Relationship between Physical Activity and Health-related Quality of Life in Hospitalized and Terminally Ill Cancer Patients

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Background : The relationship of physical activity (PA) and health-related quality of life (HRQoL) in hospitalized and terminally ill cancer patients has yet to be determined. The present study was performed to evaluate PA status and the relationships between PA and HRQoL outcomes in advanced and hospitalized terminally ill cancer patients.

Materials and Methods : Patients with advanced, and/or metastatic malignancies were eligible. PA had been measured for 1 week using a uniaxial accelerometer and divided into "light" activity level on the best PA over the past week (PA ＜150 minutes) or "high" activity on the best PA over the past week (PA ≥150 minutes). HRQoL was measured by the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30). In addition, cancer-related symptoms and the ability to perform basic movements and activities of daily living (ADL) were also measured. We examined differences in PA level by binomial logistic and multiple linear regression analyses.

Results : Ninety-seven subjects were enrolled in the study. The high PA group (PA ≥150) had significantly higher HRQoL and increased ability to perform basic movements and ADL. The most important factor associated with engagement in PA was the ability to perform basic movements.

Conclusion : This study showed that hospitalized and terminally ill cancer patients with PA ≥150 minutes per week had higher HRQoL. Advanced patients in hospitalization presenting with PA ≥150 have the potential for improved HRQoL by palliative rehabilitation. *Shinshu Med J 68 : 149—157, 2020*

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Key words : physical activity, palliative care, rehabilitation, QoL, medical service

Abbreviations : PA, Physical Activity ; HRQoL, Health-Related Quality of Life ; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QLQ-C30 ; PPS, Palliative Performance Status Scale ; BMI, Body Mass Index ; ESAS, Edmonton Symptom Assessment System-Revised ; ABMS II, Revised Version of the Ability for Basic Movement Scale

I Background

Survival in patients with advanced cancer can be prolonged with improvement of cancer treatment[1)]. However, maintenance of quality of life (QoL) and physical performance are important issues even in patients with advanced cancer, especially in cases with incurable disease and late in the clinical course and/or receiving end of life care. Health-related quality of life (HRQoL) has been used to evaluate physical and/or psychosocial adverse outcomes and symptoms. Indeed, HRQoL assessment has become a paradigm for patient-centered outcome measures

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under clinical conditions. A diverse range of symptoms are associated with declining HRQoL, including cancer-related fatigue, reduced appetite, nausea and vomiting, dyspnea, depression, and physical impairments[2)3)]. Factors that reduce HRQoL can potentially be modified, and intervention strategies to improve or prevent HRQoL are a major concern in patients with advanced cancer.

On the other hand, physical activity (PA) defined as any bodily movement produced by skeletal muscles that results in energy expenditure[4)] can improve HRQoL in patients with cancer or in cancer survivors[5)]. Several clinical trials have revealed that rehabilitation treatment may be useful in cancer patients[5)]. However, the optimal model remains to be elucidated for patients with incurable advanced cancer. Some previous studies were conducted in newly diagnosed patients with advanced incurable cancer and in outpatient settings[6)]. As disease progression is associated with deterioration of symptoms and decline of physical function[7)], the PA status and HRQoL in advanced cancer patients, particularly terminally ill cancer patients, are unknown. In Japan, patients with deterioration of cancer-related symptoms and declining physical function are commonly treated in hospital, and almost 80 % of cancer patients die in hospital[8)].

This study was performed to evaluate PA status and the relationship between PA and HRQoL outcomes in advanced and hospitalized cancer patients, i.e., terminally ill cancer patients.

Ⅱ Materials and Methods

A Study population

This study was approved by the institutional review board of Shinshu University School of Medicine (document number : #2242) and was conducted in accordance with the principles of the Declaration of Helsinki. Patients hospitalized at Shinshu University Hospital were eligible for inclusion in the present study, and enrollment and registration were performed prospectively. Patients were eligible if they had histologically or cytologically proven unresectable, locally advanced, and locally recurrent or metastatic malignancies. Other eligibility criteria included the following : 1) age ＞20 and ＜75 years ; 2) estimated life expectancy ＞3 months ; 3) Eastern Cooperative Oncology Group performance status 0-3 ; 4) able to wear the activity meter ; and 5) able to provide informed consent and comply with study requirements. Patients were excluded from the trial for any of the following reasons : 1) active infection ; 2) clinically significant cardiovascular and/or respiratory disease, including ischemic heart disease and presenting respiratory failure ; 3) pleural or pericardial effusion requiring drainage ; 4) active brain metastasis ; 5) uncontrollable diabetes mellitus or hypertension (blood pressure ≥150/100 mmHg) ; 6) Palliative Performance Status Scale (PPS) score ≤30 % , and severe medical comorbidities that grossly impaired mobility ; 7) hemoglobin ＜9 g/dL, platelet count ＜ 70000/μL ; 8) history of thrombotic or hemorrhagic disorders ; or 9) otherwise defined as ineligible by a physician. Concomitant active malignancy, dementia, and other conditions causing confusion were considered as contraindications for PA. Eligible participants were required to read about the right to withdraw, confidentiality, and the risks and benefits of participation in the study, and each patient provided written informed consent.

