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ORIGINAL ARTICLE

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Assessment of gait parameters and physical function in patients with advanced cancer participating in a 12-week exercise and nutrition programme: A controlled clinical trial

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Abstract

Objective: Gait is a sensitive marker for functional declines commonly seen in patients treated for advanced cancer. We tested the effect of a combined exercise and nutrition programme on gait parameters of advanced-stage cancer patients using a novel wearable gait analysis system.

Methods: Eighty patients were allocated to a control group with nutritional support or to an intervention group additionally receiving whole-body electromyostimulation (WB-EMS) training (2×/week). At baseline and after 12 weeks, physical function was assessed by a biosensor-based gait analysis during a six-minute walk test, a 30-s sit-to-stand test, a hand grip strength test, the Karnofsky Index and EORTC QLQ–C30 questionnaire. Body composition was measured by bioelectrical impedance analysis and inflammation by blood analysis.

Results: Final analysis included 41 patients (56.1% male; 60.0 ± 13.0 years). After 12 weeks, the WB-EMS group showed higher stride length, gait velocity ($p < .05$), six-minute walking distance ($p < .01$), bodyweight and skeletal muscle mass, and emotional functioning ($p < .05$) compared with controls. Correlations between changes in gait and in body composition, physical function and inflammation were detected.

Conclusion: Whole-body electromyostimulation combined with nutrition may help to improve gait and functional status of cancer patients. Sensor-based mobile gait analysis objectively reflects patients' physical status and could support treatment decisions.

KEYWORDS

cancer, exercise, gait, nutrition, physical function, whole-body electromyostimulation

Trial Registration: ClinicalTrials.gov Identifier: NCT02293239.

1 | INTRODUCTION

Paraneoplastic syndromes as well as surgical and pharmacological interventions have a negative impact on the quality of life of cancer patients by deteriorating physical function and thus increasing risk of falling and worsening performance (Brown et al., 2005; Niederer et al., 2014). Inflammation-induced muscle loss enhanced by decreased food intake and low physical activity contributes to this (Argiles, Busquets, Stemmler, & Lopez-Soriano, 2014) and predicts the number of hospitalisations, therapy tolerance and treatment decisions (Baracos & Kazemi-Bajestani, 2013; Sjoblom et al., 2016; Verweij et al., 2016). Moreover, muscle function can be impaired by neurological and bone metabolism disorders, surgical denervation and therapy-induced peripheral neuropathy (Banach, Juranek, & Zygulska, 2017; Dropcho, 2010; Hojan, 2012). Efficient and feasible methods to sustain and monitor physical function in advanced cancer patients are needed.

Commonly, overall functional status is determined by clinicians using the Karnofsky Index or the Eastern Cooperative Oncology Group (ECOG) performance status, or by patient-reported quality of life questionnaires (i.e. the EORTC QLQ-C30) (Karnofsky, 1949; Oken et al., 1982). These evaluations do not always reflect the patient's actual functional status that highly depends on his current psychosocial constitution (Simmonds, 2002). Several standardised objective physical performance tests have been established using single tests (e.g. the six-minute walk test) or combined approaches (e.g. short physical performance battery, SPPB) (Verweij et al., 2016). Gait is an important determinant of mobility and thus an adequate tool to measure physical function (Kramers-de Quervain et al., 2008). Clinically assessed gait velocity was related to difficulties in gait-dependent and gait-independent activities of daily living and motor-based activities (Verghese et al., 2011) and predictive for death, hospitalisation and performance status in older adults (Rydwik et al., 2012). In contrast to healthy controls, walking speed was also shown to be impaired in cancer patients and can decline during the oncological treatment predicting patients' prognosis (Monfort et al., 2017; Pamoukdjian et al., 2017; Sande et al., 2014). Despite the role of gait as a potential sensor for the health status of a patient, monitoring and analysis of intervention-related changes in different gait parameters and their relation to physical function have not been conducted in patients with advanced cancer, so far.

Various gait analysis systems have been developed, such as high-resolution three-dimensional motion capture systems, video-based gait analysis and gait carpets (Muro-de-la-Herran et al., 2014). A novel mobile body-worn and sensor-based inertial measurement system for the assessment of spatio-temporal gait parameters has been recently developed and validated to assess gait patterns in older adults (Rampp et al., 2015) or to classify patients with Parkinson's disease within standardised walking tests (Klucken et al., 2013).

The primary aim of this pilot project was to explore the preliminary effect of a 12-week physical exercise and nutrition programme on gait in advanced-stage cancer patients assessed by the novel sensor-based gait analysis system. Referring to our previous study (Schink, Herrmann, et al., 2018), we hypothesised that this dual therapy improves gait as a consequence of an increased muscle mass and function. Secondarily, the utility of the gait analysis system to objectively assess intervention-related changes in gait in correlation with objective and subjective physical function, body composition and inflammation was analysed.

2 | METHODS

2.1 | Patients

Patients (≥18 years) treated for solid advanced-stage cancers that presented a Karnofsky Index ≥ 60 at baseline were included in the study. All participants gave written informed consent before their inclusion in this clinical trial. The study was conducted according to the guidelines of the Helsinki Declaration. The protocol of this study was approved by the ethics committee of the Friedrich-Alexander Universität Erlangen-Nürnberg (Reg.Nr.155_13B). Patients were recruited from departments of the University Hospital Erlangen treating oncological patients between 2014 and 2016. Baseline and outcome assessments, WB-EMS, dietary counselling and data collection were performed at the Department of Medicine 1 of the University Hospital Erlangen. Criteria for study exclusion were the concomitant participation in other nutritional or physical exercise trials, recently occurred acute cardiovascular events, intake of anabolic drugs, epilepsy, severe neurological diseases, skin lesions within the area of the electrodes, oncological surgery in the last 3 months, acute vein thrombosis, the presence of a cardiac pacemaker, pregnancy or conductive implants that would exclude WB-EMS application (Schink, Herrmann, et al., 2018).

