intervention components (exercise,
230 relaxation, eHealth, etc.). The physical therapists' satisfaction was evaluated via an
231 online questionnaire and concerned the training that they received, the perceived
232 usefulness of the study's practice guide, the intervention components, and the
233 Physitrack eHealth platform.

234

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

241 Activities of daily living and participation were measured with the “Utrecht scale for
242 evaluation of rehabilitation-participation” (USER-P) [18]. This questionnaire was
243 developed specifically to evaluate the outcomes considered most relevant to
244 rehabilitation. It contains 32 questions about daily activities and participation,
245 organized into three sub-scales assessing the frequency with which daily activities are
246 performed (Frequency), whether one perceives any impairments in activities of daily
247 living (Restrictions), and satisfaction with current activities of daily living (Satisfaction)
248 [18]. Higher scores indicate better levels of participation (higher frequency, less
249 restrictions, higher satisfaction).[18]

250 HRQoL was assessed with the European Organisation for Research and Treatment of
251 Cancer QLQ-C30 questionnaire[19]. The QLQ-C30 incorporates nine multi-item
252 scales: five functional scales (physical, role, cognitive, emotional, and social); three
253 symptom scales (fatigue, pain, and nausea and vomiting); and a global health and
254 quality-of-life scale. Several single-item symptom measures are also included. An
255 overall QLQ-C30 summary score can be calculated. For all scales, scores range from
256 0-100, with higher scores representing better functioning (functional scales and overall
257 summary score) or more severe symptoms (symptom scales).

258

259 **Statistical analyses**

260 All analyses were performed with SPSS version 22 for Windows (IBM Corp. Somers,
261 NY, USA). We calculated summary statistics for sociodemographic and clinical data.
262 Satisfaction was analyzed at the individual item level; responses for all items are
263 presented as raw scores. For goal-attainment, we calculated frequency and
264 percentage of each score category for program completers, non-completers and the

265 combined group. To obtain an indication of changes in activities of daily living (USER-
266 P) and HRQoL, we performed analyses on an intention to treat basis, including all
267 available data at baseline and end of intervention, regardless of whether participants
268 had followed the intervention as planned. Changes in physical test scores were
269 calculated only for the most frequently used tests (≥ 10 pairs available). Mean changes
270 with 95% confidence intervals were obtained from paired samples Student's t-tests.
271 The standardized mean difference effect size (E.S.) for within-subjects designs
272 (Cohen's d_z) was calculated [20]. Effect sizes of 0.2, 0.5, and 0.8 represent small,
273 moderate and large effects, respectively [21].

274

275 **RESULTS**

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

281 **Characteristics of the provided interventions**

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

288

289 **Process measures**

290 *Uptake*

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

294 *Safety*

295 Physical therapists reported ten grade-2 and four grade-3 adverse events (AEs) that
296 were potentially related to the intervention. The grade 2 AEs consisted of transient
297 muscle pain (n=4), joint pain (n=3,) back pain (n=2), and bone pain (n=1). The grade
298 3 AEs consisted of muscle pain (n=3) and bone pain (n=1) interfering with daily
299 activities. No hospitalizations were required for any of these AEs.

300 *Adherence*

301 The median adherence rate of patients who completed the intervention was 90% (N =
302 36; IQR 80 -100%). Reasons for cancelling/not attending appointments were related
303 to illness, personal factors unrelated to the disease and hospitalization due to the
304 cancer.

305 **Outcome measures**

306 *Goal setting and -attainment*

307 Most patients set 2 or more goals. We categorized these in line with predetermined
308 categories that were already used in the practice guide for the physical therapists: (1)
309 *Sports/exercise and being physically active* (n=43) (.e.g, "Improve my strength and
310 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

335 the boundaries of the intervention program with regard to goals and duration, and
336 increased confidence in prescribing exercises for patients with bone metastases. Ten
337 physical therapists had used the Physitrack eHealth platform and favorably rated its
338 navigability and clear exercises. Some of the physical therapists mentioned the lack of
339 integration/communication with the electronic medical record (EMR) as a drawback of
340 the platform.