B Study design

The primary objective of the study was to assess the association between PA and global health status as measured by the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30)[9)]. The EORTC QLQ-C30 incorporates nine multi-item scales : five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale. Secondary objectives were evaluation of factors that could affect PA in hospitalized patients with advanced malignancies.

This was a cross-sectional study. On the first day of the study, initial assessment, including demographic variables, such as age, sex, height, weight, and medical variables, such as current medications, laboratory data, PPS, symptoms, HRQoL and physical performance, was performed. Body mass index (BMI)

was calculated from measured height and weight [weight (kg)/height (m^2)]. Physical performance was assessed by rehabilitation staff observing the participant's performance. It was assessed by the Revised Version of the Ability for Basic Movement Scale (ABMS II) which examines the limitation of performing basic movement[10], and the Functional Independence Measure score based on how much assistance was required for the individual to carry out ADL[11]. ABMS II consisted of six grades (6 = complete independence, 3 = partially dependent, 1 = total assistance) for evaluating the ability to perform the five basic movements : "turn over from the supine position," "sit up," "remain sitting," "stand up," and "remain standing." The Functional Independence Measure consisted of seven grades (7 = complete independence, 3 = moderate assistance, 1 = total assistance) for evaluating the ability to perform activities of daily living (ADL). In this study, the motor subscale (m-FIM) was ; eating, grooming, bathing, dressing (upper and lower body), toileting, bladder and bowel management, transfers, walking/wheelchair, stairs.

The patient group also completed the Japanese version of the Edmonton Symptom Assessment System-Revised (ESAS)[12], which covers nine items, including physical, psychological, and wellbeing subscales, and has also been widely tested and validated in palliative care populations. Self-efficacy was assessed by the General Self-Efficacy Scale (GSE)[13][14]. The General Self-Efficacy Scale is a 10-item psychometric scale that is designed to assess optimistic self-beliefs to cope with a variety of difficult demands in life. Physical activity (PA) was measured using Lifecoder® GS (Suzuken Co. Ltd., Nagoya, Japan). Lifecoder® GS was placed on a line with the anterior superior iliac spine of each participant, and participants were asked to wear the activity monitor for a week from the time of the survey and to remove the activity monitor when bathing or showering and during radiotherapy treatment. This activity monitor was based on a uniaxial accelerometry sensor that computed step counts, total, and walking activity level every 4s and classified it as light (<3.0 MET), moderate (3.0-6.0 MET), and vigorous (>6.0 MET) intensity activity[15]. The validity of the Lifecoder GS used in the present study has been confirmed for measuring activities, including walking, and providing an objective measure of PA[15]. At the end of this week, the patients retrospectively documented their HRQoL during the monitoring period using EORTC QLQ-C30.

C Statistical analysis

Participants were divided into two categories based on "light or greater" activity level on their best PA over the past week (PA <150 minutes per week vs. PA ≥150 minutes per week)[16][17]. Data are shown as the mean ± SD. The distribution of each variable was checked for normality using the Kolmogorov-Smirnov test. Differences in medical and demographic variables between participants in the two PA category groups were tested using Wilcoxon's rank sum test.

We analyzed differences in PA levels by binomial logistic and multiple linear regression (direct methods). The dependent variable was PA (0 = PA <150 minutes, 1 = PA ≥150 minutes). Variance Inflation Factor was used to check for multicollinearity. Predictive and complexity characteristics of the model were considered during modeling. Covariates included demographic factors (age, sex, BMI) and medical factors (comorbidities, current treatment, cancer diagnosis). Data were analyzed using SPSS version 25.0 software (IBM). In all analyses, $p<0.05$ was taken to indicate statistical significance.