2.2 | Study design

Due to the pilot study character, no formal sample size calculation was performed. The recruited sample size was based according to recommendations of Hertzog (Hertzog, 2008). The pilot study was conducted as a two-armed prospective controlled clinical trial. After baseline assessment, patients were allocated to either a WB-EMS intervention group or a control group without any exercise intervention for 12 weeks. Both groups received the same nutritional support during the study. Allocation to the study group was pre-determined by the patients' ability to attend the exercise programme twice weekly, as reported previously (Schink, Herrmann, et al., 2018).

All patients who were interested in joining the exercise intervention study but could not participate in the exercise sessions two times a week due to a long journey way to the study centre were asked to enter the control group or were excluded from the study to avoid scheduling problems.

2.3 | Dietary support

The nutritional risk of the patients was assessed at baseline and documented by the nutritional risk screening (NRS-2002) (Kondrup et al., 2003). Patients scoring ≥3 were assumed to be at nutritional risk caused by low body mass index, decreased food intake and/or prior involuntary weight loss. The dietary support and monitoring of the nutritional intake by 24-hr dietary records was described previously (Schink, Herrmann, et al., 2018). In brief, dietary intake was analysed by Prodi®6 expert (Nutri-Science GmbH, Freiburg) and a registered dietician instructed patients to achieve a daily protein intake of >1.0 g/kg and caloric intake of at least 25 kcal/kg bodyweight regarding current dietary recommendations for cancer patients (Arends et al., 2016).

2.4 | Physical exercise programme

The supervised WB-EMS training was supported by easy-to-perform dynamic exercises as described previously (Schink, Herrmann, et al., 2018). In brief, electrical muscle stimulation was applied by bipolar impulses at a frequency of 85 Hz and pulse breadth of 350 μs, mediating a stimulation for 6 s followed by a 4-s stimulation rest. The supervised WB-EMS training was performed twice a week on two non-consecutive days for 20 min per session and comprised a sequence of light, dynamic, easy-to-perform physical exercises, activating the following muscle areas: upper legs, upper arms, bottom, abdomen, chest, lower back, upper back and latissimus dorsi. Equipment was purchased from Miha bodytec (Miha bodytec GmbH, Gersthofen).

2.5 | Study outcomes

2.5.1 | Assessments

Assessments of study outcomes were performed at baseline and after 12 weeks. Demographic data were collected by an anamnesis questionnaire and medical records.

The exercise attendance of the patients was monitored by the supervising physiotherapists, and the attendance rate was calculated by the number of performed trainings from a total of 24 WB-EMS sessions.

2.5.2 | Sensor-based gait analysis and physical function tests

Different gait parameters were recorded and analysed by a mobile, sensor-based gait analysis system, previously established to evaluate gait patterns in geriatric patients (Rampp et al., 2015; Schulein et al., 2017) and patients with Parkinson's disease (Klucken et al., 2013; Kluge et al., 2017). Wearable and wireless sensors (Shimmer Research Ltd.) including accelerometers and gyroscopes were attached to the lateral heel part of provided sport shoes (Adidas AG) and recorded motion signals during the conduction of the six-minute walk test. The gait analysis system was described in detail by Klucken et al. (2013) and provides real-time kinematical motion recording. Data were captured from both feet using an accelerometer range of ±6 g (sensitivity 300 mV/g), a gyroscope range of ±500 degree/s (sensitivity 2 mV/degree/sec) and a sampling rate of 102.4 Hz. Sensor signals were transmitted via Bluetooth® to a tablet computer. A pattern recognition algorithm was used to calculate clinically relevant spatio-temporal gait parameters including stride length (cm), cadence (steps/minute), maximum toe clearance (cm), heel strike and toe-off angle (°) and gait velocity (m/s). Regularity of gait was measured by gait variability of stride time, stance time, swing time and stride length. Stride time (s), stance and swing time (%) as well as cadence (steps/minute) were recorded as measures of gait rhythm.

The maximum toe clearance is defined as maximum toe height during the swing phase, heel strike angle is the angle between foot and ground at initiation of stance phase (= heel contact), and toe-off angle is defined as angle between foot and ground at the end of the stance phase (= toe-off). Since several gait parameters are influenced by body height, stride time, stride length, maximum toe clearance, cadence and gait velocity were normalised to body height ([gait parameter/individual height] * average height of baseline study population).

Further objective functional assessments were performed using three validated physical tests:

1. Six-minute walk test (SMWT)—to measure the maximum walking distance/capacity (Schmidt et al., 2013).
2. Isometric hand grip strength (HGS)—to capture function, strength and nutritional status (Kilgour et al., 2013). Grip strength of the dominant hand was measured by hand dynamometer (SH5001, SAEHAN Corporation, Masan, South Korea) (Trampisch et al., 2012).
3. 30 s sit-to-stand (STS) test—to indirectly determine the function and strength of the lower limbs (Jones et al., 1999).

2.5.3 | Measurement of skeletal muscle mass and bodyweight

The change in bodyweight and skeletal muscle mass from baseline to 12 weeks post-intervention was measured by bioelectrical impedance analysis—BIA (Bosy-Westphal & Jensen, 2017) (seca mBCA 515; Seca GmbH & Co. KG).

2.5.4 | Patient-reported outcomes

A subjective assessment of the performance status was achieved by the Karnofsky Index (Karnofsky, 1949). Patient-reported

psychosocial and physical status was determined by the functional scales of the EORTC QLQ-C30, whereby a higher score indicated a better functioning (Aaronson et al., 1993).

2.5.5 | Analysis of blood samples

Blood samples were collected by venepuncture and analysed for inflammatory blood markers (C-reactive protein, CRP < 5.0 mg/L; albumin > 35.0 g/L; haemoglobin 12 – 13 g/L; and leucocyte count 4 – 10 $x10^9$ cells/l) by the diagnostic laboratories of the University Hospital Erlangen.

2.6 | Statistical analysis

Descriptive data are presented as means ± standard deviations (*SD*) for continuous and count and percentages for categorical variables. Laboratory variables are expressed as median with range. Normal distribution of the data was tested by Shapiro–Wilk test. Baseline differences between study groups were analysed using chi-squared test or Fisher's exact test for categorical variables. Continuous variables were analysed by independent-samples Student's *t* test, Welch test or Mann–Whitney *U* test, where appropriate. In the same way, comparisons between patients who completed and not completed the study were conducted.

