



# Safety and feasibility of electrical muscle stimulation in patients undergoing autologous and allogeneic stem cell transplantation or intensive chemotherapy

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## Abstract

Intensive chemotherapy, with or without following autologous or allogeneic stem cell transplantation (HSCT), is often the only curative treatment option for patients with hematological malignancies and leave many survivors physically and psychologically impaired. Electrical muscle stimulation (EMS) is a proven tool to improve physical performance in seniors and patients with chronic diseases. We therefore investigated the safety and feasibility of EMS in 45 patients undergoing autologous HSCT ( $n = 13$ ), allogeneic HSCT ( $n = 11$ ) and intensive chemotherapy ( $n = 21$ ). Furthermore, physical (assessed by 6-min walking distance (6MWD) and short physical performance battery (SPPB)) and psychological performance (assessed by multidimensional fatigue inventory (MFI) and the EORTC QOL-C30 questionnaire) were measured before chemotherapy (T1) and at discharge from hospital (T2). Four patients died due to septic shock, two withdrew consent before the start of EMS training and five stopped EMS training during the study because of chemotherapy-related complications, loss of motivation or loss of ability to use EMS autonomously. Thirty-four out of 45 (76%) patients used EMS throughout the study period and participated in physical and psychological tests at time points 1 and 2. EMS-related adverse events were hematoma ( $n = 1$ ) and muscle pain ( $n = 2$ ). No bleeding events  $> 1$  according to the WHO bleeding scale occurred. Decline in 6MWD from T1 to T2 was 24 m. The SPPB score stayed the same with 11 points at T1 and T2. Most MFI subscales showed stable fatigue levels and quality of life (QoL) did not decrease significantly throughout therapy. EMS is feasible and safe in patients undergoing intensive chemotherapy. Trial registration: NCT03467087

**Keywords** Electric muscle stimulation · Supportive care · Stem cell transplantation

## Introduction

For patients with advanced hematological malignancies high-dose chemotherapy with or without subsequent stem cell transplantation is often the only curative treatment option. However, many patients in complete remission, who are

potentially cured, suffer from treatment-related side effects such as fatigue, depression, cachexia, sarcopenia, and reduced quality of life for long periods of time compromising their daily life activities [1, 2].

During therapy, a patient's condition often declines rapidly and full recovery to baseline may take much longer than the treatment itself, the reasons for this being toxic effects of chemotherapeutic agents and disease-related complications like neutropenic infections and prolonged immobilization.

Physical exercise has been proven to counteract these sequelae and is strongly recommended before, during, and after intensive treatment modalities like stem cell transplantation in order to minimize the decline in physical performance, quality of life, and fatigue [3–6]. However, many patients are not able to fully participate in physical exercises due to side effects of intensive treatments and their complications such as nausea or severe infections.

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Because of this, physical exercise programs provided by physiotherapists cannot be fully exploited and it is often impossible to stop the decline in patients' physical and psychological condition.

Electric muscle stimulation (EMS) helps to improve physical performance in patients with chronic heart failure and chronic obstructive lung disease. In patients with chronic heart failure, EMS training resulted in an improvement of several functional parameters which was comparable to physical exercise. Investigated functional parameters were 6-min walking distance, maximal workload on an ergometer and maximal oxygen uptake [7, 8]. The effect of EMS training in chronic heart failure was not only evaluated by measuring functional parameters, but was also demonstrated at the molecular level [9].

Not only in patients with chronic diseases, but also in seniors, sarcopenia and the decline of physical performance are very common and even inevitable if not counteracted by exercise training. For this population, Kern et al. showed that EMS training counteracts muscle decline as demonstrated by improvement of muscle structure and function [10].

EMS proved also to be safe, feasible, and well tolerated in patients with advanced cancers, e.g., non-small cell lung cancer (NSCLC) and can induce similar changes in muscle biochemistry as do classical forms of exercise [11, 12].

We therefore performed a prospective study to investigate the safety and feasibility of EMS in patients undergoing intensive chemotherapy regimens.

## Methods

### Design and patients

This study was a prospective, single-center safety, and feasibility trial. All patients provided written informed consent and all procedures were approved by the local ethics committee (Ärztchamber des Saarlandes). Forty-five consecutive patients with various newly diagnosed or relapsed hematological neoplasia receiving intensive chemotherapy alone or with stem cell transplantation were included. Chemotherapy was considered intensive when treatment required hospitalization.