Ⅲ Results

Recruitment into the present study was performed from September 2014 to May 2017. The CONSORT diagram in study participants is summarized in **Fig. 1**. Although a total of 260 patients were recruited into the present study, 132 patients did not meet the inclusion criteria, and three withdrew consent. Therefore, 125 patients were eligible for inclusion in the present study. The reasons for withdrawal included general fatigue ($n = 1$) and feeling too ill ($n = 2$). Life recorder devices were provided to all participants, but 23 of 125 (18 %) did not fully utilize the

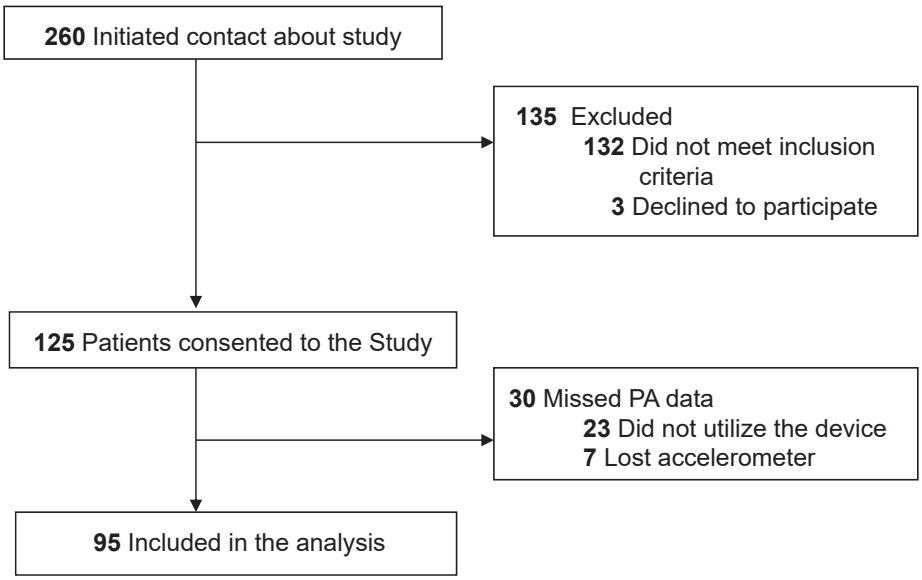

Fig. 1 Flow of participants through the study

device. Seven of these 125 patients (6 %) lost the accelerometer. Therefore, full analyses were conducted in 95 patients.

The median time spent on moderate or above PA load by all subjects in the present study was 5 [0.6–17] minutes per week, and a maximum of 145 minutes per week. The clinical characteristics of patients in the present study and the comparison between the two PA levels are shown in **Table 1**. Patients with PA <150 minutes had significantly lower albumin and PPS, and significantly higher PS compared to patients with PA ≥150 minutes. Other baseline values were not significantly different between the two PA categories. Descriptive data for PA, EORTC QLQ-C30, ABMS, m-FIM, and ESAS are presented in **Table 2**. There were no subjects with moderate activity intensity that reached the recommended levels (moderate PA ≥150 minutes)[18]. Patients with PA ≥150 minutes had higher global health status, physical functioning, role functioning, emotional functioning, and social functioning. In addition, statistically significant differences were observed in scores of ABMS, m-FIM, and GES: patients with PA ≥150 minutes had a higher status. The same results were obtained in sub-analysis, even when only light PA was classified at 150 minutes per week and analyzed (**Table 3**).

Binomial logistic and multiple linear regression analyses of predictive factors for PA were performed and the data are shown in **Table 4**. When adjusted for several factors (age, sex, BMI, number of comorbidities), ABMS was the most predictive factor for PA. Furthermore, patients with higher PA were significantly related to ABMS (OR = 2.249, 95 % CI: 1.062–4.764), when adjusted for both demographic factors and current medical treatments.

Ⅳ Discussion

We found that subjects with PA ≥150 minutes per week had higher QLQ-C30, ABMS, FIM, and GES compared to subjects with PA <150 minutes. On the other hand, ESAS results indicated no significant differences. Based on these results, we concluded that PA ≥150 minutes per week is related to improved HRQoL in hospitalized patients with advanced cancer.