Intra-group analysis of pre- to post-intervention changes in gait parameters was performed by paired-sample Student's *t* test. The effect of the exercise intervention on gait parameters and secondary outcomes compared with the controls was estimated by multiple linear regression. Model selection was based on the outcome of gait velocity as the dependent variable. Based on backward selection, the final regression model included study group, age, gender, mean daily energy intake and baseline Karnofsky Index as covariates. Each linear regression model was also adjusted by its patient-specific baseline value. As nutritional data of two patients were unavailable, mean nutrient/energy intake was estimated by linear regression.

Relationship between intervention-mediated changes in gait and changes in secondary outcomes, Spearman's rank correlation was used.

Statistical analysis was conducted in SPSS version 21 (IBM SPSS Statistics). A *p*-value <.05 was considered as statistically significant. Due to the exploratory character of the study, no correction for multiple comparisons was applied.

3 | RESULTS

3.1 | Participants

Eighty patients were enrolled into the study and received baseline gait analysis (Figure 1). Thereof, 22 participants were allocated to the control group and 58 patients to the WB-EMS group of which 15 control and 26 WB-EMS patients were available for the statistical analysis of the primary outcome of gait parameters. Within the study period of 12 weeks, 5 control patients and 26 patients with WB-EMS left the study, resulting in dropout rate of 22.7% for the control and 44.8% for the WB-EMS group (p = .070). Dropouts were not significantly different in reasons between the groups (p = .186) and primarily caused by disease-related health deterioration (Figure 1). A more precise description of dropouts is provided in the Appendix. No EMS-related adverse effects forced patients to exit the study. At study completion in week 12, two patients of the control group and 4 patients of the WB-EMS group missed final gait analysis. Additionally, two patients of the WB-EMS group refused to conduct the six-minute walking test at study end. Those patients were excluded for the statistical analysis (Figure 1).

Table 1 presents the baseline characteristics of the participants that are included in the final analysis. Study groups did not differ in cancer stage (p = .277) and treatment regimens (p = .226). Patients of the training group reported a higher Karnofsky Index but showed a lower baseline cadence than controls. Patients of the WB-EMS group who completed the 12-week study period and were included in the final analysis attended 21.3 ± 2.1 (15–24 training session/12 weeks) of the targeted 24 trainings, resulting in a mean exercise attendance rate of 88.9% ± 8.7%.

3.2 | Gait, physical function, body composition and inflammation

Table 2 presents the mean values with standard deviation of gait parameters assessed by gait analysis for each group. Patients of the WB-EMS group showed a significantly decreased stride and stance time after 12 weeks, a significant increase in swing time, stride length, cadence and gait velocity. Control patients demonstrated significant changes in the gait parameters stance and swing time, and cadence, but not as pronounced as in the WB-EMS group. No significant changes in any other gait parameters were observed within the groups.

The adjusted estimated effects of the WB-EMS intervention compared with the controls on gait parameters and secondary outcomes, calculated by multiple regression models, are presented in Table 3. After 12 weeks, patients of the WB-EMS group tended towards a shorter stride time, a larger stride length and a higher gait velocity compared with control patients. Additionally, cadence was higher in the WB-EMS group, albeit not statistically significant. A significantly higher six-minute walking distance was recorded favouring the WB-EMS group and a strong trend towards a higher number of sit-to-stand repetitions compared with controls. Exercising patients reported a significantly better emotional functioning and improved physical functioning. Bodyweight and skeletal muscle mass of WB-EMS participants were significantly higher at week 12 compared with controls. No significant effects of the WB-EMS intervention on blood parameters were detected.

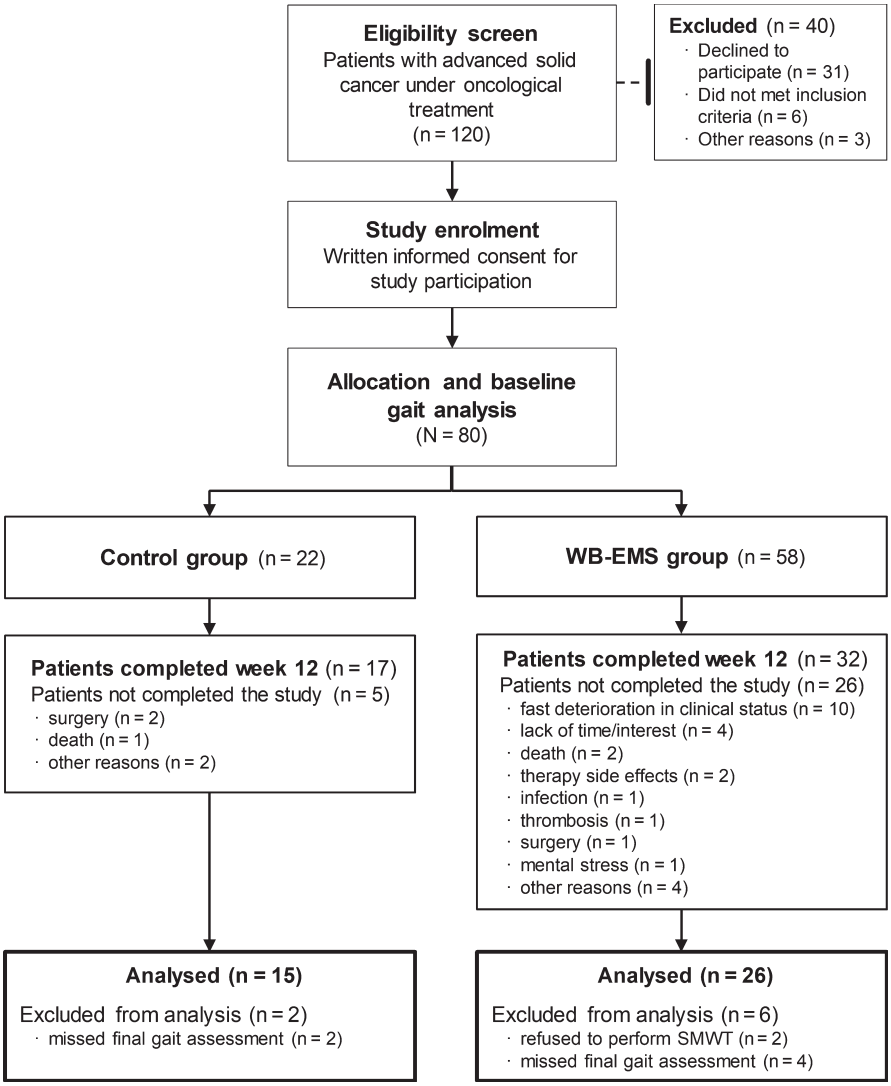

FIGURE 1 Patient flowchart. The flowchart shows the number of eligible and allocated patients, patients who dropped out during study course with dropout reasons and the number of patients who were available for analysis of changes in gait parameters after completing the whole intervention period of 12 weeks. Abbreviations: SMWT, six-minute walk test; WB-EMS, whole-body electromyostimulation