All patients received regular physiotherapy treatment at the discretion of the physical therapist and in addition EMS training. Patients were excluded if they had ischemic heart disease, a cardiac pacemaker, or had experienced a heart attack or stroke within the last 6 months, and had metallic implants, skin lesions close to the attachment sides of the electrodes, ventricular arrhythmia, epilepsy, deep vein thrombosis within the last 6 months, or severe peripheral artery disease (> Fontaine stage 2A).

### Primary endpoints were safety and feasibility

Participants were evaluated daily for the occurrence of EMS-related adverse events and treatment- or disease-related complications. Bleeding events were defined according to the WHO Bleeding Scale [13].

In order to assess training adherence, participating patients were handed a diary and told to document date and duration of EMS training.

The secondary endpoint psychological performance was measured by the multidimensional fatigue inventory and the EORTC QOL-C30 questionnaire. The secondary outcome physical performance was measured by the 6-min walking distance and the short physical performance battery.

Study enrollment was allowed from day -3 to day +1, with the first day of chemotherapy counting as day 0. EMS training started directly after enrollment and continued until the day of discharge from the hospital. Time of hospitalization was defined as time from the day of hospital admission until the day of discharge.

### Electric muscle stimulation

EMS was conducted with a "Myopuls 2000" (Curatec Services GmbH, Moers, Germany) device using 13 cm × 5 cm electrodes. Electrodes were placed subsequently on both thighs and upper arms with instructions to stimulate each limb for at least 15 min on at least 5 days per week. Good compliance was defined as completing 66% of the intended training time. Stimulation settings were as follows: 300 μs pulse width, 60 Hz frequency, 5 s on, and 5 s off. The amplitude was initially set to elicit a visible muscle contraction and patients were encouraged to increase the amplitude as much as tolerated. After an initial training session, patients were encouraged to use the devices on their own and to document their activities in an EMS diary.

In case of severe thrombocytopenia of less than 10/nl, patients were instructed to delay EMS training until they had received platelet transfusions, which is in line with the standard procedure at our institution.

### Physical and psychological assessment

In order to assess the effectiveness of EMS training, we performed physical and psychological tests before the start of EMS training (time point 1, T1) and at the time of discharge (time point 2, T2). Physical assessment included the 6-min walking distance (6MinWD) and the short physical performance battery. Psychological effects of EMS were assessed with the multidimensional fatigue inventory and the EORTC QOL-C30 questionnaire.

## Physical assessment

### Short physical performance battery

The short physical performance battery as developed by Guralnik and colleagues [14] was used to predict possible disability in the elderly and to monitor their physical function. It ranges from 0 to 12 points with 0 points indicating the worst possible performance and 12 points as the best result. In their study, a SPPB test result of less than 9 points was associated with a significantly worse overall survival [15]. The battery consists of three tests with maximally 4 points to be reached in one test: a timed walk, repeated chair stands, and standing balance.

### 8-ft walk

Gait speed was measured over a distance of 8 ft (2.4 m) at the patients' normal pace. The use of walking aids was allowed. Scores (1–4) base on previously established quartiles of timed performance according to methods developed by Guralnik et al.

### Chair stands

Patients were asked to rise five times from a straight-backed chair with a height of 45–50 cm as fast as possible with arms folded across their chests. Scores (1–4) were based on previously established quartiles of timed performance according to methods developed by Guralnik et al.

### Balance test

This test was done in three steps with both feet side by side, in a semi-tandem fashion and in a tandem position, each for 10 s. Scores (1–4) were based on previously established quartiles of timed performance according to methods developed by Guralnik et al.

Test results of all three items were added and resulted in the final SPPB test score. Short physical performance battery summary scores were modeled as a continuous measure for all analyses [14].

### 6-min walking distance

The 6-min walking distance was conducted according to a standardized protocol as described by Butland et al. Patients were told to walk on a 40-m floor with instructions to cover as much distance as possible in 6 min. Patients were allowed to stop and rest as often as necessary. Time was stopped by a technician who was also allowed to encourage participants with standardized phrases during the walk [16].

## Psychological assessment

### EORTC QOL-C30

The EORTC QOL-C30 contains five functional scales, three symptom scales, a global health status/quality of life (QoL) scale, and six single items. Functional scales assess physical function, role function, emotional function, social function, and cognitive function. Symptom scales ask for fatigue, nausea, or pain and single items measure dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact. The global health status/QoL scale rates overall health and quality of life [17]. Original data was processed according to the EORTC scoring manual into a 0- to 100-point scale. High scores in functional scales and QoL indicate adequate function and QoL. On the other hand, patients with high scores on symptom scales and single items show more severe symptoms and impairments [18].

