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ORIGINAL ARTICLE

Exercise improves functional capacity and lean body mass in patients with gastrointestinal cancer during chemotherapy: a single-blind RCT

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Abstract

Purpose Although growing evidence underlines the benefits of physical activity as supportive intervention for cancer patients, sparse data are available for exercise in patients with advanced disease stages, in particular for gastrointestinal cancer (GIC) patients who experience specific disease-associated limitations. Thus, the aim of this study is to evaluate the effects of home-based moderate intensity exercise on functional capacity, activities of daily living (ADL) and body composition in patients with advanced GIC during first-line chemotherapy.

Methods Participants (GIC, UICC III-IV; $n = 44$) were randomly assigned to home-based physical activity programme of 150 min moderate walking per week or a control group (CG). Functional status (SPPB: gait speed, balance, lower extremity muscle strength), postural sway, chemotherapy-induced peripheral neuropathy, nutritional state (Mini Nutritional Assessment, MNA) and lean body mass were assessed according to established recommendations. All tests were performed before chemotherapy (T0), after two chemotherapy cycles (T1) and after 12 weeks (T2).

Results SPPB changes from T1 to T2 differed between groups with a comparably greater decrease in the CG ($p < .05$), but no changes or group differences over the whole study period (T0 to T2) were found. Exercise improved postural sway (T0 to T1; T0 toT2) and lean body mass (T1 to T2; T0 to T2) compared to the control group ($p < .05$). Gait speed, peripheral neuropathy and strength did not differ between groups ($p > .05$).

Conclusions Our results indicate that a home-based physical activity improves postural sway and body composition and might stabilize functional capacity in patients with advanced GIC during chemotherapy. Although the other outcomes did not differ between groups, aforementioned effects might contribute to a maintenance of independency in ADL and a better treatment tolerance and thus enhance patients' quality of life.

Keywords Gastrointestinal cancer · Functional capacity · Physical activity · Activities of daily living · Chemotherapy · Advanced cancer

Introduction

Patients with gastrointestinal cancer (GIC) suffer from a variety of disease- and therapy-related side effects such as fatigue, nausea and body composition changes. Toxicity-induced changes in the neuromuscular and cardiovascular system, e.g. chemotherapy-induced peripheral neuropathy (CIPN), pose a further burden and might compromise the treatment regime. In combination with a low pre-existing physical activity level [1], these side effects contribute to a physical and functional deconditioning and reductions in well-being [2]. In addition to those common cancer and treatment-associated side effects, GIC patients have a high prevalence of cachexia. Up to 80% of patients with GIC and especially with locally or

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systemically advanced disease stages obtain a cachectic state during cancer treatment, and they are a collective with many disease-related side effects during chemotherapy [3]. Cachexia as a complex metabolic syndrome is accompanied by a significant weight loss and mostly characterized by a decreased muscle mass. Beside the marked weight loss with muscle and adipose mass wasting, anorexia, asthenia, fatigue, hypothalamic appetite control modification, intestinal malabsorption, nausea, profound endocrine alteration and metabolic chaos are frequently reported in patients with cancer cachexia [4]. Roberts et al. [5] demonstrated that cancer cachexia directly impacts functional capacity by muscle atrophy and contractile dysfunction. Aforementioned side effects and the following impairments in physical capacity negatively influence the performance of activities of daily living (ADL) [6], objective measured physical function and patients' quality of life.

Previous cross-sectional data show that patients with GIC experience impairments in physical and functional abilities which may already exist prior treatment [7]. While patients with breast cancer did not differ from age-matched healthy participants concerning muscle strength, walking speed and body composition, patients with GIC performed worse compared to the age-matched healthy counterparts and the breast cancer patients in all parameters assessed prior treatment. This might be of particular relevance as a diminished walking speed and a loss of muscle mass [8] as well as a lower physical function assessed via the short physical performance battery are related to a higher mortality rate in patients with malignancies [9].

Growing evidence shows that individually adapted exercise is beneficial during and following cancer treatment [10]. The effects of exercise range from improvements in physical function and exercise capacity over increases in treatment tolerability, mediated via a reduction of side effects such as fatigue or neurotoxicity, to improvements in quality of life. Therefore, exercise becomes increasingly established as a supportive strategy during cancer treatment [3].

However, most exercise studies up to now solely focused on patients with breast and prostate cancer and early disease stages (UICC I-II) [11]. The few exercise therapy trials where GIC patients were included considered either populations with mixed cancers or only colorectal cancer. In a pilot trial, Jensen et al. [12] demonstrated that moderate to vigorous aerobic or resistance training are feasible during palliative chemotherapy with a median exercise adherence of 65%. Despite these promising first results, no study in GIC patients included a non-exercise control group or focussed on more specific and objective assessments of physical function or global ADL. Considering aforementioned particularities in patients with GIC such as the high prevalence of cachexia or the comparably low function status, it seems reasonable that exercise effects demonstrated in breast and prostate cancer patients do not apply for GIC patients. Thus, research considering specific patient populations is highly relevant to extend the knowledge regarding exercise oncology. Consequently, the aim of this randomized controlled trial is to evaluate the effects of a home-based moderate intensity exercise programme on ADL-relevant functional capacity, nutritional status and body composition in patients with advanced GIC undergoing first-line chemotherapy.