The relationship of the pre- to post-intervention changes, including patients of both study groups, between gait parameters and secondary outcomes is shown in Table 4. Spearman's rank correlation revealed that a negative change in stride time significantly correlated with a gain in skeletal muscle mass. In addition, positive changes in stride length, toe-off angle, cadence and gait velocity were moderately associated with an increase in bodyweight and/or skeletal muscle mass. The increase in gait velocity after 12 weeks (delta/changes) showed a significant correlation with positive changes in all used objective physical function tests. An increase in stride time inversely correlated with a change in the walking distance, while increased cadence strongly correlated with a better outcome in the six-minute walk. Cadence was also positively related to sit-to-stand test changes. Significant associations between patient-reported physical functioning and gait parameters were only detected for stride length. Interestingly, an association between changes in gait and inflammation was observed. A decrease in stride time correlated with a decline in the CRP serum concentration and a rise in haemoglobin, while an improvement in stride length, cadence and gait velocity was related to a better inflammatory status. Correlation data of gait variabilities and functional EORTC QLQ-C30 scales, except of physical functioning, showed only marginally relationships (please see Appendix).

4 | DISCUSSION

This is the first study, to our knowledge, that reports about the effect of a combined physical exercise and nutrition intervention on gait parameters of advanced-stage cancer patients undergoing oncological treatment. The results of this pilot trial suggest that the improved muscle status of patients with additional WB-EMS training is related with improvements in their physical functioning, especially in gait. Gait analysis performed with a wearable sensor-based gait analysis system revealed an enhancement of the most common gait parameters and showed strong evidence for the usefulness and applicability of this system to objectively assess physical function in cancer patients.

Chronic and acute effects of cancer and oncological treatment often lead to a loss of skeletal muscle mass causing general physical

TABLE 1 Demographic and disease characteristics of included patients[e]

Parameter	Control (n = 15)	WB-EMS (n = 26)	p-value[f]
Gender			
Male	6 (40.0)	17 (65.4)	.115
Female	9 (60.0)	9 (34.6)	
Mean age	55.9 ± 13.1	62.4 ± 12.6	.126
Functional status			
Karnofsky Index	75.3 ± 5.2	80.8 ± 11.6	.134
EORTC QLQ-C30[a]			
Physical functioning	78.7 ± 16.4	76.3 ± 24.2	.934
Role functioning	60.0 ± 32.1	58.0 ± 32.7	.847
Emotional functioning	64.0 ± 18.8	64.0 ± 23.0	.998
Cognitive functioning	77.7 ± 23.3	72.0 ± 29.5	.600
Social functioning	54.4 ± 30.6	56.7 ± 28.5	.455
Max. gait velocity (m/s)	1.61 ± 0.26	1.55 ± 0.26	.493
Max. walking distance (m)	550.1 ± 85.8	543.8 ± 99.5	.602
Cadence (steps/min)	125.0 ± 13.1	116.5 ± 11.0	**.032***
Stride length (cm)	158.8 ± 17.6	158.5 ± 17.5	.954
Lower limb strength (sit-to-stand cycles)[b]	13.5 ± 5.0	13.0 ± 6.5	.489
Hand grip strength (kg)[c]	34.0 ± 8.8	38.7 ± 12.8	.224
Nutritional status			
BMI (kg/m^2)	26.4 ± 4.8	25.3 ± 3.3	.399
Fat mass index (kg/m^2)	8.7 ± 3.9	7.4 ± 2.6	.327
Fat free mass index (kg/m^2)	17.4 ± 3.0	17.9 ± 2.5	.621
Skeletal muscle mass (kg)	22.4 ± 5.5	24.3 ± 5.7	.308
Phase angle (°)	4.7 ± 0.5	4.5 ± 0.7	.481
Nutritional risk screening			
<3	10 (66.7)	10 (38.5)	.082
≥3	5 (33.3)	16 (61.5)	
Nutritional therapy			
Only dietary counselling	9 (60.0)	20 (76.9)	.300
Oral supplementation	6 (40.0)	6 (23.1)	
Parenteral	0 (0.0)	0 (0.0)	
Mean daily nutrient/caloric intake during participation (per kg bodyweight)			
Carbohydrates (g)	4.1 ± 1.2	3.3 ± 0.7	**.017***
Fat (g)	1.4 ± 0.4	1.2 ± 0.4	.271
Protein (g)	1.5 ± 0.3	1.3 ± 0.4	.076
Energy (kcal)	37.9 ± 11.8	30.7 ± 7.4	**.021***
Disease characteristics			
Cancer type			
Gastrointestinal	14 (93.3)	11 (42.3)	**.011***
Gynaecological	1 (6.7)	3 (11.5)	
Urological	0 (0.0)	10 (38.5)	
Lung	0 (0.0)	2 (7.7)	
Cancer stage			
III	2 (13.3)	8 (30.8)	.277
IV	13 (86.7)	18 (69.2)	
Anti-cancer therapy			
Chemotherapy	12 (80.0)	15 (57.7)	.226
Radiotherapy	0 (0.0)	1 (3.8)	
Targeted therapy	0 (0.0)	3 (11.5)	
Hormonal therapy	0 (0.0)	2 (7.7)	
Chemotherapy + Targeted therapy	2 (13.3)	0 (0.0)	
Radiotherapy + Hormonal therapy	0 (0.0)	2 (7.7)	
Chemotherapy + Hormonal therapy	0 (0.0)	1 (3.8)	
Targeted therapy + Hormonal therapy	1 (6.7)	2 (7.7)	
Number of medications	2.1 ± 2.4	3.2 ± 3.1	.209
Comorbidities[d]			
Cardiovascular disease	3 (20.0)	6 (23.1)	1.000
Pulmonary disease	2 (13.3)	1 (3.8)	.543
Renal failure	1 (6.7)	0 (0.0)	.366
Thyroid disease	2 (13.3)	6 (23.1)	.687
Diabetes mellitus	0 (0.0)	3 (11.5)	.287
Laboratory values			
Haemoglobin (g/dl)	12.2 (9.5–13.7)	12.9 (7.7–15.0)	.150
Leucocytes (x10^{9}cells/l)	5.7 (3.9–9.7)	5.6 (2.9–10.6)	.929
Albumin (g/l)	41.6 (38.3–46.7)	41.6 (36.7–49.9)	.890
CRP (mg/l)	5.7 (0.8–86.2)	2.8 (0.3–104.6)	.114

