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ORIGINAL ARTICLE

Physical activity, quality of life, and the interest in physical exercise programs in patients undergoing palliative chemotherapy

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Abstract
Purpose Quality of life is of major importance in patients with advanced cancers undergoing palliative chemotherapy. In contrast to the number of studies on physical activity in patients with curable malignancies, data on patients undergoing palliative chemotherapy are scarce.
Methods A total of 53 patients receiving palliative chemotherapy on an outpatient basis were interviewed using three standardized questionnaires within a time period of 4 weeks (Questionnaire for Measurement of Habitual Physical Activity, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C13 questionnaire, International Physical Activity questionnaire), and a questionnaire regarding patients' acceptance of a potential physical training program.
Results Thirty-six percent of the patients still performed self-instructed physical activities during palliative chemotherapy. Patients showed significantly higher values in the "leisure time index" during their malignancy than before ($p<0.01$). Significantly positive correlations were found between "work index" and quality of life ($p=0.004$), "work index" and physical function ($p=0.02$), and "hours of physical activity per week" and quality of life ($p<0.05$). A negative correlation was found between "work index" and fatigue ($p<0.05$). Quality of life scores were significantly higher in patients with sportive activities ≥9 metabolic equivalent (MET) h/week than in patients with <9 MET h/weeks ($p<0.01$). Sixty percent of patients indicated that they would be willing to participate in an individually adapted activity training program.
Conclusions In patients undergoing palliative chemotherapy, a statistically significant positive correlation between physical activity and quality of life could be demonstrated. About two thirds of critically ill patients are interested in participating in training programs.

Keywords Physical activity · Exercise program · Physical training · Quality of life · Palliative chemotherapy

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Introduction

Physical activity and systematic training programs are widely accepted components of rehabilitation after curative treatment of hematologic malignancies or solid tumors. A number of clinical trials have shown efficacy of physical activity on physical fitness, rehabilitation for daily practice, quality of life, and reduction of late toxicities [1–6]. In contrast, in patients undergoing antitumor treatment and in patients with incurable malignancies, relaxation by physical inactivity was considered beneficial, and patients were kept from physical training programs to protect their physical

power until recently. However, several analyses and clinical trials have investigated the impact of physical activity in patients during curatively intended chemotherapy in the last years. These studies were able to demonstrate that physical training programs are also feasible in patients while undergoing systemic chemotherapy [7–11]. In addition, these studies showed that individually adapted physical training programs not only increased the patients' quality of life and reduced their tumor-related symptoms, e.g., fatigue or pain, but were also helpful in reducing the subjective impact of treatment-related toxicities, e.g., nausea and emesis [12–17].

Due to improvements in palliative chemotherapy including modern cytotoxic drugs and targeted therapies, median survival times in patients with incurable hematologic malignancies or solid tumors are permanently increasing. Therefore, improvement of the quality of life is of primary importance. This raises the question whether physical activity and specialized training programs are able to improve the quality of life in these critically ill patients. In contrast to the large number of studies on physical activity and training programs in patients with curable malignancies, data on their impact in patients with incurable malignancies undergoing palliative chemotherapy are limited. Some preliminary analyses and pilot clinical studies have demonstrated efficacy of specialized physical training programs on subjective behavior and physical efficiency [18–23]. Until today, however, larger systematic or randomized studies on the impact of physical training in patients with incurable malignancies undergoing palliative chemotherapy are lacking. It is a widely held belief that physical relaxation should be advocated for patients with incurable malignancies in order to preserve physical power for coping with tumor- and treatment-related burden. However, little is known about the patients view on their physical power and their self-instructed physical activities during palliative chemotherapy, and data on interest in and acceptance of individualized physical training programs and their subjective ability to perform sportive activities are rare [24, 25].

The aim of this study was to analyze the impact of physical activity and self-instructed training in patients with incurable malignancies undergoing palliative chemotherapy on an outpatient basis on the quality of life and subjective physical well-being. In addition, the interest of these patients in participating in special physical training programs and their favored sportive activities were evaluated.