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

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

351

352 **DISCUSSION**

353 The results of our study indicate that the *Veerkracht* program designed to support
354 physical activity and daily functioning of patients with MBC via physical therapist-
355 supervised interventions is largely feasible as rated by several process and safety
356 indicators. Overall, patients and physical therapists were very satisfied with the
357 program, and many patients were able to meet their goals. There was some indication
358 of improved scores related to satisfaction with activities of daily living, and HRQOL

359 scores remained unchanged. However, interference and drop-out due to disease
360 progression was substantial. An in-depth exploration of the underlying reasons for
361 program cessation was beyond the scope of this study, so uncertainty remains with
362 regard to whether or not – and how – the program should or can be adapted to
363 accommodate patients' shifting needs and perspectives at the time of disease
364 progression.

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

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

384 probably a better reflection of what can be expected in clinical practice. In one recent
385 oncology rehabilitation study including women with gynecological (i.e. cervical,
386 endometrial and ovarian) cancer,[23] a goal setting and evaluation approach similar to
387 ours was used. The study showed that women's goal setting and self-assessment of
388 goal achievement was feasible in a hospital-based rehabilitation setting. Approximately
389 70% of the women achieved or exceeded their rehabilitation goals, which were not
390 limited to physical functioning, but also included social, emotional, cognitive, existential
391 and sexual functioning goals [23]. In our study, for the overall group, we found a
392 considerably lower rate of full goal attainment (+/-25% across all goals), with an
393 additional 25 to 30% attaining their goal in large part. This may be related to the
394 intervention, the different population (mainly curative vs. advanced disease), the
395 differences in types of goals, or the slightly different method of goal setting and
396 evaluation.

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

407 **Limitations**

408 Several uncertainties remain due to the scope and design of the study. First, because
409 the study was uncontrolled, we cannot determine whether observed changes in
410 physical function or HRQoL were due to the intervention, per se. Second, our goal
411 attainment scaling method was somewhat subjective as there were no formal *a priori*
412 operationalisations of "fully attained", "largely attained" or "partially attained" goals.
413 However, our approach fits into the daily routine of physical therapists, and we would
414 note that the validity of more formal procedures of goal attainment scaling remains
415 ambiguous [25]. *Though subjective, goal attainment scoring does measure exactly
416 what needs to be measured (i.e. a perceived change in [patient-specific] functioning).
417 Thus, it may be a more direct reflection of performance, whereas standardized
418 functional measures rather reflect capacity and as such is a valuable addition to
419 functional testing.* [26]. Lastly, getting the participating physical therapists to
420 systematically collect and report process-related data proved to be challenging. Data
421 collection in future similar studies might be improved by using electronic CRFs.

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

429 **Conflict of interest**

430 We have no conflicts of interest to disclose. The corresponding author has full control
431 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

529

530

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

533

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.

535

536

	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

537 Table 3. Extent of goal attainment. *percentages are provided as fraction of total

538 number of goals set.

539

	N (net)*	not applicabl e	Missin g**	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)

540 Table 4. Satisfaction with and perceived benefits of the intervention as rated by
541 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)