Abbreviations: BMI, body mass index; CRP, C-reactive protein; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; WB-EMS, whole-body electromyostimulation.

[a]WB-EMS, n = 25; Control, n = 15.

[b]WB-EMS, n = 22; Control, n = 15.

[c]WB-EMS, n = 26; Control, n = 14.

[d]Number of patients for comorbidities includes also patients with several comorbidities.

[e]Data from patients which were included in the final gait analysis are presented in numbers and proportions (%) and as mean ± *SD*. Laboratory values are expressed as median and range (min to max).

[f]Baseline comparison of WB-EMS and control group assessed by Pearson's chi-squared test and Fisher's exact test, respectively, for categorical variables and independent-samples Student's t test, Welch's test or Mann–Whitney U test for continuous variables. Statistically significant differences are indicated by $^*p < .05$ and marked in bold type.

(Continues)

TABLE 2 Gait parameters at baseline and study end of the WB-EMS and control group

	Gait parameters[a]			
	WB-EMS (n = 26)		Control (n = 15)	
Screen weeks	0	12	0	12
Stride time (s)	1.03 ± 0.09	**0.99 ± 0.08*****	1.02 ± 0.07	1.00 ± 0.62
Stride time variability (%)	2.45 ± 0.59	2.58 ± 0.74	2.88 ± 0.81	2.69 ± 0.62
Swing time (%)	36.13 ± 1.30	**36.60 ± 1.11****	36.38 ± 1.32	**36.71 ± 1.29***
Swing time variability (%)	3.78 ± 0.97	3.67 ± 0.81	3.97 ± 0.98	3.76 ± 0.61
Stance time (%)	63.87 ± 1.30	**63.40 ± 1.11****	63.66 ± 1.30	**63.29 ± 1.30***
Stance time variability (%)	2.95 ± 0.67	3.15 ± 0.91	3.40 ± 0.96	3.33 ± 0.84
Stride length (cm)	158.51 ± 17.51	**162.98 ± 16.90****	158.85 ± 17.55	160.95 ± 16.94
Stride length variability (%)	7.97 ± 2.30	7.95 ± 1.84	8.24 ± 2.89	8.31 ± 2.46
Heel strike angle (°)	16.13 ± 4.90	15.79 ± 3.35	16.60 ± 3.84	15.90 ± 3.91
Toe-off angle (°)	−70.77 ± 8.27	−71.65 ± 7.91	−71.60 ± 6.95	−72.43 ± 6.58
Maximum toe clearance (cm)	12.28 ± 2.32	12.43 ± 2.47	12.29 ± 1.78	12.26 ± 1.62
Cadence (steps/min)	116.53 ± 10.96	**120.73 ± 13.10*****	125.01 ± 13.10	**127.82 ± 13.65***
Gait velocity (m/s)	1.55 ± 0.26	**1.65 ± 0.26*****	1.61 ± 0.26	1.67 ± 0.25

Abbreviations: WB-EMS, whole-body electromyostimulation.

Gait parameters were assessed by the mobile gait analysis system within the study groups at baseline and week 12.

[a]Data are presented as mean ± standard deviation. Intra-group analysis of gait changes during the study course was performed by Student's paired-samples t test. Statistical significance is indicated by *p < .05, **p < .01, ***p < .001 and marked in bold type.

weakness. Severe consequences are postural instability and gait dysfunctions leading to immobility affecting quality of life. The commonly used report given by the patients can reveal an inaccurate or even misleading evaluation of their physical condition (Collins et al., 2015). The wearable sensor-based gait analysis concept used in this study provides an objective assessment method by recording spatio-temporal gait parameters calculated by pattern recognition algorithms.

Compared with the usual care support, there is an improvement in several gait parameters in our WB-EMS group using the sensor-based gait analysis tool. Stride length and gait velocity were significantly higher than in controls after 12 weeks, whereas a trend towards a lower stride time and higher cadence was shown for the exercising patients.

Gait velocity is a significant vital sign (Middleton et al., 2015), and the clinical relevance of stride length and gait velocity was shown to be important in assessing the patients' functional status and overall vitality; deterioration of both parameters leads to a more insecure gait, causes instability and falls in elderly people (Espy et al., 2010; MacAulay et al., 2015). Impaired walking speed is common in cancer patients. Sande et al. used the GAITrite® system to investigate cancer-induced bone pain. Here, the patients walked more slowly with a lower cadence compared to healthy adults (Sande et al., 2014). Another analysis showed a progressive decline in walking speed, measured by custom-built timing gates, of early-stage breast cancer patients during chemotherapy, due to neuromuscular disorders (Monfort et al., 2017). A study of Pamoukdjian et al. demonstrated that a slow gait speed (<0.8 m/s) is an independent predictor of early death (<6-month survival time) in older cancer patients (Pamoukdjian et al., 2017). The improvement of the above-mentioned gait parameters in the WB-EMS group clearly suggests an amelioration of physical function by the combined exercise and nutrition approach, while an impact on prognosis should be determined within future larger-scaled randomized trials. An increase in gait velocity that correlates with a higher skeletal muscle mass index has been recently reported in a population of elderly sarcopenic gastric cancer patients that underwent a combined nutrition and exercise programme before oncological surgery (Yamamoto et al., 2016). Also, patients with advanced cancer showed a benefit of a 10-week exercise intervention on functional mobility assessed by the SPPB, including mean gait speed (Litterini et al., 2013). In patients with end-stage renal disease, a 12-week Tai Chi exercise programme resulted in a significantly higher six-minute walking distance and gait velocity (Chang et al., 2017).

