Progressive Resistance Training to Impact Physical Fitness and Body Weight in Pancreatic Cancer Patients

A Randomized Controlled Trial

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Objectives: Maintaining or improving muscle mass and muscle strength is an important treatment goal in pancreatic cancer (PC) patients because of high risk of cachexia. Therefore, we assessed feasibility and effectivity of a 6-month progressive resistance training (RT) in PC patients within a randomized controlled trial.

Methods: Sixty-five PC patients were randomly assigned to either supervised progressive RT (RT1), home-based RT (RT2), or usual care control group (CON). Both exercise groups performed training 2 times per week for 6 months. Muscle strength for knee, elbow, and hip extensors and flexors and cardiorespiratory fitness and body weight were assessed before and after the intervention period.

Results: Of 65 patients, 43 patients were analyzed. Adherence rates were 64.1% (RT1) and 78.4% (RT2) of the prescribed training sessions. RT1 showed significant improvements in elbow flexor/extensor muscle strength and in maximal work load versus CON and RT2 ($P < 0.05$). Further, knee extensors were significantly improved for RT1 versus CON ($P < 0.05$). Body weight revealed no significant group differences over time.

Conclusions: Progressive RT was feasible in PC patients and improved muscle strength with significant results for some muscle groups. Supervised RT seemed to be more effective than home-based RT.

Key Words: body weight, exercise, muscle strength, pancreatic cancer, physical activity, resistance training

(*Pancreas* 2019;48: 257–266)

Exercise has beneficial effects on disease- and treatment-related adverse effects in cancer patients across various entities and therefore plays an important role in supportive cancer care.[1–3] First evidence also suggests that physical activity plays an important role with regard to cancer recurrence and survival.[4] However, most studies were done in the field of breast cancer followed by prostate, lung, and hematological malignancies. Cancer populations with limited prognosis or higher symptom burden are mostly understudied.[5] This is particularly true for pancreatic cancer (PC), which is often diagnosed at an advanced disease stage and characterized by fast and aggressive disease progression. Despite generally poor prognosis, progress has been made, and surgery in combination with adjuvant chemotherapy can achieve long-term survival in a considerable number of patients.[6] However, postoperative weight loss may occur as well as changes in glycemic control and digestive function.[7] Furthermore, up to 74% of the patients suffer from cachexia,[8] a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass, with or without fat mass.[9] Loss of muscle mass and weight loss leads to reduced muscle strength, which further worsen functional capacity. Besides functional impairments, the presence of cachexia in PC patients is associated with poor survival.[10] Resistance training (RT) is seen as a potential measure to counteract cachexia by modulating body composition through enhanced muscle protein synthesis, reducing levels of inflammation and oxidative stress, increasing insulin sensitivity, and improving muscle metabolism.[11]

Therefore, maintenance of muscle mass, muscle strength, and body weight is regarded as an important goal for supportive therapy approaches in PC patients. Resistance training with its ability to improve muscle strength and muscle mass has been considered to be an important measure in this context.[12,13] However, we are aware of only 2 randomized controlled trials, one analyzing the effects of a 3-month walking program on fatigue, physical function, and quality of life in PC patients[14] and the other analyzing a multimodal intervention to reduce cachexia.[15]

Against this background, we conducted the SUPPORT Study (SUPervised PrOgressive Resistance Training for Pancreatic Cancer Patients) aiming to investigate feasibility of progressive RT during and after chemotherapy as well as to evaluate potential effects on muscle strength and cardiorespiratory fitness.

MATERIALS AND METHODS

Sample and Procedures

The SUPPORT Study was a randomized controlled intervention trial investigating the effects of a 6-month lasting progressive RT in PC patients. Inclusion criteria were resectable or nonresectable PC (stages I–IV); treated at Heidelberg University Hospital, Germany; 18 years or older; sufficient German language skills; and signed informed consent. Because of the same medical treatment regimen, patients with adenocarcinoma of the distal bile duct (pancreatic biliary) and with ampullary ductal adenocarcinoma were also eligible. Patients with insufficient wound healing, severely impaired hematological capacity, heart insufficiency or uncertain arrhythmia,

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Received for publication May 1, 2018; accepted November 11, 2018.
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The work was supported by the German Caner Aid under grants 110513 and 110552, as well as by additional financial support of the German Cancer Research Center (Division of Physical Activity, Prevention and Cancer) and the University Hospital Heidelberg (Divisions of Medical Oncology and General, Visceral and Transplantation Surgery).
J.W. and D.C. are co–first authors.
Registration no. ClinicalTrials.gov (NCT01977066).
The authors declare no conflict of interest.
All authors contributed to the data collection, manuscript writing, and final approval of the manuscript. J.W. and K.S. contributed to the conception of the study. J.W., D.C., and K.S. contributed to the data analysis and interpretation.

DOI: 10.1097/MPA.0000000000001221

uncontrolled hypertension, severe renal dysfunction, reduced standing or walking ability, or any other comorbidities that precluded participation in study procedures were excluded. Patients were recruited between December 2013 and December 2015. After baseline assessment patients were randomized to study arms. Allocation to one of the RT groups depended on the living distance from the study center. Patients living close to the study center (about <20 km) who were able to regularly visit our training facility were randomized to the supervised progressive RT group (RT1) or the control group (CON), whereas patients living farther away were assigned to the home-based progressive RT group (RT2) or CON. A 2:1 block randomization with a computerized random-number generator was used to allocate patients to the corresponding groups. Thus, CON included patients from all living distances in proportion to the exercising patients. Randomization was stratified by sex and age and was done by an independent statistician. Assessments for outcome parameters took place prior to the intervention start (T0, baseline) and postintervention (T2, 6 months). Baseline assessments were at the earliest 3 months after surgical resection to allow for adequate wound healing. Primary outcome for this analysis was feasibility of the RT intervention. Secondary outcomes were parameters of muscle strength and cardiorespiratory fitness. The study was approved by the ethics committee of the Medical Faculty of Heidelberg University (S-409/2013) and has been registered on ClinicalTrials.gov (NCT01977066).