544

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

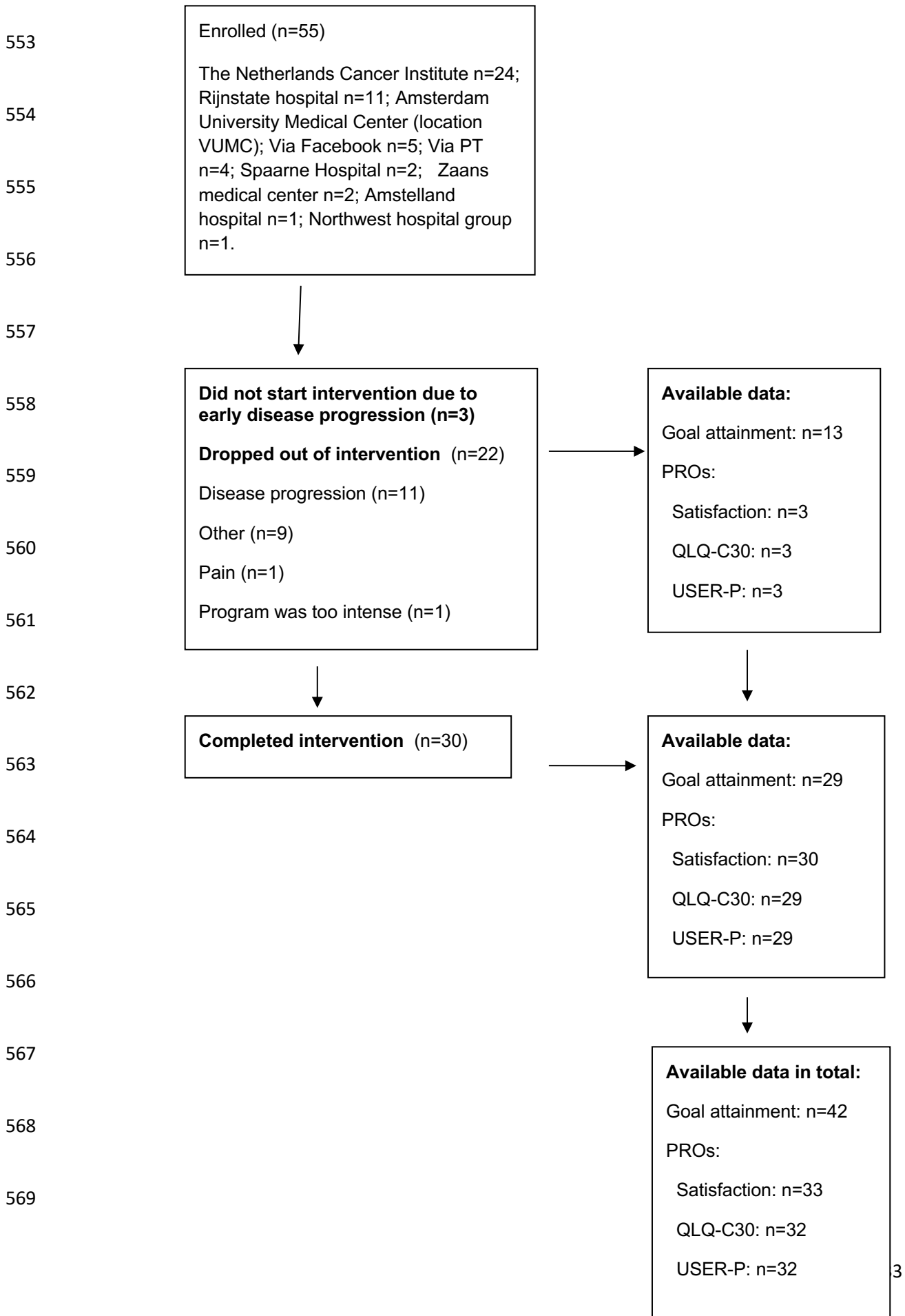
545 Table 5. Pre- and posttest values for the Utrecht Scale and the EORTC QLQ-C30;
546 scores are presented as mean (SD). * Scores range from 0-100, with 0 indicating worst
547 possible outcome and 100 indicating best possible outcome.**N=54. *** N=52. The
548 data are based on intention to treat analysis.

549

550

551

552 Figure 1 Flow of participants and data



570 **Appendix 1:** Detailed information on the tailored intervention and its components

571 **General information**

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

578 **Overview of program modules**

579 Exercise modules to target patient-specific functional goals

580 1) Resistance exercises including a range of exercises targeting the muscles that are
581 limiting performance. This can include training on resistance exercise machines,
582 training with dumbbells/free weights or exercises with own body weight. PT's are
583 educated to adjust resistance exercises in case of bone metastasis according to the
584 protocol of Cormie et al. [28]

585 2) Aerobic exercises, including exercises targeting large muscles of the body such as
586 swimming, rowing, cycling, walking or running, performed at an intensity of 55-80% of
587 estimated maximal heart rate).

588 3) Functional skill exercises (deficient skills are trained in a systematic manner, e.g.
589 balance training, stair climbing, transfer training [29].