Materials and methods

Study design and ethics

The study is designed as a prospective, randomized controlled intervention trial. The study protocol was approved by the independent ethics committee of the local medical faculty and registered at ClinicalTrials.gov (NCT02677129).

Participants and setting

Chemotherapy-naïve patients with histologically confirmed gastrointestinal cancer and a locally or systemically advanced disease stage (UICC stage III–IV) scheduled for first-line chemotherapy (neoadjuvant, adjuvant or palliative) were considered eligible.

Potential participants were recruited in a local clinic and received oral and written information about the study by their treating oncologists. After obtaining written informed consent and oncologists' approval for study participation, patients were checked for study eligibility and contraindications for exercise through clinical examination. Inclusion and exclusion criteria were as follows:

Inclusion criteria consisted of a histologically confirmed advanced gastrointestinal cancer (stage III–IV), scheduled first-line chemotherapeutic treatment (chemotherapy naïve), age ≥ 50 years, written informed consent, ability to understand and speak German as well as to understand the study protocol, and the oncologist's approval for study participation.

Exclusion criteria were ECOG status > 2, any medical condition limiting participation in physical activity and/or exercise, systemic diseases (e.g. multiple sclerosis) or disorders (neurological, skeletal, muscular, metabolic, peripheral vascular, mental or cognitive) or medication used independently of the cancer disease (e.g. analgesics, muscle relaxants) that might influence gait, balance and muscle strength or restrict mobility and elevate fall and injury risk during physical activity, inability to stand and walk, and vestibulopathies and uncorrected visual deficits.

Following baseline assessment, study participants were randomly assigned to the intervention group (IG; usual care and home-based physical activity intervention) or a wait-list control group (CG; usual care) based on a software-generated randomization list.

Intervention

The intervention comprised 12 weeks of home-based walking exercise. In line with cancer-specific guidelines [10], the aim was to complete 150 min of moderate intensity walking per week. Moderate intensity was regulated via Borg's self-rating of perceived exertion (RPE) (target RPE: 11–13 on the 6–20 point scale) [13]. Based on extensive research, the RPE scale can be considered as an easy applicable tool for exercise intensity regulation [14]. RPE ratings of 11–13 are recommended for moderate intensity exercise prescription corresponding to 46 to 63% of the maximal oxygen consumption (VO2peak) or 64 to 76% of the maximal heart rate (HRmax), both assessed via a maximal incremental exercise test [14].

Following baseline testing, participants of the IG received individualized exercise counselling for the self-managed walking by exercise specialists as well as an exercise and health log to monitor intervention adherence. The duration of walking and the number of steps (measured by a pedometer) were documented after each training session.

For patients who (1) were inactive before study enrollment or (2) who had a condition that limited the exercise duration during the study, a stepwise approach was used [15]. Initially, three walking sessions of moderate intensity with a duration of 20 min each were recommended weekly. If tolerated for consecutive 2 or 3 weeks, participants were asked to increase exercise frequency and duration until 150 min per week of moderate intense walking were achieved. Patients who were already physically active at study enrollment were encouraged to start with five sessions of 30 min or three sessions of 50 min duration per week. The study coordinator called each participant once a week to discuss potential problems and/or questions, to enhance adherence, and to adjust the training [16]. To ensure patients safety, medical and blood parameters were monitored in the oncological clinic and regularly checked for contraindications for exercise.

Wait-list control group

Wait-list control group participants received usual care dependent on the hospital guidelines as well as oncologists' and physicians' considerations. To ensure the same social support by the study team, participants of the CG also received weekly phone calls and were asked about their wellbeing.

Outcomes measures

Sociodemographic data (age, gender, height, body weight) and clinical characteristics (tumour characteristics, date of diagnosis, treatment schedule, comorbidities, further medication etc.) were documented with a standardized questionnaire based on medical records and an interview. Body weight and height in light clothing was measured using standard techniques.

Primary endpoint was ADL-relevant physical performance, assessed via the short physical performance battery (SPPB). Secondary endpoints comprised objective measured walking speed, postural control and strength of the knee extensors, as well as peripheral deep sensitivity as indicator for CIPN, body composition and nutritional status.

Assessments were scheduled in accordance with the chemotherapy cycles to ensure adequate intervals between chemotherapy infusion and testing and the same number of cycles for all patients. Assessments took place at baseline, approximately 1 day before first chemotherapy (T0), after 4–6 weeks (before the third chemotherapy cycle) (T1), and after 12 weeks (T2).

