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Feasibility and efficacy of speed-feedback therapy with a bicycle ergometer on cognitive function in elderly cancer patients in Japan

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Abstract

***Objective*: We conducted this study with the aim of demonstrating the feasibility and efficacy of speed-feedback therapy with a bicycle ergometer on cognitive function in elderly cancer patients.**

***Methods*: The subjects were patients with breast or prostate cancer who were 65 years of age or over. Among 146 patients, 78 were randomly assigned to the intervention group ($n = 38$) or the control group ($n = 40$). The intervention group received speed-feedback therapy with a bicycle ergometer once a week for four successive weeks. The control group was advised to spend the 4-week period engaged in their routine activities. Evaluations were carried out at the baseline and 4 weeks after the baseline (week 4) using the Frontal Assessment Battery, the Barthel Index, the Lawton and Brody Instrumental Activities of Daily Living, and the Functional Assessment of Cancer Therapy-General ver.4. Data were analyzed by a two-way repeated-measures analysis of variance.**

***Results*: The mean score of Frontal Assessment Battery for the intervention group was higher than that for the control group at week 4. In addition to significant main effects of time and group, we also found a significant interaction between the two groups ($p = 0.006$). Moreover, all of the subjects in the intervention group could complete all the four sessions of therapy without any pain or distress.**

***Conclusion*: These results suggest that speed-feedback therapy with a bicycle ergometer may be feasible as well as effective for improving the cognitive function in elderly cancer patients.**

Introduction

Existence of an association between cancer therapy and cognitive decline has been pointed out since the early 1990s. Recent surveys have revealed cognitive decline in 25−50% of elderly cancer patients, with the proportion of patients with cognitive decline increasing with age [1,2]. There are some reports indicating the possible factors that influence on the cognitive function in elderly cancer patients, such as aging, cancer itself [3], chemotherapy [4–6], and hormone therapy [7,8]; however, there is still ongoing debate about the influence of cancer treatments on cognitive functions [9,10]. Although no conclusive evidence has been collected regarding increased vulnerability of elderly cancer patients to cognitive functional decline, it is thought that a number of factors, including the age, the cancer itself, and various cancer treatments, may covertly or overtly affect the cognitive functions in elderly cancer patients.

Because the cognitive ability of the elderly has been reported to not only affect the decision-making abilities required to select appropriate treatment but also have an influence on the affective state, ability to perform activities of daily living and quality of life (QOL) of the patients [11], it is extremely important to strive to maintain and improve the cognitive functions in elderly cancer patients. However, there have been scarcely any reports on the rehabilitation practices in relation to cognitive decline for elderly cancer patients [12], and few studies have been designed to evaluate the effect of interventions to treat cognitive decline [13]. Thus, examination of the efficacy of rehabilitation focused on improving the cognitive decline in elderly cancer patients is an important issue [14].

In the present study, we attempted to assess the efficacy of speed-feedback therapy with a bicycle ergometer as a rehabilitation approach aimed at improving the cognitive function of elderly cancer patients. Speed-feedback therapy with a bicycle ergometer is a rehabilitation approach designed to improve the cognitive functions [15], and it has already been reported to be effective in improving the cognitive function of dementia patients; its safety even in the elderly has also been confirmed [15,16]. If the feasibility and efficacy of this therapy as a rehabilitation intervention could be demonstrated in this study, clinical application of this method for the rehabilitation of elderly cancer patients would become possible in the future, which would not only contribute to the expansion of rehabilitation in this field, but provide important suggestions in regard to the support required for maintaining a higher QOL for elderly cancer patients suffering from cognitive decline.

Methods

Study design

This study was a 4-week randomized controlled trial comparing the effects of rehabilitation by speed-feedback therapy using a bicycle ergometer (intervention group) with those of routine life activities without any rehabilitation intervention (control group). Eligible patients were randomized at a 1:1 ratio to the intervention group or the control group by the researcher in charge of the allocation using the envelope method. Patients and therapists were, however, informed about the group allocations. An independent evaluator who assessed the outcome by comparing the parameters at baseline and week 4 was masked to the assignment condition throughout the trial. The study was conducted from October 1, 2011 to May 10, 2012.