Besides the objective testing of physical functioning, we captured the patient-reported physical condition. Due to the smaller sample size compared with our previous study, the beneficial effect of the WB-EMS intervention on Karnofsky Index did not reach statistical significance (Schink, Herrmann, et al., 2018). The objective assessment of physical function of cancer patients via gait analysis might therefore be more precise than using only a subjective score system. Also, data from the EORTC QLQ-C30 revealed no significantly better patient-reported physical functioning of the WB-EMS patients compared with controls.

To investigate the validity of the recorded parameters as a surrogate for physical function and health status of the patients, we

TABLE 3 Multiple linear regression estimating the effect of WB-EMS compared with the control group

	n	Coefficient	95% CI	*p*-value[a]
Gait parameters				
Stride time (s)	41	−0.03	−0.05, 0.00	.053
Stride time variability (%)		0.19	−0.31, 0.70	.441
Swing time (%)		0.14	−0.39, 0.67	.592
Swing time variability (%)		0.05	−0.46, 0.56	.847
Stance time (%)		−0.11	−0.64, 0.42	.684
Stance time variability (%)		0.21	−0.40, 0.82	.486
Stride length (cm)		4.92	0.46, 9.38	**.032***
Stride length variability (%)		−0.27	−1.59, 1.04	.674
Heel strike angle (°)		0.60	−1.92, 3.12	.631
Toe-off angle (°)		−0.39	−2.09, 1.31	.643
Maximum toe clearance (cm)		0.43	−0.44, 1.30	.326
Cadence (steps/min)		2.59	−0.84, 6.02	.134
Gait velocity (m/s)		0.08	0.00, 0.15	**.043***
Physical function tests				
Handgrip strength (kg)	40	2.03	−2.42, 6.47	.360
SMWT (m)	41	44.57	13.83, 75.30	**.006***
30-s STS test (repetitions)	34	2.29	−0.07, 4.65	.056
Patient-reported physical function and performance				
Karnofsky Index	41	5.89	−2.79, 14.56	.177
EORTC QLQ-C30				
Physical functioning	36	9.30	−0.69, 19.30	.067
Role functioning	35	−1.89	−19.94, 16.16	.831
Emotional functioning	35	18.09	3.44, 32.73	**.017***
Cognitive functioning	34	2.00	−12.73, 16.73	.783
Social functioning	35	3.25	−9.42, 15.91	.604
Body composition				
Bodyweight (kg)	41	4.00	1.47, 6.50	**.003****
Skeletal muscle mass (kg)	40	0.99	0.09, 1.90	**.033***
Inflammatory status				
Haemoglobin (g/dl)	40	0.12	−0.56, 0.78	.746
Leucocytes (×10^9 cells/l)	40	−1.27	−2.87, −0.33	.326
Albumin (g/l)	41	1.32	−0.50, 3.14	.149
CRP (mg/l)	41	−3.26	−9.15, 2.63	.269

Abbreviations: 30-s STS test, 30-s sit-to-stand test, CRP, C-reactive protein; SMWT, six-minute walk test; 95% CI, 95% confidence interval.

[a]Model is adjusted for age, gender, baseline Karnofsky Index, mean daily caloric intake (kcal/kg) and patient-specific baseline value of the respective outcome variable. Values from patients of both study groups were included. Statistically significant effects are indicated by $^*p < .05$, $^{**}p < .01$ and marked in bold type.

carried out correlation analysis. Our results show that recorded differences in gait were reflected by the pre- to post-changes in the commonly used objective function tests, the six-minute walk test and the sit-to-stand test. Stride time, cadence and gait velocity strongly correlated with changes in the six-minute walking distance and may therefore be appropriate parameters to predict the physical capacity of cancer patients. Further, we detected that an increase in the sit-to-stand repetitions was linked to a positive pre- to post-intervention shift in most gait parameters. Detailed knowledge of lower limb function and strength is certainly beneficial to the evaluation of the disease course and therapy. From all gait parameters, gait velocity showed a moderate to strong correlation with all objective functional tests and thus might be the most significant gait determinant when assessing the functional status in cancer. In contrast to the mobile gait analysis system, we detected only a weak association between a subjective evaluation of the physical function by the patient and changes in gait. These data emphasise that a subjective as well as an objective rating of

TABLE 4 Relationship between the pre- to post-intervention changes in gait parameters and secondary outcomes

	Correlation coefficients[a]										
	Body composition		Objective physical function			Subjective physical function		Inflammatory markers			
	SMM	BW	SMWT	30-s STS	HGS	KI	PF	Leu	Hb	CRP	Alb
Gait parameters	n = 40	n = 41	n = 41	n = 32	n = 40	n = 41	n = 36	n = 40	n = 40	n = 41	n = 41
Stride time (s)	**−0.360***	**−0.416****	**−0.644****	**−0.399***	−0.219	−0.160	−0.201	0.224	−0.309	**0.314***	−0.157
Swing time (%)	0.053	−0.106	0.308	**0.397***	0.031	0.184	0.244	**0.358***	**0.328***	0.165	0.175
Stance time (%)	−0.073	0.102	**−0.313***	**−0.376***	−0.025	−0.183	−0.243	**−0.369**	**−0.336***	−0.163	−0.172
Stride length (cm)	**0.474*****	0.273	0.226	**0.473****	**0.466****	0.204	**0.341***	−0.095	**0.399***	**−0.314***	**0.378***
Heel strike angle (°)	0.085	0.220	0.070	0.160	0.014	0.156	−0.096	−0.138	0.107	0.001	0.242
Toe-off angle (°)	**0.403****	0.176	−0.263	**0.503****	−0.265	0.091	0.248	−0.048	**0.398***	−0.214	0.292
Max. toe clearance (cm)	0.201	0.186	−0.029	0.105	0.219	**0.323***	0.098	0.056	0.263	−0.037	0.249
Cadence (steps/min)	**0.328***	**0.371***	**0.641****	**0.382***	0.183	0.165	0.191	−0.195	0.308	**−0.337***	0.162
Gait velocity (m/s)	**0.473****	**0.390***	**0.515****	**0.447****	**0.407****	0.221	0.229	−0.164	**0.440****	**−0.399****	0.285