Primary outcome measure

For measuring the primary endpoint ADL-relevant physical performance, the SPPB were used. The SPPB comprises the assessment of usual gait speed, balance and ADL muscular endurance of the lower extremity [17]. For each of the aforementioned tests, patients were scored on a Likert scale from 0 to 4 points using established quantitative cut point criteria [17], with a summary SPPB performance score ranging from 0 to 12 points. This ordinal scale has been demonstrated to have predictive validity in analyses showing a gradient of risk for mortality, nursing home admission, and incident disability in ADL. The internal consistency of the summary scale as assessed by Cronbach's alpha was 0.76 [17]. For interval-scaled analysis and comparisons with other studies, the objective measured physical function was applied. For gait speed testing, participants were asked to walk at their normal comfortable pace over a capacitive force-measuring platform (WinFDM v0.0.41®; Zebris© GmbH, Isny, Germany). Gait was monitored in the middle of a 10 m walkway when participants were required to walk across the sensor platform in a self-determined (usual) free walking speed (100 Hz) [18]. For SPPB, the average velocity of three trials was calculated. For balance testing, the participants had to hold three different static standing positions: feet side by side, semitandem and full tandem (heel of 1 ft in front of and touching the toes of the other foot) for at least 10 s. The muscular endurance of the lower extremity was tested via chair rise test. Participants were asked to stand up from a chair and sit down five times in a row as quickly as possible. Data from gait speed, balance and chair rise were classified according to the standardized cut point criterions and rated from 0 to 4, finally resulting in an overall SPPB rating from 0 to 12 points.

Secondary outcomes

Postural stability was assessed using the aforementioned capacitive force-measuring platform. Postural sway on the static surface in a bipedal stance represents postural stability and is characterized by the length of the track of the centre of pressure (CoP). Participants were asked to maintain stance as still as possible with the hands at the hips in a neutral position, looking straight ahead at a fix point for three intervals of 90 s with a 2-min rest in-between. For analysis, the mean of the three measurements was used. Acceptable test-retest reliability has been described for this approach [19]. Isolated gait speed analyses were done based on the five strides on the same platform, described in the SPPB method section.

Maximal isometric voluntary force of the randomly chosen knee extensor side was measured with a strain gauge force transducer (ASYS®; SPOREG; 100 Hz) in a standardized seating position (predefined knee and hip angle = 90°). After warm-up (two submaximal practice trials), three tests with contractions lasting 5 s, separated by 2 min rest intervals, were performed. The highest value of the three trials relative to body weight [*N*] is considered to characterize maximal strength of the knee extensors. Sufficient test-retest reliability and construct validity has been shown [20].

Peripheral deep sensitivity as indicator for CIPN was evaluated via the Rydel-Seiffer tuning fork test. It assesses a person's ability to discriminate between different vibration intensities on a scale from 0 (no sensitivity) to 8 (highest sensitivity) [21]. Tests were performed at proceccus styloideus, basis phalangis III on the hand and the internal malleolus and basis phalangis I on the foot of a randomly chosen side. The tuning fork was applied at predefined points, resting on its own weight while swinging. Patients had to indicate when they no longer feel the vibration stimulus. Values in the range of 0–5 or 0–4 were considered as pathological for patients < 60 years and ≥ 60 years, respectively [21, 22]. The Rydel-Seiffer tuning fork has high inter- and intrarater reliability [23].

Participants documented their dietary behaviour using the Mini Nutritional Assessment (MNA). It consists of four parts: anthropometric measurements, general status, diet information and subjective assessment [24]. A score of less than 17 points (out of a maximum of 30) is regarded as an indication of malnutrition, 17–23.5 points indicate a risk for malnutrition and > 23.5 points indicate a well nourishment. The MNA is also an established screening tool for cancer patients [25].

Body composition was assessed via bioelectrical impedance analysis (BIA) with a phase-sensitive multi-frequency Nutriguard MS (Data Input GmbH, Darmstadt, Germany) following a standardized procedure [26].This non-invasive method determines the electrical impedance, or opposition to the flow of an electric current through body tissues to calculate total body water, fat-free body mass and body fat as well as extracellular and intracellular water [26]. BIA results are reliable measurements with minimal intra- and inter-observer variability [27].

Sample size determination and statistical analyses

As no study was available to derive an effect size concerning our primary outcome, we consider a medium effect size of .3 and a statistical power of 80% (1-ß) at a two-sided level of $\alpha > 5\%$ for both the sample size calculation (G-power) and the statistical analyses (IBM SPSS 21) as relevant. To detect time × group differences in SPPB using multifactorial analyses of variance with repeated measurements, a minimal sample size of 24 patients was calculated. Considering an estimated dropout rate of 35% [28], a total of 37 patients had to be enrolled in the study.

After checking the underlying assumptions for parametric testing (normal distribution of data and variances, variance homogeneity), parametric or nonparametric analyses were performed. Parametric analysis included (if parametric analyses is applicable) multifactorial gain score (pre to post intervention differences) analyses of variance with repeated measurements and including baseline values as co-factors. Omnibus tests were performed once for differences between T0 and T1, and between T1 and T2. In case of significant omnibus gain score testing, descriptive post-hoc analyses using real value mean/median and 95% confidence intervals were conducted. In case of systematic baseline influence, z-transformed mean/median and 95% confidence interval values were used for post-hoc analysis. Z-transformation was performed for adjusting the data for baseline biasing and only for differences which were significantly influenced by baseline co-variate/confounder.