The current guidelines for cancer survivors recommend 150 minutes or more of moderate or higher PA per week[17]. However, the PA level in patients enrolled in the present study was lower than that in the PA guidelines for cancer survivors[17], and none of the participants achieved 150 minutes or more of moderate or higher PA per week. Very few of our participants could perform moderate or higher PA,

Table 1 Characteristics of the participants

Characteristic	PA ≥150 minutes $n=43$	PA <150 minutes $n=52$
Age, yr	66.2 ± 10.6	70.6 ± 9.0
Male sex, no. (%)	27 (63)	31 (60)
Body-mass index, no. (%)		
Thin (<18.5)	8 (19)	15 (29)
Healthy (18.5-25)	25 (58)	30 (58)
Obesity (>25)	10 (23)	7 (14)
Comorbidities, no. (%)		
Heart disease	11 (26)	19 (37)
Diabetes	6 (14)	7 (14)
Other	13 (30)	9 (17)
Laboratory data		
Alb*	3.4 ± 0.7	3.1 ± 0.6
Hb	11.4 ± 1.7	11.5 ± 1.8
CRP	2.7 ± 3.5	3.4 ± 4.5[a]
Cancer diagnosis, no. (%)		
Lung	18 (42)	22 (42)
Head and Neck	10 (23)	11 (21)
Gastrointestinal/Liver	5 (12)	9 (17)
Unknown	4 (9)	2 (4)
Others	6 (14)	8 (16)
PS Median [IQR]*	2 [1, 2]	3 [2, 3]
PPS Median [IQR]*	70 [70, 90]	55 [40, 60]
Current treatment, no. (%)		
Chemotherapy	12 (28)	10 (19)
Radiation	16 (37)	10 (19)
Death (<180 days), no. (%)	7 (16)	16 (31)
Discharge, no. (%)		
Home	37 (86)	36 (69)
Other hospital	3 (7)	9 (17)
Death	3 (7)	7 (14)
In-hospital days	30.0 ± 21.3	36.7 ± 28.9

Data are means ± SD. [a]Data were available for 49 patients
PA : physical activity. *$p<0.05$

considering the fatigue, cachexia, and weakness encountered by advanced cancer patients. It is difficult for patients with advanced cancer to increase moderate or higher PA. Therefore, based on our results, the recommendation was unsuitable for hospitalized and terminally ill cancer patients in Japan. However, systematic reviews have provided evidence that higher PA levels in patients with advanced cancer are associated with greater HRQoL and improved physical status[19)20)]. For those engaging in physical inactivity, the recommendation is to incorporate a few minutes of increased activity, to build up gradually to 150 minutes per week of PA[21)]. Our results showed that even if most of the PA is of light intensity, PA >150 minutes per week can have a positive impact on HRQoL in hospitalized and terminally ill cancer patients. This finding may be significant for cancer patients who are unable to participate in moderate systematic PA programs. Evidence from observational studies suggests that light PA, independent of moderate PA, is associated with better health benefits[22)]. Previous study suggested that increasing light PA may be a viable approach to reducing HRQoL decline in cancer survivors who were

Table 2　Quality of life, symptoms, basic movement, self-efficacy, and ADL differences between participants with PA ≥150 minutes and PA ＜150 minutes

Median [IQR]

	PA ≥150 minutes (n = 43)	PA ＜150 minutes (n = 52)	p-value
EORTC QLQ-C30			
Global health status	33.3 [16.7, 50.0]	25.0 [8.3, 41.7]	0.032
Physical functioning	66.7 [40.0, 80.0]	20.0 [0, 46.7]	p＜0.01
Role functioning	33.0 [16.7, 66.7]	0 [0, 33.3]	p＜0.01
Emotion functioning	75.0 [33.3, 91.7]	41.7 [16.7, 72.9]	0.030
Cognitive functioning	50.0 [0, 83.3]	50.0 [16.7, 66.7]	0.611
Social functioning	50.0 [16.7, 83.3]	8.35 [0, 50.0]	p＜0.01
ESAS	20.0 [15.0, 27.0]	40.0 [23.5, 53.5]	0.298
ABMS	30.0 [29.0, 30.0]	28.0 [26.0, 29.0]	p＜0.01
GES	24.0 [21.0, 30.0]	20.0 [11.0, 28.0]	p＜0.01
m-FIM	86.0 [77.0, 91.0]	62.5 [50.0, 76.8]	p＜0.01
PA, minutes/week			
Light	213.7 [168.1, 285.6]	46.5 [19.7, 81.7]	p＜0.01
Moderate	19.4 [7.6, 37.5]	0.9 [0.1, 4.4]	p＜0.01
Vigorous	0.7 [0, 0.7]	0 [0, 0.2]	0.026
Steps	20811 [15138, 28078]	3957 [1740, 7105]	p＜0.01