Abbreviations: 30-s STS, 30-s sit-to-stand test; Alb, albumin; BW, bodyweight; CRP, C-reactive protein; Hb, haemoglobin; HGS, hand grip strength; KI, Karnofsky Index; Leu, leucocyte count; PF, physical functioning; SMWT, six-minute walk test; SMM, skeletal muscle mass.

[a]Spearman's rank correlation coefficients of pre-/post-changes in gait parameters and body composition, objective physical functioning tests, patient-reported physical function, quality of life and inflammatory blood markers. Pre-/post-changes in patients of both study groups with gait analysis at baseline and week 12 are included. A statistically significant relationship is indicated by $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$ and marked in bold type.

the physical capabilities is needed in order to get an accurate picture of the patients' functional constitution.

The clinical applicability of the mobile gait analysis system was good. It uses minimal equipment and space, in contrast to systems based on gait carpets or video tools, and it is easy to handle and time-saving. Even though instrumented walkway systems such as the GAITrite® system are also validated to record spatio-temporal gait parameters with a comparable efficacy as a three-dimensional motional analysis system (Webster et al., 2005), the use of a sensor-based carpet may be a too space-consuming equipment requirement for the implementation in the clinical routine.

Common assessment methods of the lower limb strength, for example using pressure plates to measure the maximum isometric leg strength, can be harmful for advanced tumour patients. These patients often suffer from bone metastasis, post-operative hernia and muscle weakness (Milgrom et al., 2017). A good correlation between several gait parameters and leg strength leads to the conclusion that sensor-based gait analysis system can potentially replace hard-to-perform physical tests for vulnerable patients.

In concordance with our previous data, WB-EMS and nutritional support stabilized bodyweight and muscle mass of advanced cancer patients resulting in functional improvements (Schink, Herrmann, et al., 2018). We observed positive correlations between a gain in muscle mass and improvements of gait parameters, including stride time and length, cadence and velocity. An association between physical function and skeletal muscle mass was reported by a sarcopenia-defining study in elderly (Chen et al., 2011) and in cancer patients during chemotherapy (Naito et al., 2017). Skeletal muscle mass is an important prognostic factor for cancer patients (Blauwhoff-Buskermolen et al., 2016). Gait analysis could potentially serve as an indirect assessment of the muscular status of these patients.

In addition, we found a moderate correlation between changes in inflammation and gait parameters. A higher serum CRP level was in line with a worsening of the gait pattern, indicated by the parameters stride length and time, cadence and velocity. Comparable results were published for elderly individuals (Sousa et al., 2016). In contrast, an increase in haemoglobin correlated with improvements in several gait parameters. Low haemoglobin in elderly was reported to predict a low future gait speed (Zakai et al., 2013).

Our study results are based on a relatively small analysed study population failing to reach significance for the superior effect of the WB-EMS group on stride time, cadence and 30-s sit-to-stand test compared with controls, most likely due to insufficient statistical power. The high dropout rate in the WB-EMS group also contributed to this. Reasons for the higher attrition levels in the exercise intervention group were discussed in our prior publication (Schink, Herrmann, et al., 2018). Patients treated for advanced malignant diseases are faced with a highly intensive and exhausting oncological treatment that can cause severe physiological and psychological effects. The dropouts of both groups showed a higher initial inflammatory burden and a poorer physical condition compared

with the patients who finished the 12-week intervention period (please see Appendix). Therefore, those patients may have already suffered from pre-/cachexia and a more advanced disease stage. No statistically significant differences between the dropouts of the WB-EMS and the control group were detected. Nearly two-third of the dropped out patients of the WB-EMS group had to stop study participation because of negative effects and health deterioration as a result of their pharmacological treatment and/or disease progression. No harmful effects caused by the WB-EMS training leading to study exit were reported by the patients. This observation underlines the necessity of anti-cachexia measures in the early phase of a cancer disease and treatment to efficiently counteract muscle wasting and functional declines. A poor clinical status may hinder patients to be physically active, and disease-related metabolic changes diminish anabolic processes initiated by an adjuvant exercise and nutrition therapy (Aversa, Costelli, & Muscaritoli, 2017). Nevertheless, to reduce dropout rates especially in exercise studies with advanced-stage cancer patients, a concomitant psychological support to improve perseverance and self-motivation of the patients could be considered (Schink, Reljic, et al., 2018).

The non-randomization and the unequal group size might have led to group differences and non-blinding to bias, although we accounted for those differences in the statistical analysis by adjusting the calculated estimated effects by the relevant patient-specific baseline values. Of note, even though a higher percentage of gastrointestinal cancer patients were allocated to the control group, the backward selection process during the setting up of the linear regression model excluded cancer type from the final regression model. Thus, cancer type did not predict changes in gait velocity in response to the exercise and nutrition programme. Nonetheless, it should be taken into account that patients with gastrointestinal cancer have a greater potential to lose muscle mass due to the cancer location and the application of chemotherapy that may led to faster functional declines in the control group and thus favoured the effects of the WB-EMS intervention. In contrast to that, the WB-EMS patients showed a lower physical fitness and a poorer nutritional status at study entry compared with the controls. Future studies should therefore focus on more homogenous cancer groups. Stratifying patients after a thorough initial evaluation of their physical condition, especially regarding parameters that may influence the targeted outcome, might be considered before allocating them into the study groups to obtain results for more reliable clinical recommendations regarding a specific patient group (Shang et al., 2012).