Results

In total, 44 patients were enrolled in the study. Figure 1 shows the participants flow including reasons for dropout and/or non-adherence. Into analysis of the intervention effects, 28 patients who completed the assessments could be included. Participants' sociodemographic, baseline and disease-related characteristics are presented in Table 1. No significant group differences were observed for demographic or baseline variables. Table 2 further displays baseline values of the primary outcome SPPB for all participants. Dropout patients and such with complete datasets do not differ significantly in the total baseline score.

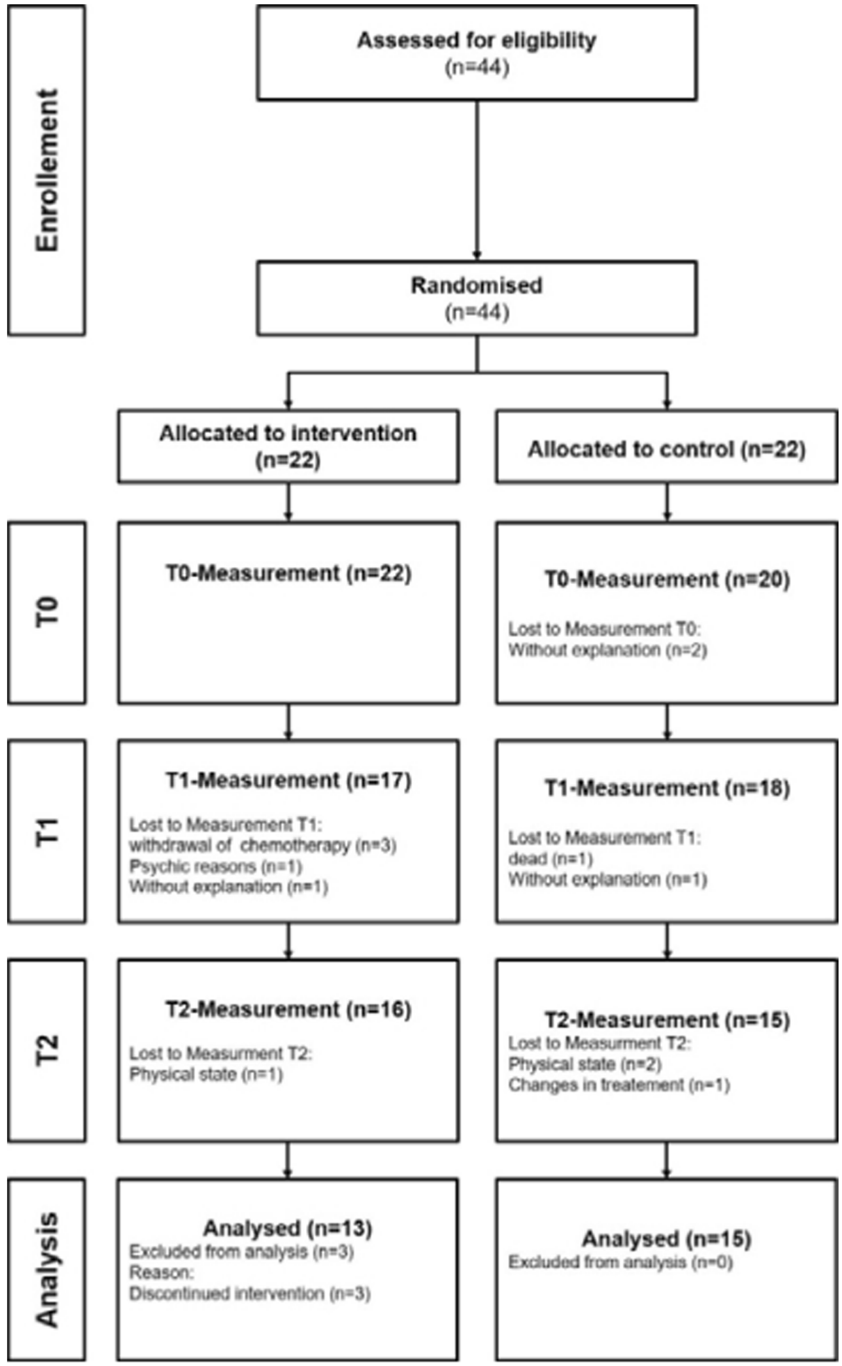

Fig. 1 Patients' flow and number during the single trial steps. N = number, T = visit number

Based on the exercise log analyzation, patients of the intervention group were physically active for 146 ± 15 min per week. Mean exercise adherence rate was 81.3%. Main reasons for reducing the exercise minutes per week or for training interruptions comprised pain, time constraints, personal reasons, or adverse weather conditions. One participant switched his exercise mode from walking to a cycle ergometer due to severe polyneuropathy. Three participants discontinued the walking programme prematurely after 4–5 weeks because of hospitalization due to a bacterial infection or severe fatigue and decided to discontinue study participation. None of the interruptions or discontinuations were attributed to the walking programme.

Primary outcome SPPB

With respect to the total study period (baseline to T2, Table 3) SPPB did not change, but a systematic baseline influence was detected. The corresponding post-hoc analyses (Fig. 2) revealed no overall changes.