Materials and methods

Patients eligible to participate in this study had to be older than 18 years of age and had to suffer from advanced incurable hematologic malignancy or metastatic solid tumor. All participants were undergoing palliative chemotherapy on an outpatient basis during a time period of 4 weeks in June 2008 at the outpatients' clinic of the Oncology Center of the University Hospital Hamburg-Eppendorf and were asked to fill out a total of four questionnaires on physical activity and quality of life. Three questionnaires were international standardized questionnaires: Questionnaire for Measurement of Habitual Physical Activity [26, 27], Quality of life questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C13) [28], and the International Physical Activity questionnaire [29].

The Questionnaire for Measurement of Habitual Physical Activity [27] records and quantifies physical activity during professional work, sportive activity, and during leisure time. Physical activities in all three items were correlated with age- and gender-adjusted "total physical activity" to reveal activity indices for all three dimensions: work, sports, and leisure time. This questionnaire has been evaluated in adults in a large trial and has demonstrated high internal consistence and retest reliability [27]. The questions focus on different aspects of activity at work (seven questions, e.g., sitting, standing, or walking while working), sports (four questions), or leisure time (three questions), and answers are graded from 1 = never to 5 = always. Patients were asked to state their actual activities during palliative chemotherapy. In addition, patient's habits prior to tumor diagnosis were assessed retrospectively.

The International Physical Activity questionnaire [29] records the intensity and time of physical activity. Patients were asked to record their physical habits within the last 7 days prior to study evaluation while undergoing palliative chemotherapy. For standardized evaluation of physical activity, the metabolic equivalent (MET) time was estimated. One metabolic equivalent was defined by Ainsworth et al. as the metabolic turnover of 3.5 ml oxygen per kilogram body weight per minute in males and 3.15 ml/kg/min in females [30]. The weighted MET minutes per week were calculated as duration × frequency per week × MET intensity, which were summed across activity domains to produce a weighted estimate of total physical activity from all reported activities per week (MET minutes per week) [29].

In addition, a special questionnaire focusing on patients' demographic data, their physical habits, and their acceptance of a potential training program was developed. The evaluation included gender, age, and profession. Patients were asked to quantify their physical activity both prior to cancer diagnosis retrospectively and actually during the previous 7 days while undergoing palliative chemotherapy. In addition, patients were asked whether they would be interested in participating in a potential training physical program. Furthermore, they were asked which kind of sportive activities they would prefer, and their self-rated ability to perform sportive activities was recorded.

For statistical evaluation, a descriptive analysis was performed and questionnaire results were correlated with personal or clinical characteristics, including Karnofsky performance status [31] classified by the treating physician, and details of previous medical history, e.g., histology of primary malignant disease, tumor status, line of chemotherapy, chemotherapy regimen. In univariate analysis, gender and physical activity with <9 vs. ≥9 MET h/week [32] were included as independent factors, while clinical characteristics and parameters from the EORCT-QLQ entered univariate analysis as dependent factors. Statistic analyses were performed using SPSS for windows version 15.00.

Results

During the time period of 4 weeks, all 76 consecutive patients undergoing ambulatory palliative chemotherapy for incurable malignancies in the oncological outpatients' clinic of University Hospital Hamburg-Eppendorf were asked to participate in this study. A total of 53 patients (70%), 29 female and 24 male, median age 58 years (range, 29–76 years), gave written informed consent to participate in this study and filled out all four questionnaires completely. Patients not willing to participate were not asked for their reasons respecting their privacy.

The underlying malignancies at the time of the questionnaire analysis were as follows: hematologic malignancy 21%, breast cancer 11%, lung cancer 17%, gastrointestinal cancer 21%, pancreatic, hepatocellular or cholangiocarcinoma 17%, and other 13%. Median time from primary diagnosis was 30 months (range, 1–167 months). At the time of study evaluation, 39% of patients received first-line therapy, and 30% of patients received second- or further-line therapy after tumor progression after primary diagnosis. Another 31% of patients were treated with palliative chemotherapy for relapsed disease after a previous treatment-free period. Median performance status (Karnofsky index) was 80% (range, 70–100%). Further details on patients' characteristics and treatment are presented in Table 1.