Intervention

Patients were asked to perform RT twice a week during a 6-month intervention period. Both RT interventions comprised corresponding resistance exercises for major upper and lower muscle groups. During the first training session, each patient received an individual training introduction at the exercise facility or at the study center in Heidelberg. Contraindications to start a training session for both groups were infections, body temperature 38°C or greater, severe pain, impaired hematopoietic capacity, and having received chemotherapy within the last 24 hours.

Supervised Progressive RT

Patients trained at an exercise facility located at Heidelberg University's campus supervised by specialized exercise therapists. Following machine-based resistance exercises were performed: leg press, leg extension, leg curl, seated row, latissimus pull-down, back extension, butterfly reverse, and crunch. After 2 familiarization sessions including 1-repetition maximum (1-RM) testing according to the Brzycki[16] method, patients performed the first 5 exercises with 1 to 2 sets with 20 repetitions for a 4-week adaptation period with a low to moderate intensity (50%–60% 1-RM). As of week 5, the number of exercises was increased up to 8 exercises per session, and patients were asked to perform 3 sets with 8 to 12 repetitions with a moderate to vigorous intensity (60%–80% 1-RM). A complete training session took approximately 60 minutes. Training was progressive in terms of weight increase to the next machine weight level (at least 5%) after successfully completing 3 sets of an exercise with 12 repetitions in 3 consecutive sessions. Resistance training setup was in accordance with the American College of Sports Medicine (ACSM) exercise guidelines for cancer survivors.[17]

Home-Based Progressive RT

Patients received an exercise manual, resistance bands, dumbbells, and detailed training information during an individual in-person training introduction session. Resistance exercises corresponded to exercises of RT1. During the first 4 weeks (adaptation period), patients performed 5 exercises with intensities ranging from low to moderate (1–2 sets with 20 repetitions). From week 5 on, the number of exercises was also raised up to 8 exercises per session, and patients were also asked to perform 3 sets with 8 to 12 repetitions. Training intensity was adapted using the Rate of Perceived Exertion Scale (BORG Scale) with target scores of 14 to 16.[18] If necessary, adaptations with regard to exercise difficulty level were provided. A complete training session took approximately 60 minutes. The exercise specialist called once a week to inquire about difficulties, adapt training if necessary, and review adherence.

Control Group

The usual care control group received no exercise intervention. Patients were called by the exercise specialist by telephone once a month to ask about possible adverse effects in the context of their cancer treatment. During chemotherapy treatment, patients had the opportunity to receive nutrition and psychosocial counseling.

Measures

Patients of both exercise intervention groups (RT1 and RT2) documented each training session in a log, and the number of performed training sessions was counted. Feasibility was defined as fulfilled if patients adhered to more than 50% of prescribed training sessions.

Muscle strength was assessed with an isokinetic dynamometer (IsoMed2000; D&R Ferstl GmbH, Hemau, Germany). Maximal isokinetic peak torque (MIPT) was assessed bilaterally for extensors and flexors of the elbow, knee, and hip with angular velocity of 60°/s. Range of motion for isokinetic measurements was from 10° to 90° flexion in the knee (straight leg is 0°), from 20° to 110° in the elbow, and from 10° to 100° in the hip (straight leg in dorsal position is 0°). Patients were instructed to move the machine arm as strong and as fast as they can for 10 repetitions. We further tested maximal voluntary isometric contraction (MVIC) bilaterally for elbow flexor in the angle position of 80°, knee extensor (angle position 36°), and hip flexor (angle position 33°), which consistently were the strongest angle positions each. Patients were instructed to exert maximum force and to keep it for 6 seconds. Only values of the dominant side (MVIC and MIPT) were included in the analysis.

Additionally, we measured the MVIC with handheld dynamometry (HHD) (Citec, Haren, Groningen, the Netherlands) using a standardized test protocol.[19] The tests were repeated 3 times for extensors and flexors of the elbow and knee and for flexors and abductors of the hip. The highest value out of the 3 values from each muscle group of the dominant side was included in the analysis. If the highest value showed a deviation larger than 30% from the median, this value was excluded from the analysis because of implausibility. In this case, the median was used as the new highest value.

Cardiopulmonary exercise testing (CPET) was used for assessing cardiorespiratory fitness. The CPET was performed on an electronically braked cycle ergometer (Ergoselect 100; Ergoline, Bitz, Germany), using an incremental exercise protocol with increases of 10 W every minute starting at 20 W. The detailed protocol was published elsewhere[20] and followed the American Thoracic Society guidelines.[21] All CPET data were recorded as the highest 30-second average value elicited during or immediately after the exercise test, except that the peak respiratory exchange ratio was elicited during the test. Ventilatory threshold was determined according to the V-slope method[22] by 2 independent assessors.

Additionally, the 6-minute walk test was performed, which is an objective and reliable test to measure functional exercise capacity. Using a standardized protocol according to the American Thoracic Society guidelines,[23] patients were instructed to walk up and

down a 58-m flat hallway and to reach as many meters as possible in the allotted 6 minutes.

Clinical data and patient characteristics were extracted from the medical records or by self-report of the patients. Weight and height were measured during the assessments.

Statistical Analyses

For between-group differences with respect to demographics, treatment, and assessments at baseline, 1-way analysis of variance was used for continuous variables and Fisher exact test for categorical variables. There were no indications for deviations from normality assumptions.

Differences among the groups with changes in physical fitness from preintervention to postintervention on an intent-to-treat basis were conducted with analyses of covariance. We used changes in parameters of muscle strength and cardiorespiratory fitness from preintervention to postintervention as dependent variables and intervention group as independent variable. Our primary analysis was adjusted for the baseline value of the outcome measure only. To explore potential confounding, models were additionally adjusted for covariates including age, sex, previous chemotherapy, or sport behavior. There were no substantial changes in the results compared with the primary model. As the presented analyses on muscle strength and cardiorespiratory fitness were exploratory, no adjustment for multiple testing was performed. In subgroup analyses considering only the 2 RT intervention groups (RT1, RT2), categories for feasibility of the training (<50%, 50%–75%, >75%) were performed to describe adjusted percent mean strength gain by training adherence. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SAS Enterprise Guide (version 6.1; SAS Statistics, Cary, NC).