590 4) Relaxation exercises (e.g. progressive muscle relaxation) [30].

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

593 5) Modified Onco-Move. OncoMove is based on the original program as described by
594 van Waart et al. [31] and is adapted for our current population. It is a home-based, low
595 intensity, individualized, self-managed physical activity program as proposed by Mock
596 et al. with the addition of behavioral reinforcement techniques. These comprise written
597 information tailored to the individual's preparedness to exercise according to the
598 Transtheoretical model, and an activity diary that is discussed at each chemotherapy
599 cycle. Specially trained physical therapists will encourage participants to engage in at
600 least 30 minutes of physical activity per day, 5 days a week, with an intensity level of
601 12-14 on the Borg Scale of perceived exertion.

602 6) Modified OnTrack. OnTrack is a moderate-high intensity, combined resistance and
603 aerobic exercise program, supervised by specially trained physical therapists. The
604 participants attend two sessions per week. Six large muscle groups are trained for 20
605 minutes per session, with 2 series of 8 repetitions at 80% of 1 repetition maximum
606 (1RM). (Indirect) 1RM testing repeated every 3 weeks. Each session incorporates 30
607 minutes of aerobic exercises, with an intensity of 50 to 80% of the maximal workload
608 (Wmax) as estimated by the Steep Ramp Test. The intensity is adjusted using the Borg
609 Scale, with a threshold of <12 for increase and >16 for decrease of intensity.
610 Participants who follow this program will also be encouraged to be physically active 5
611 days a week for 30 minutes. On-track is based on the original program as described
612 by van Waart et al. [31], and has been adapted for the metastatic setting. For example,
613 the resistance training exercises of the original On-Track protocol have been adapted
614 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

639 potential use of exercise to improve or maintain functional status. The novelty of the
640 proposed intervention is that it adapts standard physical therapy interventions by using
641 a structured intake procedure that includes an evaluation of adaptive capacity and
642 safety that is specific to the target population, and by explicitly incorporating restrictions
643 that are specific to the target population. The addition of an e-health component is
644 intended to provide additional support in learning, carrying out, and adhering to the
645 exercise program.

646 **Frequency, intensity and duration of the program**

647 PTs are trained to set proper treatment goals with the patient based on patient-
648 dependent factors (e.g. personal goals, exercise history, preferences, context, and
649 financial possibilities). Consequently, there is no uniform recommendation with regard
650 to frequency, intensity and amount of supervision. The total program duration will
651 depend on the specific schedule and is anticipated to last a maximum of 12 weeks, but
652 PTs could choose to alter this duration if needed.

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

662

663 **Appendix 2:** Detailed information on the Onconet-network

664 Onconet is a nation-wide network of physical therapists. These physiotherapists have
665 received 67 hours or more of additional training in subjects such as basic oncology,
666 exercise oncology, behavioral support, dealing with cancer-specific side effects,
667 dealing with comorbidity, using clinimetrics and clinical reasoning in an oncology
668 context. All the physical therapists in the network follow mandatory refresher courses
669 and have to pass summative tests related to these courses. Both the initial courses
670 as the refresher courses are offered via a not for profit post-graduate education
671 institute, in close collaboration with the Onconet board. For initial registration, several
672 other Dutch institutes also provide accredited trainings (including MSc-level oncology
673 physical therapy specializations). Patients and referrers can identify the nearest
674 Onconet physical therapist using a searchable index on the Onconet website. Those
675 who do not attend the refresher courses, or who fail the tests, are subsequently
676 removed from the index. This policy ensures that only physical therapists who are
677 willing to do the extra effort needed and who possess sufficient skills and knowledge
678 remain in the network, and that those who remain in the network are up to date with
679 the latest evidence and best practices. Currently, the network covers most of the
680 populated areas in the Netherlands and an Onconet therapist is available anywhere
681 within a 15' commute for most people. Since September 2020, Onconet is formal
682 partner of the Oncology section of the Royal Dutch Society of Physical Therapy
683 (KNGF).

684

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: Multidimensional fatigue
691 inventory. VAS fatigue: visual analogue scale for fatigue. AFQ: abbreviated fatigue
692 questionnaire.