Participants

Breast cancer or prostate cancer patients attending the outpatient clinic of Hiroshima University Hospital who were 65 years of age or over at the time of provision of informed consent for participation, whose performance status was 0 or 1, and who were capable of walking unassisted were enrolled as the subjects of this study. The reason to select breast and prostate cancer patients as the participants was that there are many common characteristics between breast and prostate cancer patients, including the beneficial effects of sex hormones, slow progression and tendency to retain functional status, increasing morbidity in Japan, the possibility of treatment selection (operation, chemotherapy, hormone therapy, and radiotherapy), and previous reports of an association with cognitive decline. Patients who had bone-metastasis, had received whole-brain irradiation, required medical risk factor management for cardiorespiratory disease, or whose ability to pedal the ergometer was impeded by an orthopedic disease, or central nervous system paralysis were excluded from the study.

Intervention method

We conducted speed-feedback therapy with a bicycle ergometer for the intervention group at the rehabilitation room of Hiroshima University Hospital. It is a rehabilitation approach designed to improve the cognitive functions, involving the use of a training machine consisting of a bicycle ergometer connected to a PC. The subjects were instructed to pedal the bicycle ergometer to match the target speed arbitrarily displayed on the PC screen. A standard path corresponding to the target number of revolutions is displayed on the screen (standard number of revolutions), and the subject pedals the ergometer while visually tracking and paying attention so as to follow the path (Figure 1). The actual path pedaled by the subject (actual number of

Figure 1. Speed-feedback therapy with a bicycle ergometer

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revolutions) is displayed in real time, with the standard path changing constantly. The efficacy of this therapy in improving cognitive impairment in elderly people has been reported previously [15,16]. For this study, we set the exercise load at 20 W and the maximal number of rotations at 80 rpm, and the pedaling time at 5 min based on our previous studies [15,16]. A total of four sessions of the exercise program was undertaken over 4 weeks, at the frequency of one session per week. The subjects' vital signs and health status were checked before, during, and after the program by the therapists. On the other hand, we requested the control group to spend the 4-week period engaged in their routine activities.

Assessment

We investigated the age, gender, number of years of education, employment status, exercise habit, site of the primary cancer lesion, date of diagnosis, stage of cancer, treatment history, and ongoing treatment as sociomedical parameters. We used the Frontal Assessment Battery (FAB), which was developed as a short bedside cognitive and behavioral battery to assess the frontal lobe functions and consists of six domains: (1) similarities (conceptualization), (2) lexical fluency (mental flexibility), (3) Luria motor sequences (programming), (4) conflicting instructions (sensitivity to interference), (5) a go-no go test (inhibitory control), and (6) comprehension behavior (environmental autonomy) [17]. The reliability and validity of the Japanese version of FAB for dementia has previously been confirmed [18]. FAB has been reported to be useful as a cognitive evaluation instrument for measuring the cognitive function of elderly cancer patients [19]. In our previous study, we confirmed the FAB, as compared with other scales such as the Mini-Mental State Examination [19], as a highly useful tool for evaluating the cognitive function in elderly cancer patients. The Barthel Index (BI) [20] and Lawton and Brody Instrumental Activities of Daily Living (IADL) [21] were used to evaluate the activities of daily living, and the Functional Assessment of Cancer Therapy-General ver.4 (FACT-G) [22] was used as the QOL scale. We were granted license by FACIT.org to use the Japanese version of FACT-G for this study. The assessments were carried out at the baseline and immediately after the fourth intervention session for the intervention group, and 4 weeks after the baseline for control group (week 4), by an independent evaluator who was masked to the assignment condition throughout the trial.

Sample size

Using previous studies as reference [16,19], we calculated the sample size that would be required to obtain results with a statistical power of 80% for a two-tailed test (5% significance level) based on an efficacy rate (change in FAB score from the baseline to completion of therapy) of 10% (2 points) and standard deviation of 2.6 in the intervention group, and determined that 28 patients per group would be required. Assuming a dropout rate of 10%, we decided to enroll 31 patients per group, that is, a total of 62 patients.

Statistical analysis

Descriptive statistical analysis was performed in regard to the subjects' background characteristics and scores on each of the scales in order to obtain an overview of the subjects as a whole at the baseline. Next, the Mann–Whitney *U*-test was used to analyze continuous variables after performing the Kolmogorov–Smirnov test of normality and the chi-squared test or Fisher exact test for analysis of the categorical data such as the background factors of the subjects at baseline and their scores on each of the evaluation scales, as appropriate. Then, we performed a two-way repeated-measures analysis of variance (ANOVA) by using the scores on each of the evaluation scales as the dependent variables in order to assess differences in the changes of the scores on each of the evaluation scales between the baseline and completion of the intervention (week 4) between the two groups. We finally investigated the independent factors that might affect the changes of the FAB score by using stepwise multiple regression analysis. The analysis included all baseline factors except the primary cancer site, which was coincident with gender, as explanatory variables (Table 1). The p values in all of the tests were two-sided, and $p < 0.05$ was considered to denote significance. All of the statistical analyses were performed using the IBM SPSS 21.0 Statistics (IBM Japan, Tokyo, Japan).