Table 1 Subjects' sociodemographic, disease-related and baseline characteristics: means ± standard deviation (SD)

			Total ($n = 44$)	Control		Intervention	
				Complete ($n = 15$)	Dropout ($n = 7$)	Complete ($n = 13$)	Loss to follow-up ($n = 9$)
Sex	Male	*n* (%)	25 (56.8%)	8 (53.3%)	5 (71.4%)	8 (61.5%)	5 (55.6%)
	Female	*n* (%)	19 (43.2%)	7 (46.7%)	2 (28.6%)	5 (38.5%)	4 (44.4%)
Age	Years	Mean + SD (range)	67.1 ± 7.8 (50–79)	65.9 ± 7.9 (50–79)	69.2 ± 10.3 (52–76)	66.8 ± 7.8 (51–75)	68.1 ± 6.9 (59–75)
Tumour	Pancreas	*n*	9	4	2	3	2
	Gastric	*n*	6	4	1	1	0
	Colon	*n*	23	5	3	17	7
	Oesophagus	*n*	4	2	1	1	0
Therapy	Adjuvant	*n*	19	5	4	12	5
	Neoadjuvant	*n*	5	2	1	2	0
	Palliative	*n*	18	8	2	8	4

No significant changes between T0 and T1 ($p > .05$) occurred (Table 3). There was a significant group difference concerning the changes from T1 to T2 with a greater decrease in the CG (Table 3; Fig. 2).

Secondary outcomes

For the whole intervention period and thus the differences from baseline to T2 (T2-T0) the analysis determined between-group differences regarding postural sway and lean body mass (Table 3). Further, a systematic influence of the covariate (baseline values) was seen for postural sway, lean body mass and MNA. The baseline values for the secondary outcomes were as follows: COP: IG = 380.7 ± 158.7, CG = 471.9 ± 206.7 mm; lean body mass: IG = 77.1 ± 8.2, CG = 75.1 ± 8.2; and MNA: IG = 23.5 ± 3.5; CG = 22.9 ± 2.9. The following post-hoc analyses revealed that postural stability improved in the IG from T0 to T2, while there was a decrease in the CG. Furthermore, the IG significantly increased their lean body mass from baseline to the end of the study (Fig. 3).

There were no group differences in gait speed, knee extensor strength, phase angle, postural sway, lean body mass or MNA, neither in the T0 to T1 or in T1 to T2 change score (T1-T0; T2-T1) (Table 3). Significant time effects were found on postural sway (COP), lean body mass and MNA (Table 3). For postural sway and MNA, a significant influence of the covariate (baseline values) was found. The corresponding post-hoc analyses revealed that the IG improved postural stability from T0 to T1 while the CG worsened their balance ability (Fig. 4). Furthermore, the IG improved their lean body mass from T1 to T2. No significant changes occurred in MNA values, but a significant group difference was detected for the change from T1 to T2 (Fig. 4).

Discussion

As one of the first a randomized controlled design in this population our results indicate that a chemotherapy- and cancer-associated decline in physical performance and body composition can be retarded or even reversed by moderate aerobic exercise in patients with GIC. Overall, our findings points toward the relevance and feasibility of physical exercise for this patient population.

Maintaining ADL-relevant physical performance following an exercise intervention while undergoing anti-cancer treatment corresponds to previous studies [3]. As several authors describe an association of functional declines and health outcomes such as mortality and hospitalization time [25], one may speculate that such results are of direct relevance for the

Table 2 Baseline characteristics of SPPB, 95% confidence interval (95% CI) IG

		Number	Mean	Standard deviation	95% CI		Minimum	Maximum	*p* value
					Lower level	Upper level			
SPPB [points]	Control group	15	8.1	2.6	6.61	9.5	4	12	0.17
	Intervention	13	9.4	2.3	7.99	10.8	5	12	
	Loss to follow-up control	5	6.6	3.4	2.43	10.8	3	11	
	Loss to follow-up intervention	9	9	2.5	7.1	10.9	4	11	

Table 3 Short physical performance battery (SPPB), gait speed, COP, strength knee extensor, phase angle, lean body mass and Mini Nutritional Assessment (MNA) differences ± 95% CI of means *p* and *F* value of repeated measurement ANCOVA and one-way ANCOVA. T = visit number

		SPPB			Gait speed [km/h]			COP [mm]			Strength knee extensor [N/kg/BW]	
		T0-T1	T1-T2	T0-T2	T0-T1	T1-T2	T0-T2	T0-T1	T1-T2	T0-T2	T0-T1	T1-T2
control		0.62 ± 1.71	− 0.54 ± 1.33	0.08 ± 2.72	0.22 ± 0.62	− 0.04 ± 0.5	0.18 ± 0.8	20.55 ± 111.5	38.12 ± 97.5	58.7 ± 102.8	0.22 ± 0.98	− 0.02 ± 0.87
intervention		0.58 ± 0.99	− 0.17 ± 0.58	0.42 ± 1.16	0.26 ± 0.45	− 0.10 ± 0.35	0.16 ± 0.49	− 51.9 ± 132.3	−6.9 ± 62.9	− 58.8 ± 139.3	0.44 ± 1.62	0.38 ± 0.98
		rmANCOVA		ANCOVA	rmANCOVA		ANCOVA	rmANCOVA		ANCOVA		
Time effect	*p* value	0.04			0.25			0.003			0.15	
	F value	4.2			1.40			11.1			2.3	
Co-variate	*p* value	0.24		0.02	0.61		0.92	0.19		0.002	0.84	
	F value	1.5		5.9	0.27		0.01	1.8		12.49	0.04	
Group effect	*p* value	0.6		0.36	0.45		0.48	0.001		0.003	0.17	
	F value	0.28		0.86	0.6		0.51	15.7		11.0	2.06	