RESULTS

In total, 65 (21.4%) of 304 eligible PC patients gave written informed consent and were randomized after baseline assessment, 12 patients to RT1, 31 to RT2, and 22 patients to CON (Fig. 1). All 65 patients completed baseline assessments, and 48 patients (73.8%) completed the 6-month intervention phase. Reasons for premature dropout were withdrawal (n = 11), disease progression (n = 3), and death (n = 3). Group specific dropout rates were 25% in RT1, 29% in RT2, and 23% in CON. Preintervention and postintervention assessments of muscle strength and cardiorespiratory fitness were available in a total of 43 patients (66.2%). Patient characteristics are described in Table 1. Mean age was 60.4 years. Most patients had a normal weight (mean body mass index 23.3 kg/m^2) and were diagnosed with stage IIB cancer (65.1%). Approximately half of the patients (55.8%) experienced weight loss of 10% or more in the last 6 months before baseline testing. Furthermore, they were on average 112.8 days after surgery and 67.8 days after their first chemotherapy. Concomitant to the intervention, 36 patients received on average 113.4 days of chemotherapy. There were no differences between the groups with respect to demographics, treatment, and other assessments at baseline as well as compared with dropouts except for a slight difference regarding days since first chemotherapy ($P < 0.05$; Table 1). One adverse event, incisional hernia temporally after baseline assessment (CON), was reported during the assessments.

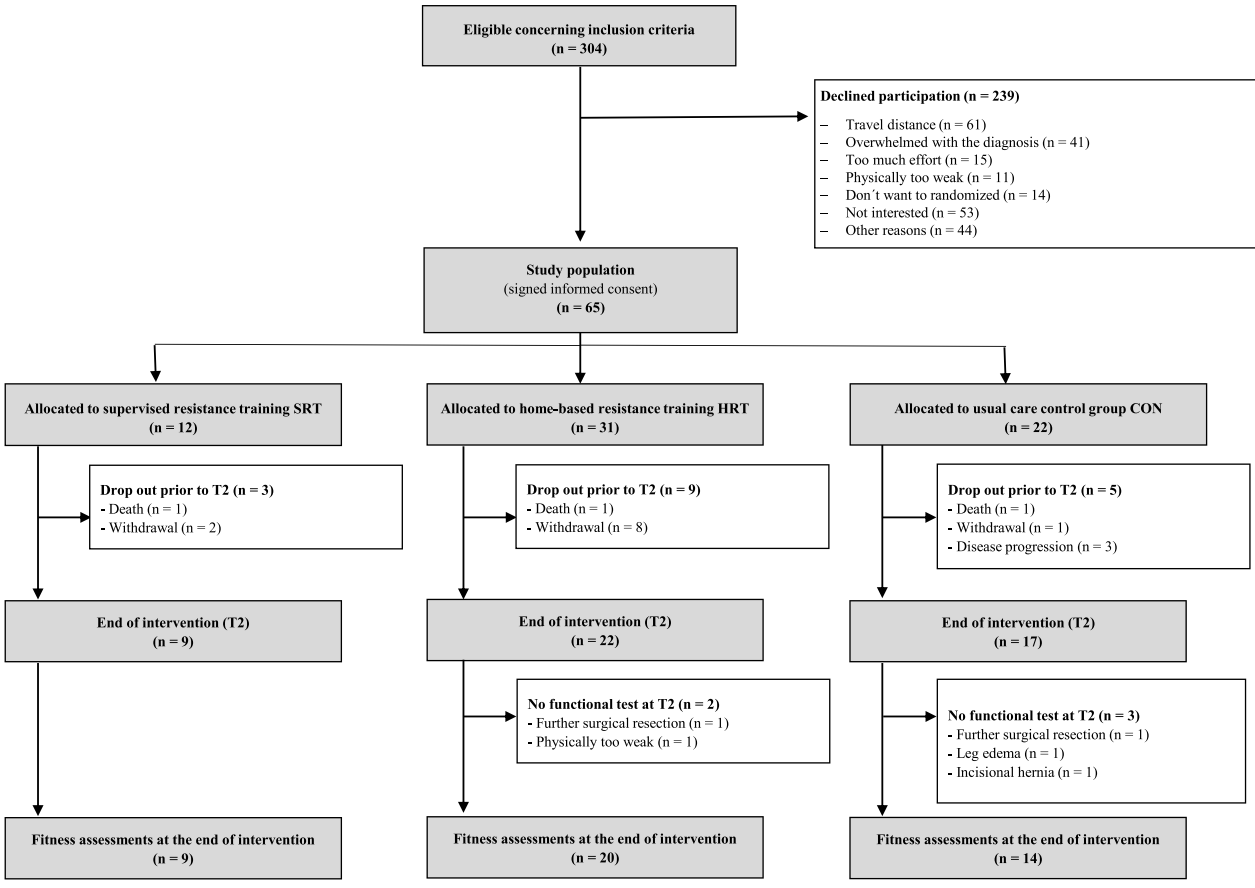

FIGURE 1. Patient flow chart.

TABLE 1. Baseline Demographic and Clinical Characteristics of the Study Population