Thirty-eight of 53 patients (72%) declared that they had been performing physical activities regularly prior to diagnosis of their malignancy. At the time point of the interview, 19 patients (36%) still performed sportive activities regularly, while another 19 patients had stopped physical activity due to their malignant disease and chemotherapy. The median time of sportive activities per week had decreased significantly from 1.6 h prior to tumor diagnosis to 0.8 h ($p<0.01$). While the median time of

Table 1 Patients' characteristics and treatment ($N=53$ patients)

		Number of patients	Percent
Type of malignant disease	Gastrointestinal carcinoma	11	21
	Hematologic malignancy	11	21
	Pancreas, liver, gall bladder cancer	9	17
	Lung cancer	9	17
	Breast cancer	6	11
	Other solid tumors	7	13
Location of metastases of solid tumors ($N=42$)	Liver	13	31
	Retroperitoneum	14	33
	Lungs	15	36
	Bones	8	19
	Cerebrum	5	12
	Mediastinum	9	21
	Other	4	10
Line of chemotherapy	First line	21	39
	Second line	10	19
	Third line	9	17
	> Third line	7	13
	Not evaluable	6	11
Type of chemotherapy regimen	Gemcitabine	5	9
	Oxaliplatin	3	6
	Other single drug	8	15
	5-FU-based combinations	7	13
	Cisplatin-based combinations	8	15
	Other combinations	8	15

physical activity was lower in women than in men prior to chemotherapy (1.3 vs. 2.9 h), there was no difference between female and male patients during chemotherapy (0.8 vs. 0.7 h). Physical activity was not significantly different in patients undergoing first- or further-line chemotherapy.

The analysis of the Questionnaire for Measurement of Habitual Physical Activity [27] revealed significant decreases in two components of habitual physical activity in patients undergoing palliative chemotherapy compared to the time prior to tumor diagnosis: The median "work index" decreased from 2.25 to 0.56 ($p<0.001$) and the "sports index" decreased from 2.91 to 2.47 ($p<0.001$). On the contrary, the "leisure time index" increased significantly from 2.81 prior to tumor diagnosis up to 3.01 during palliative chemotherapy ($p<0.01$). Prior to tumor diagnosis, no significant difference between female and male patients were detected in "work index" (2.1 vs. 2.4) and "leisure time index" (2.8 vs. 2.8), but the "sports index" was higher in male patients prior to tumor diagnosis ($p<0.05$). During palliative chemotherapy, this gender-specific difference disappeared, and no difference between female and male patients was found in any of the indices.

The International Physical Activity questionnaire [29] evaluated the intensity and quantity of physical activity within the last 7 days prior to study evaluation. Patients reported a median time of intensive physical activity, e.g., fast cycling, carrying heavy weights, or garden working, of 0.7 h/day and a median time of moderate physical activity of 1.0 h/day. Median time with low physical activity, e.g., walking, was quantified with 1.0 h/day on 4.6 days/weeks. Patients declared that they spend most of their time being seated at home with a median time of 5.2 h (range, 2.0–8.4 h)/day. The metabolic equivalent (MET minutes per week) of intensive physical activity was 235 MET min $week^{-1}$, 480 MET min $week^{-1}$ for moderate physical activity, and 910 MET min $week^{-1}$ for low physical activity. Combining all grades of physical activity, the MET minutes per week was 1,625 in these patients.

Habitual physical activity (Questionnaire for Measurement of Habitual Physical Activity [27]) during palliative chemotherapy was correlated with different aspects of quality of life according to the EORTC QLQ-C13 questionnaire (global health status, physical functioning, cognitive functioning, role functioning, emotional functioning, social functioning, fatigue, nausea, pain) [28]. Significant positive correlations were found between "work index" and quality of life ($p=0.004$), "work index" and physical function ($p=0.021$), and "hours of physical activity per week" and quality of life ($p=0.019$). Significant negative correlations were found between "work index" and fatigue ($p=0.012$) and "leisure time index" and social function ($p=0.012$). No significant correlation existed between "sports index" and quality of life or physical function and fatigue, respectively. Details are presented in Table 2.