Improving the muscular status of advanced cancer patients during oncological treatment using a combined therapy of WB-EMS and adjusted nutrition may help to stabilise and improve their physical function, particularly their gait. Larger-scaled, randomized controlled trials are needed to confirm the relevance of these findings on the quality of life and survival of cancer patients in the future. The use of sensor-based gait analysis as an objective and precise tool to monitor and assess patients' mobility may lead to a better understanding of the effects of anti-cachexia interventions and pharmacological treatments on the functional status of cancer patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX

CHARACTERISTICS OF STUDY PATIENTS WHO DROPPED OUT

Within the study period of 12 weeks, five control patients and 26 patients with WB-EMS left the study, resulting in dropout rate of 22.7% for the control and 44.8% for the WB-EMS group (p = .070). Dropout reasons were not significantly different between the groups (p = .186) and are listed in Figure 1. There were no EMS-related side effects or adverse events that forced patients to a pre-mature withdrawal from the study. Dropouts of both study groups did not differ significantly in Karnofsky Index (p = .940) or in nutrient or energy intake (mean protein p = .809, carbohydrate p = .820, fat p = .111 and caloric intake p = .504) from patients who completed the trial. However, gait velocity (1.43 ± 0.26 m/s vs. 1.55 ± 2.8 m/s; p = .056) was slower, and six-minute walking distance (498.0 ± 121.5 m vs. 540.3 ± 105.2 m; p = .103) and stride length (149.7 ± 19.7 cm vs. 157.6 ± 18.5 cm; p = .074) were shorter at baseline compared with the patients who completed the study. Further, more dropped out patients were supported by supplemental nutrition (54.8% vs. 36.7%; p = .087), whereof 2 patients received parenteral nutrition and had a significantly lower BMI than patients who completed (23.4 ± 5.7 kg/m^2 vs. 25.5 ± 3.7 kg/m^2; p = .047). Also, patients who quit the study showed a significantly higher inflammatory burden at baseline (higher CRP, 27.8 ± 38.2 mg/L vs. 14.4 ± 24.9 mg/L; p = .041 and lower albumin, 38.7 ± 5.0 g/L vs. 41.4 ± 3.3 g/L; p = .004). No significant differences were observed between the dropouts of both study groups in the parameters mentioned above.

TABLE A1 Relationship between the pre- to post-intervention changes of gait parameters and physical function tests, quality of life and inflammatory blood markers

	Correlation coefficients													
	Body composition		Objective physical function			Subjective physical function & quality of life						Inflammatory markers			
Gait parameters	SMM *n* = 40	BW *n* = 41	SMWT *n* = 41	30s STS *n* = 32	HGS *n* = 40	KI *n* = 41	PF *n* = 36	RF *n* = 35	EF *n* = 35	SF *N* = 35	CF *n* = 35	Leu *n* = 40	Hb *n* = 40	CRP *n* = 41	Alb *n* = 41
Stride time (s)	**−0.360***	**−0.416****	**−0.644****	**−0.399***	−0.218	−0.160	−0.201	0.079	0.157	−0.290	0.011	0.224	−0.309	**0.314***	−0.157
Stride time variability (%)	0.179	0.206	−0.038	−0.232	0.171	0.266	0.256	0.066	**0.343***	0.134	0.157	−0.010	−0.217	−0.044	−0.132
Swing time (%)	0.053	−0.106	0.308	**0.397***	0.031	0.184	0.244	0.038	−0.049	0.082	0.140	**0.358***	**0.328***	0.165	0.175
Swing time variability (%)	**0.313***	**0.349***	0.067	0.139	0.269	0.224	0.326	0.058	0.055	0.211	0.117	−0.299	−0.012	−0.174	−0.095
Stance time (%)	−0.073	0.102	**−0.313***	**−0.376***	−0.025	−0.183	−0.243	−0.067	0.060	−0.071	−0.139	**−0.369***	**−0.336***	−0.163	−0.172
Stance time variability (%)	0.125	0.170	−0.093	−0.305	0.146	0.271	0.129	0.094	0.268	0.127	0.119	0.076	−0.238	−0.058	−0.100
Stride length (cm)	**0.474*****	0.273	0.226	**0.473****	**0.466****	0.204	**0.341***	0.160	−0.034	0.298	−0.060	−0.095	**0.399***	**−0.314***	**0.378***
Stride length variability (%)	0.246	0.247	0.159	0.185	−0.075	0.213	**0.344***	0.103	−0.237	−0.190	−0.189	−0.091	0.001	0.052	−0.065
Heel strike angle (°)	0.085	0.220	0.070	0.160	0.014	0.156	−0.096	−0.041	−0.089	0.057	**−0.338***	−0.138	0.107	0.001	0.242
Toe-off angle (°)	**0.403****	0.176	0.263	**0.503****	−0.265	0.091	0.248	0.094	−0.014	−0.079	−0.141	−0.048	**0.398***	−0.214	0.292
Maximum toe clearance (cm)	0.201	0.186	−0.029	0.105	0.219	**0.323***	0.098	**0.401***	0.219	0.232	0.096	0.056	0.263	−0.037	0.249
Cadence (steps/min)	**0.328***	**0.371***	**0.641****	**0.382***	0.183	0.165	0.191	−0.103	−0.171	0.237	−0.032	−0.195	0.308	**−0.337***	0.162
Gait velocity (m/s)	**0.473****	**0.390***	**0.515****	**0.447****	**0.407****	0.221	0.229	0.014	−0.106	0.300	−0.053	−0.164	**0.440****	**−0.399****	0.285

Abbreviations: 30s STS, 30 second sit-to-stand test; Alb, albumin; BW, body weight; CF, cognitive functioning; CRP, C-reactive protein; EF, emotional functioning; Hb, haemoglobin; HGS, hand grip strength; KI, Karnofsky-Index; Leu, leucocyte count; PF, physical functioning; RF, role functioning; SMWT, six-minute-walk test; SMM, skeletal muscle mass; SF, social functioning.

[a]Spearman's rank correlation coefficients of pre-/post-intervention changes in gait parameters and body composition, objective physical functioning tests, patient-reported physical function, quality of life and inflammatory blood markers. Patients of both study groups with gait analysis at baseline and week 12 are included.

A statistically significant relationship is indicated by $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$ and marked in bold type.