	Strength knee extensor [N/kg/BW]	Phase angle [°]			Lean body mass [%]			MNA		
	T0-T2	T0-T1	T1-T2	T0-T2	T0-T1	T1-T2	T0-T2	T0-T1	T1-T2	T0-T2
control	0.20 ± 1.45	− 0.36 ± 0.78	0.03 ± 0.61	− 0.01 ± 0.69	1.2 ± 4.1	− 0.51 ± 5.2	0.64 ± 3.4	0.2 ± 2.5	− 0.57 ± 3.6	− 0.37 ± 5.5
intervention	0.83 ± 1.59	− 0.08 ± 0.38	0.21 ± 0.71	0.13 ± 0.91	− 0.65 ± 3.8	4.06 ± 4.6	3.4 ± 4.6	0.46 ± 3.05	− 1.7 ± 2.7	2.2 ± 3.5
	ANCOVA	rmANCOVA		ANCOVA	rmANCOVA		ANCOVA	rmANCOVA		ANCOVA
Time effect		0.09			0.26			0.049		
		3.25			1.3			4.3		
Co-variate	0.30	0.28		0.42	0.14		0.02	0.21		0.98
	1.11	1.2		0.68	2.3		6.1	1.7		2.9
Group effect	0.75	0.11		0.2	0.23		0.02	0.04		0.04
	0.10	2.9		1.8	1.6		6.3	4.6		4.9

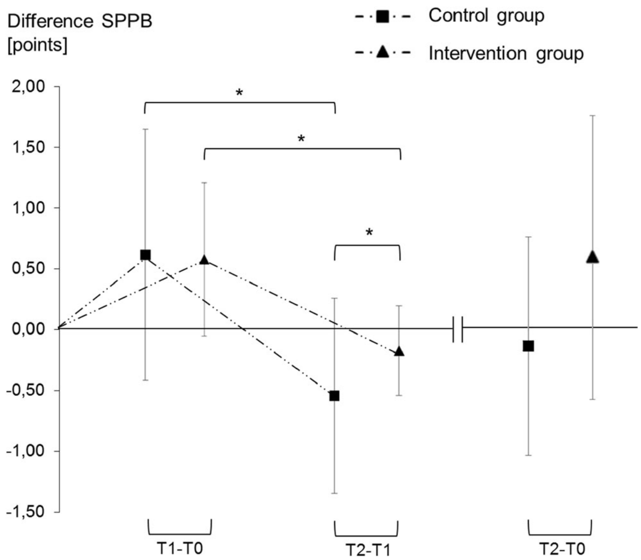

Fig. 2 Means and 95% confidence intervals for the the short performance physical battery (overall score). A: real difference values T1-T0, T2-T1; B: z-transformed differences T2-T0. **p* < .05

patients' health status. Our results point toward a stabilization of ADL-relevant physical performance (SPPB) in the IG despite undergoing aggressive chemotherapeutic treatment which is usually postulated to induce a decline in physical performance and capacity [2].

Comparable to the SPPB, habitual gait speed and knee extensor strength showed no significant changes over time or significant differences between groups. Gait is a multidimensional construct including energy, movement control and demands on multiple organ systems. Thus, a decreased gait speed not only reflects deficits in motor function, but can also be seen as an indicator of impaired vitality itself. In older subjects, decreased gait speed is associated with cognitive impairments and muscle atrophy [29]. In previous studies, gait speed below 1 m/s was defined to be associated with a high risk of a functional decline, adverse health outcomes, hospitalization and mortality [25]. However, the gait speed of both our groups are comparable to healthy participants in the same age and are thus above the proposed cut off value [18]. The intervention may consequently be helpful to maintain patients' mobility. Causes why the CG preserved their usual gait speed, knee extensor strength, and SPPB performance, likewise, could also be found in the aforementioned possible volunteer bias.

It is well known that CIPN induced by neurotoxic chemotherapy causes postural impairments and balance disorders [30]. Our CG showed an overall decline in postural stability over the whole study period while an improvement in the IG was documented. Thus, a home-based walking intervention seems to be able to improve postural stability in patients with GIC. Although an impact on COP was found, no intervention-related effects on CIPN could be determined. To our knowledge, the only study that evaluated exercise-related effects on CIPN during chemotherapy with beneficial results for exercise versus control adopted a multimodal exercise approach with supervised balance, aerobic and resistance components [31]. Thus, one might speculate that an unidimensional exercise intervention such as walking might not be sufficient enough to induce changes in neurological symptoms.