	Supervised RT	Home-Based RT	Usual Care Control
Total, n	9	20	14
Sex, n (%)			
Male	5 (55.6)	12 (60.0)	7 (50.0)
Female	4 (44.4)	8 (40.0)	7 (50.0)
Age, mean (SD), y	62.8 (6.4)	61.1 (8.7)	57.8 (8.2)
Body mass index, mean (SD), kg/m^2	23.5 (3.1)	22.7 (2.8)	23.9 (3.5)
Days since surgery, mean (SD)	95.7 (21.6)	110.0 (41.9)	127.8 (98.3)
Days since first chemotherapy, mean (SD)*	44.9 (19.9)	67.2 (44.8)	79.9 (104.5)
Hemoglobin, mean (SD), g/dL	11.8 (1.6)	11.3 (1.1)	11.6 (1.3)
Adenocarcinoma type, n (%)			
Pancreatic ductal	7 (77.8)	19 (95.0)	12 (85.7)
Distal bile duct†	2 (22.2)	1 (5.0)	1 (7.1)
Ampullary ductal	—	—	1 (7.1)
Stage, n (%)			
None	—	1 (5.0)	—
IA	—	1 (5.0)	1 (7.1)
IB	2 (22.2)	—	1 (7.1)
IIA	3 (33.3)	3 (15.0)	2 (14.3)
IIB	4 (44.4)	14 (70.0)	10 (71.4)
IV	—	1 (5.0)	—
Treatment, n (%)			
Surgery, adjuvant CT	8 (88.9)	16 (80.0)	14 (100.0)
Neoadjuvant CT, surgery	—	2 (10.0)	—
Neoadjuvant CT, surgery, adjuvant CT	1 (11.1)	1 (5.0)	—
CT	—	1 (5.0)	—
Operative procedures, n (%)			
None	—	1 (5.0)	—
Total pancreatectomy	—	3 (15.0)	1 (7.1)
Distal pancreatectomy	2 (22.2)	2 (10.0)	3 (21.4)
PD	4 (44.4)	6 (30.0)	5 (35.7)
PD pylorus preserving	3 (33.3)	8 (40.0)	5 (35.7)
Smoking, n (%)			
Nonsmoker	7 (77.8)	13 (65.0)	11 (78.6)
Recent smoker	2 (22.2)	4 (20.0)	3 (21.4)
Still smoker	—	3 (15.0)	—
Exercise in the year before diagnosis, n (%)			
None	2 (22.2)	8 (40.0)	6 (42.9)
0 to <9 MET × h/wk	2 (22.2)	2 (10.0)	3 (21.4)
9 to <18 MET × h/wk	2 (22.2)	7 (35.0)	4 (28.6)
≥18 MET × h/wk	3 (33.3)	3 (15.0)	1 (7.1)
Weight loss ≥10% in last 6 mo, n (%)			
No	5 (55.6)	7 (35.0)	7 (50.0)
Yes	4 (44.4)	13 (65.0)	7 (50.0)

*Difference at baseline ($P = 0.04$).

†Pancreatic biliary.

CT indicates chemotherapy; MET, metabolic equivalent (in hours per week); PD, pancreaticoduodenectomy.

Adherence and Feasibility

Mean overall training adherence rate of RT1 and RT2 (n = 43) was 59.2% (standard deviation [SD], 35.4%), with performing 28.2 of 48 scheduled training sessions. Twenty-five patients (58.1%) performed more than 50% of the scheduled training sessions (58.3% patients in RT1 and 58.1% patients in RT2). For those patients of RT1 and RT2 who completed the postinterventional assessment T2 (n = 29), adherence to the RT protocol was 35.8 training sessions (74.0%) on average. With respect to the different intervention groups, RT1 showed an adherence rate of 64.1% (30.4 of 48 sessions), and RT2 showed 78.4% (38.2 of 48 sessions). Two patients of RT1 were not able to train according to our training prescription because of medical complications (not related to the disease or the treatment): 1 patient could only perform 8 weeks of training because of

TABLE 2. Feasibility of RT Categorized in Adherence Rate Less Than 50%, 50% to 75%, Greater Than 75% of Scheduled 48 Training Sessions

	Total (n = 27)	Supervised RT (n = 7)			Home-Based RT (n = 20)		
	n (%)	n	No. Performed Training Sessions, Mean (SD)	Training Sessions, %	n	No. Performed Training Sessions, Mean (SD)	Training Sessions, %
Training adherence							
<50%	5 (19)	2	25 (2.8)	45	3	15 (6.1)	31
50%–75%	7 (26)	3	38 (3.0)	72	4	32 (2.6)	67
>75%	15 (55)	2	40 (1.4)	82	13	46 (10.2)	93

wound healing dysfunction after melanoma resection of the leg; the other had to terminate training at week 18 after a fracture of the patella (the accident happened on the way to chemotherapy). In total, 22 study completers (81.5%) performed more than 50% of the scheduled training sessions (Table 2). Looking at both intervention groups separately, 2 patients (28.6%) of RT1 performed more than 75% of the scheduled sessions compared with 13 patients (65.0%) of RT2. No adverse event relating to the exercise intervention program occurred.

Muscle Strength

Maximal isokinetic peak torque and MVIC values for each muscle group of the upper and lower extremities of the dominant side are presented in Table 3. For MIPT, differences for RT1 compared with CON were statistically significant in elbow flexors ($P = 0.02$) and extensors ($P = 0.01$) but not in the muscles of the lower extremities. For RT2 compared with CON, there were no statistically significant differences for all assessed muscle groups. Comparing both intervention groups, RT1 gained statistically significant more strength in elbow flexors and extensors (both $P < 0.05$) than RT2. For MVIC, data indicated that RT1 gained more strength in elbow flexors ($P = 0.02$) and knee extensors ($P = 0.01$) compared with CON. For RT2, we observed a significant difference in knee extensors compared with CON ($P < 0.05$). Comparing intervention groups RT1 and RT2, no significant differences for assessed muscle groups for MVIC were found.

For MVIC parameters measured with the HHD (Table 4), RT2 compared with CON showed significant difference in knee extensors ($P < 0.05$). Significant differences for knee flexors ($P = 0.01$) in favor for RT1 were observed when comparing both intervention groups. RT1 furthermore showed borderline significant advantages for elbow flexors (vs RT2), knee extensors (vs CON), and hip abductors (vs RT2). Considering the association between the number of training sessions performed categorized in less than 50%, 50% to 75%, and greater than 75% of scheduled sessions and improvements in muscle strength, strength changes (%) were to be strongest for patients who performed 50% to 75% of scheduled training sessions (Fig. 2).

Cardiorespiratory Fitness

Cardiopulmonary exercise testing results are shown in Table 5. Most parameters showed no differences between groups. Only peak work rate revealed a significant improvement in RT1 compared with CON as well as compared with RT2 (both $P < 0.05$). There were no differences in results when comparing patients who fully completed CPET and terminated prematurely (data not shown).