Table 3　Quality of life, symptoms, basic movement, self-efficacy, and ADL differences between participants with light PA ≥150 minutes and light PA ＜150 minutes

Median [IQR]

	light PA ≥150 minutes (n = 39)	light PA ＜150 minutes (n = 56)	p-value
EORTC QLQ-C30			
Global health status	41.7 [16.7, 50.0]	29.2 [8.3, 41.7]	0.048
Physical functioning	66.7 [46.7, 80.0]	23.4 [1.7, 46.7]	p＜0.01
Role functioning	33.3 [16.7, 66.7]	0 [0, 33.3]	p＜0.01
Emotion functioning	66.7 [33.3, 83.3]	41.7 [16.7, 72.9]	0.033
Cognitive functioning	66.7 [0, 83.3]	50.0 [16.7, 66.7]	0.420
Social functioning	50.0 [16.7, 83.3]	16.7 [0, 50.0]	p＜0.01
ESAS	32.0 [26.0, 44.0]	40.0 [25.0, 51.8]	0.346
ABMS	30.0 [29.0, 30.0]	28.0 [26.0, 29.0]	p＜0.01
GES	24.0 [20.0, 30.0]	20.0 [11.3, 28.0]	0.016
m-FIM	85.0 [77.0, 91.0]	63.0 [50.5, 83.0]	p＜0.01

Table 4　Predictors of PA

	Multivariable Model 1[a] OR (95 % CI)	Multivariable Model 2[b] OR (95 % CI)
ABMS	2.326 (1.114-4.859)	2.249 (1.062-4.764)
m-FIM	1.055 (0.978-1.138)	1.067 (0.983-1.158)
ESAS	1.037 (0.986-1.090)	1.028 (0.976-1.083)
GES	1.069 (0.982-1.163)	1.063 (0.976-1.159)

[a] Adjusted for age, sex, BMI, number of comorbidities.

[b] Adjusted for model 1 plus chemotherapy, radiation.

unable or reluctant to initiate or maintain moderate PA[23]. We found that a certain amount of PA (PA ≥ 150 minutes per week) had a positive effect on improving HRQoL even in terminally ill cancer patients. The results of the present study suggest that PA ≥150 minutes per week, even if mostly of light intensity, such as walking, may be beneficial for terminally ill cancer patients. To our knowledge, no models of palliative rehabilitation for patients with advanced cancer have yet been established. Our data could provide new insight for clinicians to integrate palliative cancer care, especially in patients with incurable disease and terminally ill cancer patients. A randomized phase III study indicated that early palliative care was associated with prolonged survival in patients with advanced and/or metastatic non-small cell lung cancer[22]. Interestingly, the survival benefit was associated with improvements in HRQoL and depressed mood. Given the progressive nature of the illness, improving HRQoL and mood in terminally ill cancer patients is a major challenge. Our data suggested that palliative rehabilitation using a protocol with PA ≥150 minutes per week could contribute to better HRQoL in terminally ill cancer patients.

In the present study, we found no significant difference in ESAS (cancer-related symptoms) between the two PA categories. It is unlikely that the cancer-related symptoms could affect the PA status. This may be because patients in both PA categories were recruited after improvement of symptoms by medical treatments, such as administration of opioids, etc.

To our knowledge, this is the first study to clarify the relationship between light PA and HRQoL, and the capability to perform basic movement in terminally ill cancer patients. However, the present study had several limitations. First, the study population consisted of hospitalized cancer patients in a single institute. The criteria for hospitalization varied among patients and the conditions of the disease. In addition, there were many types of cancer and the clinical backgrounds also varied among the enrolled patients. Further studies are required to clarify what types of cancer patients could benefit from cancer rehabilitation. Second, our study did not measure sitting time, which is known to be a health risk factor independent of PA[24)25]. Studies in advanced cancer patients revealed that sitting time affected psychosocial functionality rather than time spent on PA[26]. Further evaluation of sitting time in addition to PA may be more informative for terminally ill cancer patients. Finally, health insurance for medical services, particularly during hospitalization, is quite different among countries. Therefore, the results of the present study may not be generalizable to cancer patients in other countries.

In conclusion, we showed that PA ≥150 minutes per week was associated with higher HRQoL even among hospitalized and terminally ill cancer patients. Palliative rehabilitation using PA ≥150 minutes per week of physical activity may be useful to improve QoL in terminally ill cancer patients.

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