Therefore, in the subscales global health and functional scales, positive values in the difference between time points one and two mean a decline in global health and functioning. For symptom scales, negative values in the difference between both time points (T1–T2) mean increasing symptoms.

### MFI

The multidimensional fatigue inventory (MFI-20) consists of five subscales including general, physical, and mental fatigue, reduced motivation, and reduced activity with 20 items in total (four items per subscale). Each item is rated on a 5-point scale (1–5) and each subscale ranges from 4 to 20. The test is validated in German and has been applied in cancer patients [19–21]. Tests were done at T1 and T2. Contrary to physical assessment, high scores in the MFI subscales mean greater fatigue and therefore worse psychological functioning. A decline in psychological functioning from T1 to T2 would reflect in negative values when subtracting scores at T2 from scores at T1.

### Statistical analysis

Descriptive statistics for quantitative variables are given as median and interquartile range, for qualitative variables as absolute and relative frequencies. IBM-SPSS version 23 was used for statistical analysis. Differences between T1 and T2 are given as median of the differences of all patients.

## Results

Of 45 enrolled patients, 11 underwent allogeneic stem cell transplantation, 13 underwent autologous stem cell transplantation, and 21 received chemotherapy alone (Table 1). Most common chemotherapy regimens were CHOP or CHOEP ( $n =$

**Table 1** Baseline characteristics

Number of patients	45
Age in years	58
ECOG status	<i>N</i> (%)
ECOG 0	14 (31.1%)
ECOG 1	21 (46.7%)
ECOG 2	10 (22.2%)
Sex	<i>N</i> (%)
Female	19 (42.2%)
Male	26 (57.8%)
Treatment regimens	<i>N</i> (%)
Allogeneic SCT	11 (24.4%)
Autologous SCT	13 (28.9%)
Chemotherapy	21 (46.7%)
Chemotherapy regimens	
CHOP or CHOEP	3
Anthracycline + cytarabine (7 + 3)	8
Other	10
Conditioning regimen allogeneic SCT	
Flu/Bu/Cy	2
Flu/Bu	2
Bu/Cy	4
BEAM	1
Treo/Flu	1
TBI/Flu/Cy	1
Conditioning regimen autologous SCT	
High dose melphalan	8
BEAM	4
R-BCNU/thiotepa	1
Diagnoses	
AML	13
Aggressive lymphoma	11
Myeloma	9
Indolent lymphoma	4
MDS	5
T-PLL	2
M. Hodgkin	1

SCT, stem cell transplantation; CHOP or CHOEP, cyclophosphamide, doxorubicin, vincristine, prednisolone, (etoposide); Flu, fludarabine; Bu, busulfan; Cy, cyclophosphamide; TBI, total body irradiation; Treo, treosulfan; BEAM, carmustine, etoposide, cytarabine, melphalan; R, rituximab; BCNU, carmustine; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; PLL, prolymphocytic leukemia

3) and AML standard induction therapy with 7 days of cytarabine and 3 days of anthracyclines ( $n = 8$ ). The most common conditioning regimen for autologous SCT was high-dose melphalan and busulfan/cyclophosphamide for allogeneic SCT. Most common diagnoses causing hospitalization and initiation of treatment were AML, aggressive lymphoma, and multiple myeloma. Diagnoses, treatment regimens, ECOG status, sex, and age of all patients are shown in Table 1.

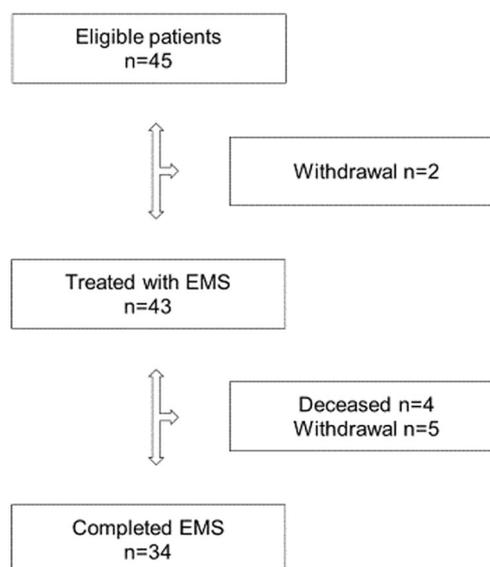
Forty-five patients received standardized physical therapy with EMS training while undergoing intensive chemotherapy regimens. Four patients died during the study. Cause of death was septic shock in all patients. The site of infection could be identified in only one patient who had pulmonary infiltrates; in the remaining three patients, a site of infection could not be identified. Seven patients withdrew consent to participate in our study. Two of them withdrew consent shortly after study enrollment and before the start of EMS training and five stopped EMS training during the study because of chemotherapy- or transplantation-related complications, loss of motivation, or loss of physical and mental ability to use EMS autonomously. Altogether, 34 patients completed the study and were evaluated at T1 and T2 (Fig. 1).