Body Weight

Body weight slightly increased during the intervention period in RT1 by 3.2% (SD, 3.7; T0: 71.1 kg, T2: 73.5 kg), whereas it stayed almost unchanged in RT2 with a −0.4% decrease (SD, 6.2; T0: 68.0 kg, T2: 67.9 kg). In CON, a minimal increase of 0.8% (SD, 5.8; T0: 71.6 kg, T2: 72.1 kg) was observed. There were no significant group differences in changes since baseline. A weight loss larger than 5% was observed in 6 patients (14.0%) during the intervention period (RT2: n = 4; CON: n = 2; $P = 0.79$).

DISCUSSION

This is the first randomized controlled trial investigating the effect of progressive RT in PC patients. Our study revealed that supervised as well as home-based progressive RT was feasible. We furthermore showed that a 6-month progressive RT seems to improve muscle strength, with significant results for some muscle groups. Strength gain was always higher in patients who trained under supervision than exercised at home.

An adequate adherence rate is the most important factor to expect beneficial results from an exercise intervention. Overall, 58.1% of the patients of both RT groups together fulfilled our feasibility criterion of the study. However, 12 of these 43 patients were not able to finish the exercise intervention because of non–intervention-related reasons and dropped out during the course of the intervention phase. Those who were able to stay in the program and performed assessments at T2 (n = 29) showed adherence rates of 64.1% in the supervised and 78.4% in the home-based group. Referring to the ACSM RT recommendations for cancer survivors,[17] only 37.2% of the patients were able to nearly (>75% adherence rate) perform 2 RT sessions a week. A comparable study on a single-group home-based walking and RT intervention in the neoadjuvant treatment situation showed that only 40% of the patients adhered to ACSM resistance exercise recommendations, whereas 80% adhered to walking recommendations of 20 minutes at least 3 times a week.[24] Our completers' adherence rate of 74.0% on average is also slightly better or in line with other studies investigating progressive RT adherence in cancer patients with other primary diagnosis.[25–27]

Differences in adherence rates revealed between RT groups. Participants of our home-based RT performed 5.5% more training sessions than the supervised group. This is in accordance with studies in breast cancer patients during chemotherapy,[28] as well as in older sedentary people with peripheral vascular diseases.[29] One explanation for this finding could be that it is much easier to perform exercises at home, instead of motivate oneself to go to the training center, in particular during chemotherapy treatment that might lead to increased fatigue. Another explanation might be a reporting bias due to self-reported documentation in the home-based versus trainer-assessed data in the supervised setting.

A growing number of randomized controlled trials showed positive effects on muscle strength and body composition due to RT, primarily in breast cancer[30,31] and prostate cancer patients.[32] Comparing our results with other studies investigating strength performance during cancer treatment, we reached lower improvements in muscle strength. Courneya et al,[33] for example, showed

TABLE 3. Changes in Isokinetic and Isometric Muscle Strength (Newton Meter) for Upper and Lower Extremities by Stationary Dynamometry

	Group	n	Baseline, T0, Mean (SD)	End of Intervention, T2, Mean (SD)	Adjusted* Mean Change (95% CI) From T0 to T2	Adjusted Between-Group Differences Estimated Least-Squares Mean (95% CI)		*P*
MIPT								
Elbow flexors	RT1	9	27.1 (6.5)	33.4 (11.4)	6.3 (2.7–9.8)	RT1–CON	**5.7 (1.1–10.3)**	**0.02**
	RT2	18	27.4 (9.3)	29.3 (11.8)	1.8 (−0.7 to 4.3)	RT2–CON	1.2 (−2.6 to 5.1)	0.51
	CON	14	26.4 (8.0)	26.9 (8.1)	0.6 (−2.3 to 3.4)	RT1–RT2	**4.4 (0.1–8.8)**	**0.046**
Elbow extensors	RT1	9	28.2 (8.5)	35.4 (11.1)	7.0 (3.1–10.9)	RT1–CON	**6.3 (1.3–11.4)**	**0.01**
	RT2	18	29.7 (9.7)	31.4 (11.1)	1.7 (−1.1 to 4.4)	RT2–CON	1.0 (−3.2 to 5.2)	0.63
	CON	14	32.6 (13.1)	33.0 (11.5)	0.7 (−2.4 to 3.8)	RT1–RT2	**5.3 (0.6–10.1)**	**0.03**
Knee flexors	RT1	9	66.2 (17.0)	78.2 (26.9)	12.1 (3.0–21.1)	RT1–CON	6.7 (−5.0 to 18.5)	0.25
	RT2	18	61.7 (20.5)	66.2 (22.7)	4.4 (−2.0 to 10.8)	RT2–CON	−0.9 (−10.8 to 9.0)	0.85
	CON	13	67.5 (26.6)	72.8 (27.6)	5.3 (−2.2 to 12.9)	RT1–RT2	7.6 (−3.5 to 18.7)	0.17
Knee extensors	RT1	9	96.0 (23.7)	103.8 (26.4)	7.6 (−1.1 to 16.3)	RT1–CON	3.8 (−7.6 to 15.2)	0.50
	RT2	18	100.8 (26.9)	106.5 (28.8)	5.6 (−0.5 to 11.8)	RT2–CON	1.8 (−7.7 to 11.3)	0.70
	CON	13	103.2 (37.7)	106.9 (37.9)	3.8 (−3.4 to 11.1)	RT1–RT2	2.0 (−8.7 to 12.7)	0.71
Hip flexors	RT1	9	86.8 (27.7)	100.5 (33.4)	13.6 (4.2–23.1)	RT1–CON	5.6 (−6.9 to 18.2)	0.37
	RT2	17	84.9 (26.2)	88.1 (30.9)	3.2 (−3.7 to 10.0)	RT2–CON	−4.8 (−15.5 to 5.9)	0.37
	CON	12	78.6 (28.6)	86.5 (29.7)	8.0 (−0.2 to 16.2)	RT1–RT2	10.5 (−1.2 to 22.1)	0.08
Hip extensors	RT1	9	124.6 (40.6)	162.8 (54.0)	38.1 (13.6–62.6)	RT1–CON	19.0 (−13.4 to 51.4)	0.24
	RT2	17	127.0 (56.6)	139.1 (60.8)	12.3 (−5.5 to 30.2)	RT2–CON	−6.8 (−34.5 to 20.9)	0.62
	CON	12	122.9 (50.9)	142.4 (52.4)	19.1 (−2.1 to 40.3)	RT1–RT2	25.8 (−4.5 to 56.1)	0.09
MVIC								
Elbow flexors	RT1	9	36.9 (10.4)	42.3 (14.0)	5.4 (1.9–9.0)	RT1–CON	**5.3 (0.8–9.9)**	**0.02**
	RT2	18	36.1 (11.7)	37.6 (13.4)	1.5 (−1.0 to 4.1)	RT2–CON	1.4 (−2.4 to 5.2)	0.45
	CON	14	34.9 (13.4)	35.1 (11.3)	0.1 (−2.7 to 3.0)	RT1–RT2	3.9 (−0.4 to 8.2)	0.08
Knee extensors	RT1	9	125.7 (34.9)	142.9 (41.4)	13.5 (−4.5 to 31.6)	RT1–CON	**31.4 (8.0–54.9)**	**0.01**
	RT2	18	141.3 (35.8)	142.5 (37.1)	2.4 (−10.2 to 15.0)	RT2–CON	**20.3 (0.8–39.8)**	**0.04**
	CON	13	140.4 (42.2)	121.6 (32.6)	−17.9 (−32.8 to −3.1)	RT1–RT2	11.1 (−11.0 to 33.3)	0.31
Hip flexors	RT1	9	112.5 (47.2)	121.4 (43.0)	9.2 (−5.5 to 23.8)	RT1–CON	−1.6 (−21.7 to 18.4)	0.87
	RT2	17	104.4 (34.6)	111.1 (44.7)	6.8 (−3.7 to 17.4)	RT2–CON	−4.0 (−20.9 to 12.9)	0.63
	CON	12	84.0 (22.6)	95.1 (29.6)	10.8 (−2.1 to 23.8)	RT1–RT2	2.4 (−15.6 to 20.3)	0.79