Ethical considerations

This study was conducted in compliance with the Declaration of Helsinki adopted by the World Medical Association and the Ethical Guidelines for Clinical Research of the Japanese Ministry of Health, Education and Labor; prior approval for conduct of the study was obtained from the Clinical Research Ethics Committee of Hiroshima University.

Results

Summary of the circumstances of the subjects' participation

The circumstances of the subjects' participation are summarized in Figure 2. Informed consent for participation in this study was obtained from 78 of the 146 patients who met the eligibility criteria. Random assignment of these 78 subjects resulted in 38 subjects being allocated to the intervention group and 40 subjects being allocated to the control group. Because there were no dropouts from either of the groups, all of the 78 subjects were included in

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Table 1. Comparison between the groups at the baseline

		Intervention ($n = 38$)	Control ($n = 40$)	p value[a]
Mean age (years: SD)	Years (SD)	72.97(4.57)	75.45(6.57)	0.15
Gender	Male (%)	17(44.7)	18(45.0)	0.98
	Female (%)	21(55.3)	22(55.0)	
Years of education	Mean years (SD)	12.03(2.05)	12.20(3.27)	0.54
Employed	Yes (%)	8(21.1)	11(27.5)	0.51
	No (%)	30(78.9)	29(72.5)	
Exercise habit	Less than once a week (%)	18(47.4)	24(60.0)	0.26
	More than once a week (%)	20(52.6)	16(40.0)	
Primary cancer site	Breast (%)	21(55.3)	22(55.0)	0.98
	Prostate (%)	17(44.7)	18(45.0)	
Time since the diagnosis	Mean months (SD)	56.57(32.52)	68.88(54.77)	0.68
Stage of cancer	Stage I (%)	11(28.9)	13(32.5)	0.51
	Stage II (%)	22(57.9)	15(37.5)	
	Stage III (%)	1(2.6)	5(12.5)	
	Stage IV (%)	4(10.5)	7(17.5)	
Treatment history[b]	Operation (%)	31(81.6)	29(72.5)	0.34
	Chemotherapy (%)	9(23.7)	11(27.5)	0.70
	Hormone therapy (%)	26(68.4)	32(80.0)	0.24
	Radiation therapy (%)	26(68.4)	16(40.0)	0.01
Ongoing treatment	Chemotherapy (%)	1(2.6)	4(10.0)	0.36
	Hormone therapy (%)	18(47.4)	23(57.5)	0.37
	Radiation therapy (%)	1(2.6)	1(2.5)	1.00
FAB	Mean score (SD)	15.0(1.59)	14.50(1.87)	0.15
BI		100.0(0)	99.75(1.58)	0.33
IADL		9.55(1.08)	9.15(1.53)	0.08
FACT-G		75.29(15.76)	74.30(14.27)	0.75

SD, standard deviation; FAB, Frontal Assessment Battery; BI, Barthel Index; IADL: Instrumental Activities of Daily Living; FACT-G, Functional Assessment of Cancer Therapy-General (ver.4).
[a]Chi-squared-tests or Fisher exacts test were used for categorical data, as appropriate. Mann–Whitney *U*-tests were used for continuous variables.
[b]There were multiple answers.