The correlation of physical activity during palliative chemotherapy (classification according to Ainsworth et al. [30]) with quality of life (EORTC QLQ-C13 [28]) revealed significantly higher quality of life ($p=0.005$) and physical function ($p=0.048$) in patients with nine or more MET hours per week of physical activity than patients with less

Table 2 Correlation of habitual physical activity and quality of life (EORTC-QLQ-C13)

		Work index	Sports index	Leisure time index
Global health status	Correlation (Pearson)	0.387	0.095	0.028
	p value	0.004	0.497	0.842
Physical functioning	correlation (Pearson)	0.316	0.269	−0.236
	p value	0.021	0.051	0.089
Role functioning	correlation (Pearson)	−0.232	−0.058	0.043
	p value	0.094	0.682	0.757
Emotional functioning	correlation (Pearson)	−0.161	0.099	−0.050
	p value	0.248	0.481	0.724
Cognitive functioning	correlation (Pearson)	−0.163	−0.023	−0.106
	p value	0.244	0.869	0.452
Social functioning	correlation (Pearson)	−0.012	0.005	−0.343
	p value	0.932	0.973	0.012
Fatigue	correlation (Pearson)	−0.321	−0.136	0.018
	p value	0.019	0.331	0.898
Nausea	correlation (Pearson)	−0.260	−0.129	0.024
	p value	0.060	0.358	0.863
Pain	correlation (Pearson)	−0.155	−0.035	−0.039
	p value	0.267	0.806	0.784

than 9 MET h/week. Fatigue was less severe in patients with nine or more MET hours per week (p=0.25). Clinical performance status (Karnofsky index) was not different between these two subgroups. For further details, see Table 3.

Comparing quality of life (EORTC QLQ-C13) in men and women, reduction of emotional functioning (p=0.32) and fatigue (p=0.37) were more severe in men. However, no gender-specific differences were found in global health status, physical functioning, cognitive functioning, role functioning, social functioning, nausea, or pain.

Concerning the interest in a potential individually adapted physical training program, 32 of 53 patients (60%) stated that they would participate in physical training programs. Patients without any interest in participating in training programs gave the following reasons: "feeling too sick" five patients (22%), "distance to far from home" eight patients (36%), "too time consuming" two patients (11%), "never been interested in sports" one patient (5%), and "other reasons" five patients (22%).

Patients, who were interested in participating in an individualized physical training program, would like to take part in physical training programs once a week in 39%, twice weekly in 30%, more than twice weekly in 13%, and daily in 18%. Concerning the different possibilities in training concepts, patients preferred cycling in 20% and swimming or relaxing techniques in 16% each. Further favorite sportive activities were walking in 13%, power training in 10%, gymnastics in 10%, jogging in 8%, ball games in 5%, and others in 2% of the patients.

Discussion

In recent years, several studies have demonstrated that physical training programs in patients undergoing systemic chemotherapy were able to increase quality of life and to reduce both tumor-related symptoms and the impact of treatment-related toxicities [12–17]. This effect has been demonstrated within different settings, e.g., during adjuvant chemotherapy [33], high-dose chemotherapy with autologous stem cell reinfusion [34], or allogeneic bone marrow transplantation [35, 36]. Furthermore, studies have been performed during other treatment modalities as surgery [37], radiotherapy [38], or antihormonal therapy [39].

So far, only preliminary analyses and pilot studies have investigated the impact of physical training in patients with incurable malignancies undergoing palliative chemotherapy [18–23]. Therefore, little is known about patients' self-instructed physical activities during palliative chemotherapy and their interest in physical training programs in general.

In our analysis, we were able to demonstrate that about one third of patients undergoing palliative chemotherapy still perform self-instructed physical training regularly, which is about half the incidence as compared to prior to the tumor diagnosis. The median time of sportive activities decreased significantly due to disease- and treatment-related burden. On the other hand, leisure-time activity had significantly increased compared to the time prior to tumor diagnosis. It is not surprising that leisure time is increasing in patients stopping professional work due to cancer diagnosis. Interesting is the fact that patients seem to be able to enjoy this leisure time being physically active despite of their disease and chemotherapy treatment. However, the decrease in the incidence of self-instructed sportive activities could be attributable to the lack of knowledge about the positive effects of sportive activities for palliatively treated patients.