Bold font indicates significant group difference ($P < 0.05$).

*Adjusted for baseline value.

CI indicates confidence interval; CON, usual care control group; RT1, supervised RT group; RT2, home-based RT group; MIPT, maximal isokinetic peak torque; MVIC, maximal voluntary isometric contraction.

an improvement of 34.4% in muscle strength of knee extensors (5.7% MVIC in our study for both RT groups together) in breast cancer patients during chemotherapy. A 24-week supervised RT intervention in prostate cancer patients during radiation therapy revealed improvements of 28.2% for knee extensor strength.[34] However, these studies assessed muscle strength by using the 1-RM method rather than by stationary dynamometry or HHD as we did. Therefore, comparability seems to be limited. Only a few randomized controlled trials so far used stationary isokinetic dynamometry, which is considered to be the criterion-standard method to analyze muscle strength.[35] One study evaluating the effect of a 24-month RT in breast cancer survivors reported slightly smaller increases after 6 months compared with our results (mean for both RT groups together) for isokinetic knee extension (3.2% vs 7.0%) and knee flexion (9.8% vs 11.6%).[27] Another trial in head and neck cancer patients after radiotherapy proved larger increases of isokinetic muscle strength in knee extensors (20.4% vs 7.0%) and knee flexors (30.9% vs 11.6%).[36] Lastly, a study from our group in breast cancer patients during radiotherapy showed smaller improvements in isokinetic knee extension (4.0% vs 8.6%) and knee flexion (12.6% vs 17.7%) after a 12-week supervised progressive RT.[37]

For cardiorespiratory fitness parameters, we observed no change in VO_2peak between groups. With regard to training specificity, this result is not surprising. Resistance training leads to increased muscle strength and muscle mass by improved neuromuscular function followed by a cross-sectional area increase in muscle fibers, as opposed to endurance training, which leads to increased endurance capacity and a higher effectiveness of the cardiorespiratory system.[12] However, improved muscle strength of leg extensors and flexors due to RT seems to have impact on peak work rate during a bicycle CPET. There was a slight increase in peak work rate for RT1 of mean 19.1 W, whereas values for RT2 (mean, 4.9 W) and CON (mean, 4.0 W) remained relatively unchanged. Peripheral intramuscular changes combined with an increase in cross-sectional area of muscle fibers might be responsible for the improved peak work rate. Comparable results were found by another study in cancer survivors.[38]

In terms of the effectiveness, we observed that supervised RT on machines seemed to be more effective to gain muscle strength than a self-administered home-based training program. This

TABLE 4. Changes in Isometric Muscle Strength (Newton) for Muscle Groups of the Upper and Lower Extremities by HHD