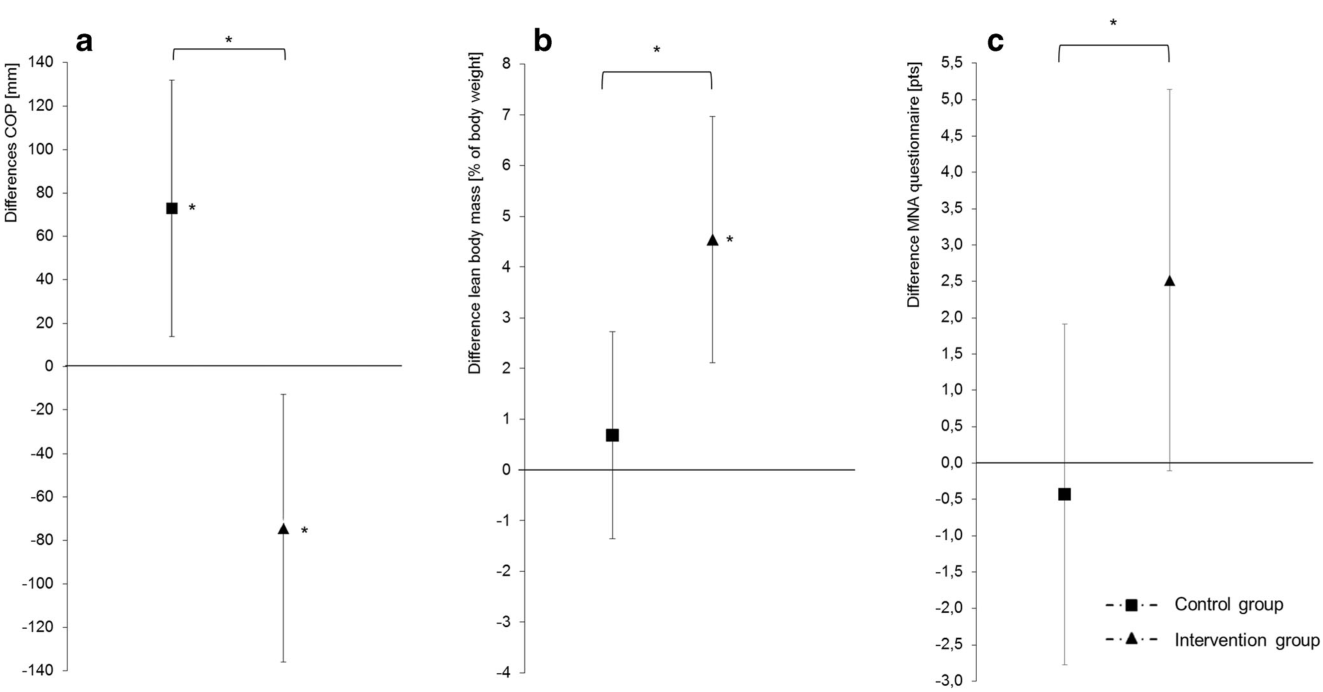

Fig. 3 Means of the total (baseline to T2, T2-T0) differences ± 95% confidence interval of **a** postural sway by centre of pressure (COP), length of the trail, **b** lean body mass, and **c** MNA. **p* < .05