### Adverse events and complications

Two patients treated with EMS complained about muscle pain the day after start of electrostimulation, which resolved under continuous stimulation within a week.

EMS induced hematoma (size  $5 \times 2$  cm) in one patient who had a normal thrombocyte count but was treated with acetylsalicylic acid. In three patients, petechiae appeared at the sites where EMS was used. In all of them thrombocytes were less than 30/nl. No major bleeding events as defined as grade  $> 1$  according to the WHO bleeding scale occurred.

The median time of a platelet count of  $< 20$ /nl was 7 days. No cardiac arrhythmia or rhabdomyolysis occurred during EMS stimulation.



**Fig. 1** Study overview. After study, enrollment and introduction to EMS training two patients withdrew consent to participate in the study and did not start EMS training. Five patients dropped out of our study during EMS training

## Feasibility

Thirty-four out of 45 (76%) patients used EMS throughout the study period and participated in physical and psychological tests at time points 1 and 2. Sufficient EMS adherence was defined as completion of at least 66% of the intended training time of 15 min for both upper arms and thighs per day for at least 5 days a week. This was achieved by 24 of 34 (70.6%) patients with respect to thighs and 22 of 34 (64.7%) patients with respect to upper arms, indicating better training adherence for thigh stimulation than upper arm stimulation.

## Time of hospitalization

The median time of hospitalization was 30.5 days.

## Physical assessment

### 6minWD

The 6-min walking distance at the beginning of therapy was 447 m and declined to 436 m at the time of discharge. The difference between both time points was calculated and showed a median decline in the 6-min walking distance between T1 and T2 of 24 m [− 36.75; 71.25].

### SPPB

Using the short physical performance battery, we observed that patients scored 11 out of 12 points at T1 and maintained their SPPB score until T2 with a difference of 0 [− 1; 0.75] points (Table 2).

## Psychological assessment

### MFI

MFI subscales “general fatigue” and “reduced activity” showed a decline in psychological condition of our patients

**Table 2** Physical assessment

6MinWD		
T1	446.5	[399.75; 499.75]
T2	435.5	[373.5; 485.5]
Dif T1–T2	24	[− 36.75; 71.25]
SPPB		
T1	11	[9; 12]
T2	11	[9.25; 12]
Dif T1–T2	0	[− 1; 0.75]

The 6MinWD and SPPB test results for both time points T1 and T2. All values are given as median (interquartile range in brackets) in meters for the 6MinWD and in points for the SPPB

from T1 to T2. Scores of the subscales “physical fatigue,” “mental fatigue,” and “reduced motivation” were almost the same at the end of chemotherapy as they were at the beginning (Table 3).

## EORTC QOL-C30

### Global health status/QoL

Study patients experienced a decline in self-reported global health and quality of life. Global health status decreased by 4.2 points [− 16.7; 16.7] in patients receiving chemotherapy while undergoing EMS stimulation (Table 4).

### Functional scales

“Physical functioning” and “role functioning” worsened from T1 to T2 by 6.7 and 8.3 points, respectively. Scoring in “cognitive functioning” and “social functioning” did not change during the same time period and “emotional functioning” improved by 8.3 points after chemotherapy treatment was completed (Table 4).