	Group	n	Baseline, T0, Mean (SD)	End of Intervention, T2, Mean (SD)	Adjusted* Mean Change (95% CI) From T0 to T2	Adjusted Between-group Differences Estimated Least-Squares Mean (95% CI)		*P*
Elbow flexors	RT1	9	175.8 (46.5)	221.1 (40.0)	42.6 (14.1–71.0)	RT1−CON	26.1 (−10.2 to 62.4)	0.15
	RT2	20	198.4 (65.2)	210.7 (70.8)	14.1 (−5.0 to 33.2)	RT2−CON	−2.4 (−32.1 to 27.3)	0.87
	CON	14	185.7 (55.3)	202.9 (61.1)	16.4 (−6.2 to 39.1)	RT1−RT2	28.5 (−5.9 to 62.9)	0.10
Elbow extensors	RT1	9	129.4 (44.3)	142.8 (42.1)	11.3 (−6.8 to 29.3)	RT1−CON	16.9 (−6.2 to 40.0)	0.15
	RT2	20	146.4 (59.3)	148.9 (55.4)	3.8 (−8.3 to 16.0)	RT2−CON	9.5 (−9.4 to 28.3)	0.32
	CON	14	136.1 (45.6)	131.2 (43.7)	−5.6 (−20.0 to 8.8)	RT1−RT2	7.4 (−14.4 to 29.3)	0.49
Knee flexors	RT1	9	178.7 (43.5)	226.9 (63.7)	46.0 (14.5–77.4)	RT1−CON	28.4 (−11.8 to 68.6)	0.16
	RT2	20	198.7 (46.6)	190.9 (51.1)	−4.3 (−25.7 to 17.1)	RT2−CON	−21.9 (−55.5 to 11.8)	0.20
	CON	14	174.5 (47.5)	195.5 (59.6)	17.6 (−7.9 to 43.0)	RT1−RT2	**50.3 (12.0–88.6)**	**0.01**
Knee extensors	RT1	9	341.4 (95.5)	378.9 (99.3)	31.5 (−20.9 to 84.0)	RT1−CON	62.7 (−5.6 to 131.0)	0.07
	RT2	20	363.4 (99.7)	388.6 (109.5)	26.4 (−8.7 to 61.4)	RT2−CON	**57.5 (1.6–113.4)**	**0.04**
	CON	13	366.6 (84.4)	333.2 (81.7)	−31.1 (−74.7 to 12.4)	RT1−RT2	5.2 (−58.0 to 68.4)	0.87
Hip flexors	RT1	9	131.7 (41.1)	157.4 (40.4)	23.3 (1.4–45.2)	RT1−CON	15.5 (−13.2 to 44.3)	0.28
	RT2	20	151.9 (42.6)	154.7 (46.4)	4.6 (−10.1 to 19.3)	RT2−CON	−3.2 (−27.1 to 20.8)	0.79
	CON	12	138.7 (46.4)	147.4 (51.2)	7.7 (−11.1 to 26.5)	RT1−RT2	18.7 (−7.9 to 45.3)	0.16
Hip abductors	RT1	9	133.1 (40.0)	160.4 (22.9)	22.8 (4.2–41.4)	RT1−CON	16.7 (−7.4 to 40.7)	0.17
	RT2	20	150.0 (35.1)	150.7 (35.3)	2.4 (−10.0 to 14.7)	RT2−CON	−3.8 (−23.4 to 15.8)	0.70
	CON	13	147.4 (31.9)	152.8 (40.4)	6.1 (−9.1 to 21.4)	RT1−RT2	20.4 (−2.0 to 42.9)	0.07

Bold font indicates significant group difference ($P < 0.05$).

*Adjusted for baseline value.

CI indicates confidence interval; RT1, supervised RT group; RT2, home-based RT group; CON, usual care control group.

observation is supported by a study in breast cancer patients during chemotherapy.[28] A possible explanation for this observation might be related to a different exercise intensity exposure related to machine-based training itself. Further, RT under supervision might be more intense than performing RT alone at home without direct supervision. The intensity prescription for RT2 was adapted through the BORG Scale. Therefore, it cannot be ruled out that patients' perceived level of exertion was different from the intensity level needed to gain muscle strength improvements. Consequently, it might be that the performed exercises of RT2 were not intense enough. This might also explain that RT2 mainly developed not superior in comparison to CON over the intervention period, which

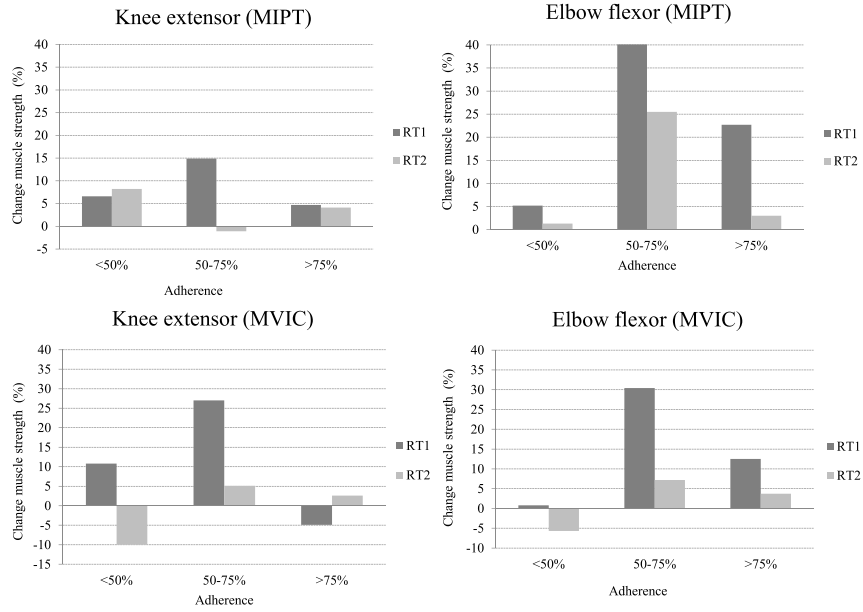

FIGURE 2. Maximal isokinetic peak torque (MIPT) and maximal voluntary isometric contration (MVIC) gain (%) of knee extension and elbow flexion in relation to training adherence. RT1 indicates supervised RT group; RT2, home-based RT group.

TABLE 5. Changes in Cardiorespiratory Fitness Parameter by Cardiopulmonary Exercise Testing