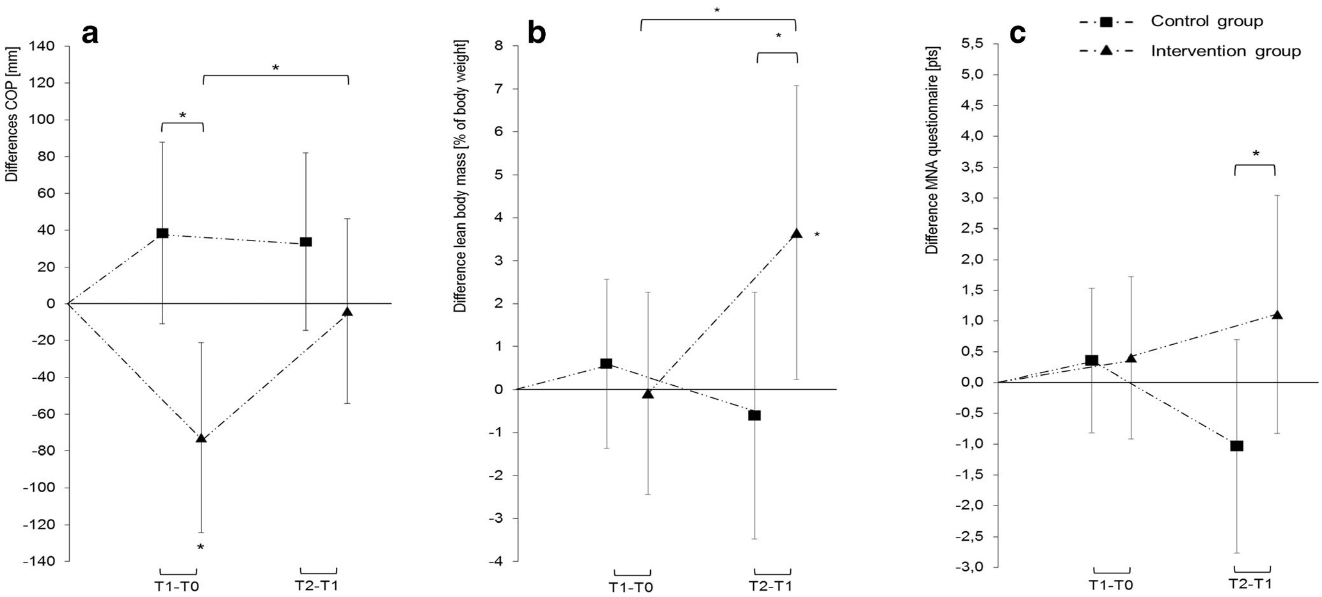

Fig. 4 Means of the differences ± 95% CI of **a** balance, centre of pressure, z-transformed, **b** lean body mass, and **c** MNA, z-transformed (T1-T0; T2-T1). $^{*}p < .05$. COP, centre of pressure; MNA, Mini Nutritional Assessment; T, measurement

The lean body mass and nutritional status (MNA) of the groups behaved different. While the status of the CG tendentially decreased, IG participants increased their lean body mass and tendentially improved their nutritional situation. In previous studies, malnutrition of patients with colorectal cancer, described by comparably poor scores for MNA, was associated with an increased mortality risk and reductions in the planned number of palliative chemotherapy cycles and thus chemotherapy tolerance [32]. This could be of particular relevance as the lean body mass might impact chemotherapeutic toxicity and consecutive comorbidities. For example, Ali et al. [33] reported an increased toxicity with reduced lean body mass. Oxaliplatin doses of less than 3.1 mg per kg of lean body mass were associated with a low risk of dose-limiting toxicity. In addition, chemotherapy-induced toxicity in patients treated with paclitaxel and cisplatin was associated with malnutrition and hypoalbuminemia [34].

From a physiologic point of view, moderate aerobic exercise can attenuate motor deficits potentially induced by PNP. Physical activity prevents muscle loss and also improves inter- and intramuscular coordination as well as neural control, contributing to improved stability and gait. Stabilisation of muscle losses or regain of lean tissue mass are the targets of interventions that are currently sought. Reduced nitrogen balance in cancer cachexia results from a fundamental metabolic shift that results in decreased anabolism and increased catabolism [35], the simultaneous presence of both of these defects results in the most rapid muscle atrophy. This is believed to be mediated by the actions of growth factors and cytokines. Indeed, tumour necrosis factor-alpha (TNF-a) levels are raised in several animal models of cachectic muscle wasting [36], whereas the insulin-like growth factor (IGF) system which acts potently to regulate muscle development, hypertrophy and maintenance is suppressed. Exercise plays a role in mediating the effects of chronic inflammation, reducing inflammatory markers such as C-reactive protein (CRP), tumour necrosis factor alpha, and various types of interleukin (IL), including IL6, in people with and without cancer. Furthermore, the protective effects of exercise have been attributed to the creation of an anti-inflammatory environment through increasing anti-inflammatory cytokines such as IL10 in healthy people [37]. To get insight into potential physiological pathways future studies should incorporate specific biomarker analysis.

Mean exercise adherence was 81.3% and no adverse events were reported. Thus a home-based walking programme seems to be a feasible intervention. The adherence rate corresponds to the results of a pilot study investigating the effects of supervised exercise in patients with advanced GIC [12]. Additionally, in our sample extreme weather conditions or treatment-related side effects affect outdoor walking in some cases. Thus, one might speculate that an exercise intervention with more flexibility concerning the exercise mode and setting might further enhance exercise adherence.

Further studies are warranted to extend the knowledge about exercise effects in patients with GIC and to identify options for enhancing adherence, especially in inactive patients. As already discussed, following studies should incorporate a more flexible exercise approach with different exercise forms and supervised sessions to improve intervention compliance and practicality. Further, it might be useful to adopt a multidimensional exercise programme including endurance, strength and balance components in following studies to address aspects that did not benefit from the chosen home-based walking programme such as strength and gait, although such a programme might be more challenging in terms of supervised exercise sessions and logistics. Additionally, the incorporation of clinical outcomes and biomarkers might be beneficial to monitor possible differences in chemotherapy toxicity and chemotherapy completion rate as well as potential underlying physiological pathways and possible influences concerning relevant and highly prevalent side effects such as cancer cachexia.

Conclusion

Physical activity programmes for patients with GIC might be of great value during chemotherapy. Our study indicates that chemotherapy accompanying home-based aerobic exercise seems to be safe and feasible in patients with locally or systemically advanced GIC during chemotherapy. Further, it seems to have the potential to stabilize or improve functional capacity, postural stability and body composition. Thus, exercise might contribute to counteract treatment- and disease-related side effects and might diminish cancer- and therapy-related impairments in the physical condition and activities of daily living. Following studies are needed to confirm our results, to identify favourable exercise approaches and to extend the rationale for including physical activity as supportive strategy in the management of patients with GIC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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