### Symptom scales/single items

The symptom scales “fatigue” and “pain” did not change between the two time points. The remaining symptom scale

**Table 3** Multidimensional fatigue inventory

MFI—general fatigue		
T1	13	[8; 14.5]
T2	12	[10; 13.25]
Dif T1–T2	− 1	[− 3; 2.5]
MFI—physical fatigue		
T1	12	[8.25; 15.5]
T2	11.5	[8; 14.25]
Dif T1–T2	0.25	[− 2.75; 3]
MFI—reduced activity		
T1	11	[8; 14]
T2	12	[10; 14.5]
Dif T1–T2	− 1.5	[− 3; 2]
MFI—reduced motivation		
T1	8	[5; 9.25]
T2	8.5	[5; 9]
Dif T1–T2	0	[− 2; 3]
MFI—mental fatigue		
T1	9	[5; 12.125]
T2	7.5	[5; 12]
Dif T1–T2	0.25	[− 1.25; 3.25]

Test results from MFI subscales at T1 and T2 are given as median (interquartile range in brackets)

**Table 4** EORTC—global health status/QoL and functional scales

EORTC—global health status/QoL		
T1	50	[33.33; 77.08]
T2	50	[33.33; 66.67]
Dif T1–T2	4.17	[– 16.67; 16.67]
EORTC—Physical Functioning		
T1	70	[53.33; 93.33]
T2	70	[60; 84.17]
Dif T1–T2	6.67	[– 8.33; 17.5]
EORTC—role functioning		
T1	66.67	[33.33; 83.33]
T2	33.33	[16.67; 66.67]
Dif T1–T2	8.33	[0; 33.33]
EORTC—emotional functioning		
T1	62.5	[39.58; 83.33]
T2	75	[56.25; 83.33]
Dif T1–T2	– 8.33	[– 21.88; 0]
EORTC—cognitive functioning		
T1	91.67	[45.83; 100]
T2	83.33	[50; 100]
Dif T1–T2	0	[– 16.67; 0]
EORTC—social functioning		
T1	50	[20.83; 66.67]
T2	50	[0; 100]
Dif T1–T2	0	[– 33.33; 33.33]

Global health status/QoL and Functional scales were assessed at T1 and T2. The difference between T1 and T2 was calculated for all participants individually and the results are given as median (Dif T1–T2)

“nausea and vomiting” worsened by 8.3 points from T1 to T2. Out of six single items only the reported item “dyspnea” changed during the course of treatment. “Dyspnea” was not as severe at the time of discharge with a score of 33.3 points less than at T1. All other single items were reported to have stayed the same at T2 as they were at T1 (Table 5).

## Discussion

To our knowledge, this is the first study investigating the use of EMS in patients with hemato-oncological malignancies. More than 50% of our patients received stem cell transplantation and 69% of study participants had an ECOG performance status of 1 or 2. With a study population of impaired performance status undergoing intensive chemotherapy regimens, safety, and feasibility of EMS treatment have to be addressed first.

EMS proved to be safe and was performed without any serious adverse events. This first study of EMS in patients with hematological malignancies triggered

**Table 5** EORTC—symptom scales and single items

EORTC—fatigue		
T1	55.33	[22; 69.42]
T2	44.33	[33; 66.67]
Dif T1–T2	0	[– 22.33; 14]
EORTC—nausea and vomiting		
T1	0	[0; 0]
T2	16.67	[0; 37.5]
Dif T1–T2	– 8.33	[– 33.33; 0]
EORTC—pain		
T1	33.33	[0; 54.17]
T2	33.33	[0; 58.33]
Dif T1–T2	0	[– 16.67; 16.67]
EORTC—dyspnea		
T1	33.33	[0; 66.67]
T2	33.33	[0; 66.67]
Dif T1–T2	33.33	[0; 33.33]
EORTC—insomnia		
T1	33.33	[0; 66.67]
T2	33.33	[0; 66.67]
Dif T1–T2	0	[– 33.33; 8.33]
EORTC—appetite loss		
T1	0	[0; 41.667]
T2	33.33	[0; 100]
Dif T1–T2	0	[– 66.67; 0]
EORTC—constipation		
T1	0	[0; 8.33]
T2	0	[0; 16.67]
Dif T1–T2	0	[0; 0]
EORTC—diarrhea		
T1	0	[0; 0]
T2	0	[0; 33.33]
Dif T1–T2	0	[– 33.33; 0]
EORTC—Financial difficulties		
T1	0	[0; 66.67]
T2	16.67	[0; 66.67]
Dif T1–T2	0	[0; 0]

Results of symptom scales and single items of the EORTC QoL 30 questionnaire as reported by study participants at T1 and T2. The difference between T1 and T2 was calculated for all participants individually and the results are given as median (Dif T1–T2)

several main concerns: muscle hemorrhage in patients with low platelets, cardiac arrhythmias in vulnerable patients, e.g., with electrolyte disturbance and rhabdomyolysis under electrical muscle stimulation.