	Group	n	Baseline, T0, Mean (SD)	End of Intervention, T2, Mean (SD)	Adjusted* Mean Change (95% CI) From T0 to T2	Adjusted Between-Group Differences Estimated Least-Squares Mean (95% CI)		*P*
VO_2 peak, L/min	RT1	8	1.7 (0.4)	1.8 (0.6)	0.1 (−0.1 to 0.4)	RT1−CON	0.1 (−0.2 to 0.4)	0.43
	RT2	17	1.4 (0.4)	1.6 (0.6)	0.2 (0.0–0.3)	RT2−CON	0.2 (−0.1 to 0.4)	0.22
	CON	12	1.6 (0.5)	1.6 (0.5)	0.0 (−0.2 to 0.2)	RT1−RT2	−0.0 (−0.3 to 0.2)	0.79
VT, L/min	RT1	8	1.0 (0.4)	0.9 (0.2)	−0.0 (−0.2 to 0.1)	RT1−CON	−0.0 (−0.2 to 0.2)	0.64
	RT2	15	0.9 (0.3)	0.9 (0.3)	0.0 (−0.1 to 0.1)	RT2−CON	0.0 (−0.2 to 0.2)	0.94
	CON	11	0.9 (0.2)	0.9 (0.2)	0.0 (−0.1 to 0.1)	RT1−RT2	−0.1 (−0.2 to 0.1)	0.57
Work rate peak, W	RT1	8	117.3 (32.9)	136.4 (39.0)	19.1 (8.8–29.3)	RT1−CON	**15.1 (1.8–28.3)**	**0.03**
	RT2	17	111.6 (35.4)	116.4 (41.0)	4.9 (−2.2 to 11.9)	RT2−CON	0.9 (−10.1 to 11.9)	0.87
	CON	12	118.5 (40.2)	122.6 (39.9)	4.0 (−4.4 to 12.4)	RT1−RT2	**14.2 (1.7–26.7)**	**0.03**
VE peak, L/min	RT1	8	74.1 (12.6)	77.5 (15.8)	3.7 (−8.1 to 15.6)	RT1−CON	6.5 (−8.7 to 21.7)	0.39
	RT2	17	63.8 (21.9)	70.4 (27.6)	6.5 (−1.5 to 14.5)	RT2−CON	9.3 (−3.2 to 21.7)	0.14
	CON	12	66.1 (18.0)	63.4 (23.5)	−2.8 (−12.3 to 6.7)	RT1−RT2	−2.8 (−17.2 to 11.7)	0.70
6MWT, m	RT1	9	563.4 (85.9)	608.1 (68.0)	43.6 (18.4–68.9)	RT1−CON	13.1 (−19.3 to 45.5)	0.42
	RT2	20	573.1 (79.6)	597.5 (94.9)	24.4 (7.4–41.3)	RT2−CON	−6.2 (−32.5 to 20.2)	0.64
	CON	14	580.5 (71.5)	610.3 (57.7)	30.5 (10.3–50.8)	RT1−RT2	19.3 (−11.1 to 49.6)	0.21

Bold font indicates significant group difference ($P < 0.05$).

*Adjusted for baseline value.

6MWT indicates 6-minute walk test; CI, confidence interval; CON, usual care control group; RT1, supervised RT group; RT2, home-based RT group; VE, ventilation; VO_2, peak maximal oxygen consumption; VT, ventilatory threshold.

was an unexpected finding. A further explanation for this could be related to a potential contamination of CON, which is well known from the literature and could be also true in our investigation.[39,40] An indication for that can be seen in the increasing values for various physical fitness measures in CON over time.

Bringing the findings of the SUPPORT Study together, the question may arise whether the observed gain in muscle strength could lead to prevent or even stabilize loss of muscle mass or cachexia in these patients.[13,41] It is well known that cachexia is associated with impaired physical fitness and poor prognosis.[8,10] Losses in skeletal muscle mass of 4% or more were associated with worse survival.[42] Further, weight loss is used as a key criterion for the diagnosis of cachexia and has been seen as an unfavorable factor on survival in PC.[43,44] Within our study, we observed small increases in body weight in RT1 by 3.2%, whereas the other 2 groups only slightly changed (RT2 decreased by −0.4%, CON increased by 0.8%). However, we do not know whether this finding went hand in hand with favorable changes in body composition because we were not able to include more refined assessments (eg, dual-energy x-ray absorptiometry). But, given these first observations, we can conservatively underline the capability of progressive RT to improve muscle strength (and therefore also maybe muscle mass), or at least to maintain muscle strength, and to prevent a further decline of physical function in PC patients. Taking into account that RT also seems to have a positive effect on cancer cachexia by several mechanisms such as enhanced muscle protein synthesis, modulated levels of inflammation, insulin sensitivity, and muscle metabolism,[45] RT might play an important role in the supportive therapy of PC patients.

Our study had some limitations. Because of the sample size of 65 patients in total, respectively, 43 patients who completed postinterventional physical fitness assessments, generalizability is limited. Further, as our allocation scheme depended on the living distance from the study center, numbers of patients in groups were unequal because of different numbers of patients available in the 2 living distance groups (more patients available and enrolled in the distant group). This makes comparisons between the groups difficult. Another restriction was our 21.4% recruitment rate. However, a recent study in this patient population showed the same rate.[46] Therefore, a self-selection bias might exist in terms that the study population was eligible for and agreed to take part in an exercise trial. This has potentially resulted in a selected patient group that was interested in a physically active/healthy lifestyle. However, only 52.3% of the patients were physically active in the year before the diagnosis, which is less than that reported for older German adults.[47]

On the other hand, our study had several strengths. It is the first study that investigated the effect of a progressive RT in PC patients during and after adjuvant chemotherapy within a randomized controlled trial. Further, we compared 2 pragmatic RT interventions, supervised versus home-based, against a usual care control group, which gave first impressions about the feasibility, dissemination capability, and the effectivity of progressive RT in this patient population. Finally, we used criterion-standard assessments to quantify muscle strength and cardiorespiratory fitness.

In conclusion, we revealed that a 6-month supervised as well as a home-based progressive RT was feasible in PC patients. Furthermore, training led to various improvements in muscle strength of upper and lower extremities. Taking into account that loss of muscle mass, reduced muscle strength, and loss of body weight are often present in PC patients as well as being an indicator for cachexia, RT might serve as an important supportive measure to counteract these problems. Based on the observation that supervised RT was more efficient in gaining muscle strength than home-based RT, supervised RT should be preferred if possible. However, there is also a vital role for home-based RT focusing on rural areas where a supervised training facility is not easily available or if the patients prefer to train that way. Based on our findings, future studies should further explore the potential of RT to mitigate weight loss and prevent cachexia in PC patients by focusing on very early RT interventions in the treatment

process (prehabilitation) and combine them with other promising intervention approaches (nutritional support).

ACKNOWLEDGMENTS

The authors thank the patients who participated in this clinical trial. They also thank Martina Schmidt, PhD, and Sabine Holzmeier for support in statistics and data management; Friederike Rosenberger, PhD, for her expertise and assistance in determining the ventilatory threshold; Lena Kempf and Marcel Bannasch for training support of the supervised training group; Emanuel Schembri for support in the assessments; and Jens Werner, MD, for clinical advice on designing the trial.

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