The correlation of habitual physical activity during palliative chemotherapy with quality of life revealed that patients who were still actively taking part in professional life despite of their illness showed higher general quality of life, physical function, and lower fatigue symptoms. However, causality of this phenomenon remains to be elucidated, as it remains unclear whether patients with better subjective well-being and physical function are able to continue their professional work for a longer time or if continuing professional work supports subjective behavior and quality of life even during palliative chemotherapy.

Table 3 Correlation of quality of life (EORTC-QLQ-C13) and physical activity

Parameter	Number	Physical activity		p value
		<9 MET h/week	≥9 MET h/week	
Quality of life	53	7.5±2.8	10.4±2.5	0.005[a]
Physical function	53	8.0±1.3	9.0±1.2	0.048[a]
Emotional functions	53	9.2±3.3	7.4±2.6	0.137
Cognitive functions	53	3.6±1.7	2.9±1.1	0.205
Social function	53	5.2±1.9	4.9±1.9	0.681
Fatigue	53	8.7±2.6	6.6±2.6	0.025[a]
Nausea/emesis	53	3.1±1.6	2.1±0.3	0.058
Pain	53	4.3±2.2	2.9±1.7	0.069

[a] Statistically significant

MET metabolic equivalent

Quality of life in the total cohort of patients correlated significantly with the number of hours of physical activity, but no correlation between "sports index" and quality of life, physical function, or fatigue could be demonstrated. This lack in correlation could be explained by the high-performance demand in sportive activity for the "sports index" in the Habitual Physical Activity Questionnaire, which was not developed for ill patients.

Defining higher physical activity as nine or more metabolic equivalent hours of physical activity per week, a significantly higher general quality of life, physical function, and less severe fatigue symptoms could be demonstrated in patients with high physical activity. In our view, this demonstrates that physical activity improves the quality of life even in patients undergoing palliative chemotherapy. In contrast, emotional, cognitive, and social function tended to be higher and pain as well as nausea tended to be lower in patients showing less activity. These differences did not reach statistical significance. In or view, this shows that although higher physical activity seems to be associated with better quality of life in general, there seems to be a great interpersonal variability in specific items of quality of life assessment, most likely due to specific differences in personality and/or coping strategies. This individual profile should therefore be kept in mind when physical training programs are developed for cancer patients in a palliative setting.

A weakness of our study is the heterogeneous of the time points of study enrollment: Patients were able to participate in the study at any time during palliative chemotherapy, irrespective of previous therapy. However, a subgroup analysis revealed no differences in patients with different lines of chemotherapy indicating that the time point of study participation might be of minor relevance.

In the underlying, analysis 60% of patients stated interest in participating in individually adapted physical training programs. Most of them preferred training programs once or twice weekly. In a similar analysis presented by Oldervoll et al., 101 patients with incurable malignancies and a life expectancy of less than 1 year were asked to participate in a physical training program twice weekly for 6 weeks and 63 patients (62%) agreed to participate [24]. Sixteen patients in this study dropped out due to medical or social reasons prior to the beginning of the program, and 13 patients dropped out during the physical training. Therefore, 34 of 63 patients (54%) completed the exercise program.

In a second, recently published study by Lowe et al., 78% of 50 cancer patients in a palliative setting stated interest in a physical activity program, and 58% felt to be able to participate in a physical activity program [25]. While in our analysis the majority of about 40% of patients would prefer to perform physical training only once weekly, in the analysis of Lowe et al., 52% of patients were interested in physical training two or three times a week. Favorite sportive activities were walking (64%) in the analysis of Lowe et al. and cycling (20%) in our study. Therefore, endurance training activities with low intensity which can be performed outdoor and self-instructed seem to be the most favored.

In conclusion, about one third of patients with incurable malignancies undergoing palliative chemotherapy are still performing self-instructed physical training. Two thirds of these patients indicate interest in participating in individualized training programs. These results should encourage the design of physical training programs not only for cancer patients with curative treatment but also for patients undergoing palliative treatment. Higher physical activity in patients undergoing palliative chemotherapy is correlated with improved quality of life and physical function, as well as reduced fatigue symptoms.

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