The median time patients had a platelet count of < 20/nl was 7 days. Patients who had a platelet count of less than 10/nl received platelet transfusions and were encouraged to continue with EMS after substitution. Applying this institutional standard

for patients with low platelets, we did not observe any bleeding events exceeding WHO grade 1 in patients using EMS.

Furthermore, no cardiac arrhythmias occurred, demonstrating that EMS can be safely performed in patients with low platelet counts, impaired performance status and under intensive chemotherapy. Though only described in case reports and not observed in other EMS studies, rhabdomyolysis remained a possible side effect of electrical muscle stimulation [22]. Nevertheless, we did not observe any EMS-related elevation of creatinine kinase.

Adherence to the EMS protocol is also of particular interest in our patient cohort because disease- and treatment-related inability to exercise and participate in physical therapy contributes to the decline in physical and mental functioning in patients undergoing stem cell transplantation or intensive chemotherapy regimens [4–6]. Only 7 of 45 (15.6%) patients stopped EMS training and most of the study participants continued EMS training throughout therapy ( $n = 34$ ). Out of these 34 patients, 24 (70.6%) were able to use it with relevant intensity of at least 2/3 of the pre-set training time. Interestingly, adherence to thigh muscle stimulation was greater than to stimulation of upper arms with only 22 of 34 patients completing at least 2/3 of the targeted training time. In summary, despite the morbidity of the cohort, strong adherence to EMS training was observed, making it a feasible tool in the prophylaxis of physical and mental deterioration after intensive chemotherapy.

It is well known that muscle mass and physical functioning decline considerably after chemotherapy regimens. In this study, physical functioning before and after treatment was assessed using the 6-min walking distance and the short physical performance battery.

Applicability and value of the SPPB in hospitalized elders was shown by Steve Fisher et al [23]. On the 12-point SPPB scale, our patients scored 11 points before and after treatment. Compared to another study, where SPPB scores declined from 7.5 to 5.9 points in patients using EMS while undergoing intensive chemotherapy, they did not decline in this study [24].

The measurement of the distance walked in 6 min (6MinWD) has been one of the most important tools for objective evaluation of functional exercise capacity for decades [25, 26].

After therapy (T2), patients walked 24 m (median) less during the 6-min WD test than before chemotherapy (T1). This observation is consistent with the results of other studies including patients with similar treatment regimens [6, 27].

Furthermore, the psychological condition of patients undergoing intensive chemotherapy regimens and stem cell transplantation procedures declines significantly during therapy [28, 29]. In this study, we used the MFI and the EORTC QoL-C30 questionnaire to measure and report psychological functioning before and after intensive chemotherapy with concurrent EMS training [17, 30].

As compared to a study which included only patients undergoing allogeneic stem cell transplantation, we observed a decline in the subscales “general fatigue” and “reduced activity,” whereas the remaining subscales did not change [28]. Since all patients in the study of Esser et al. received an allogeneic SCT, the differences in psychological functioning to our results are most likely due to the more intense treatment regimens.

The EORTC (European Organisation for Research and Treatment of Cancer) QOL-C30 questionnaire was used to assess quality of life [17]. In a Swedish study, evaluating the effects of intensive chemotherapy and allogeneic stem cell transplantation on psychological functioning using the EORTC QOL-C30 questionnaire baseline measurements of all EORTC QOL-C30 categories is comparable to our results [29]. In contrast to their results, most of the EORTC QOL-C30 subcategories did not change in our patients when comparing pre- to post-therapeutic scores.

Due to the heterogeneity and small number of our patient cohort, any further conclusions regarding the effects of EMS training on physical and psychological performance cannot be drawn.

To summarize, our results suggest that EMS can be applied safely and is feasible in patients undergoing intensive chemotherapy regimens. Future studies can now focus on investigating the effects of EMS training on physical and psychological functioning of patients undergoing intensive chemotherapy. In order to produce reliable results, these studies should include a much larger patient cohort with a control group receiving sham stimulation and blinded testing of physical and psychological performance.

Such studies should pave the way to make EMS a trusted and widely used tool in the supportive care of hospitalized patients undergoing intensive chemotherapy.

## Compliance with ethical standards

All patients provided written informed consent and all procedures were approved by the local ethics committee (Ärztchamber des Saarlandes).

**Conflict of interest** The authors declare that there are no conflicts of interest.

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