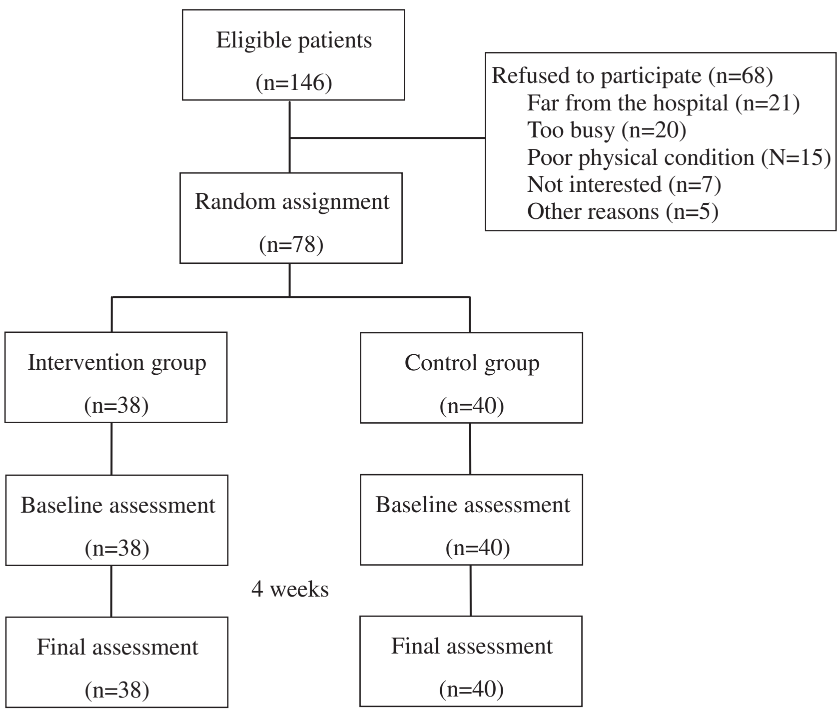

Figure 2. Flow of participants through the trial

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the evaluations. No subjects in the intervention group had any trouble with the use of the bicycle during the speed-feedback therapy using a bicycle ergometer. Moreover, the heart rate criterion for stopping the exercise was not exceeded in any of the patients during the conduct of the therapy sessions nor was there any abnormal changes of the blood pressure in any of the patients either before or after the therapy; none of the patients complained of any pain or distress.

Comparison of the characteristics between the intervention group and the control group at baseline

At the baseline, there were no significant differences in the age, gender, years of education, employment status, exercise habit, primary cancer site, time since diagnosis, stage of cancer, treatment history, except radiation therapy, ongoing therapy, or total or subscale scores on any of the evaluation scales between the intervention group and the control group (Table 1). However, there was one significant difference ($p = 0.01$) between the two groups, related to the history of treatment: the proportion of patients who had received radiation therapy was higher in the intervention group than that in the control group (there were multiple answers).

Comparison of the changes in the scores on each of the scales between the intervention group and the control group

In all scales we evaluated, the mean score for the intervention group tended to be higher than that for the control group at both baseline and week 4. In all scales but BI, the mean score at week 4 tended to be higher than that at baseline for both intervention and control groups (Table 2). As a result, two-way ANOVA revealed a significant time effect ($F = 24.39$, $p < 0.001$, partial $\eta^2 = 0.247$) and a significant group effect ($F = 9.26$, $p = 0.003$, partial $\eta^2 = 0.109$) only on the FAB score, and not on other scales. In addition to two main effects, we also found a significant interaction between the two groups only on the FAB score ($F = 7.88$, $p = 0.006$, partial $\eta^2 = 0.094$) (Figure 3).

Independent factors affecting the changes in the FAB score

At the baseline, we observed a significantly higher proportion of patients with a previous history of radiation therapy in the intervention group as compared with that in the control group. To exclude the possibility of this finding affecting the results of our analysis, we evaluated the changes in the FAB scores according to previous radiation therapy and intervention. In patients with previous radiation therapy, the mean changes of the FAB scores were 1.50 (standard deviation (SD) = 1.55) and 0.75 (SD = 1.82) in the intervention and control groups, respectively. In patients without previous radiation therapy, on the other hand, the mean changes of the FAB scores were 1.83 (SD = 0.99) and 0.25 (SD = 2.24) in the intervention and control groups, respectively. From these results, it was concluded that previous radiation therapy was unlikely to have been a confounding factor causing potential overestimation of the effect of the intervention on the FAB scores. Furthermore, we reevaluated the effect of our intervention on the changes of the FAB scores by stepwise multiple regression analysis, including all the baseline factors, except for the primary cancer site, which was coincident with the gender (Table 1). After adjusting for potential confounding factors, the intervention remained an independent factor influencing the changes in the FAB scores ($p = 0.030$, beta = 0.241). In

Table 2. Baseline and week 4 scores on outcome measures

	Intervention	Control	Interaction		Main effect			
					Time		Group	
	(*n* = 38)	(*n* = 40)	group × time					
	Mean (SD)		*F*	*p* value	*F*	*p* value	*F*	*p* value
FAB			7.88	0.006	24.93	<0.001	9.26	0.003
Baseline	15.00(1.59)	14.50(1.87)						
Week 4	16.61(1.37)	14.95(2.25)						
BI							0.95	0.333
Baseline	100.00(0)	99.75(1.58)						
Week 4	100.00(0)	99.75(1.58)						
IADL			0.07	0.789	1.96	0.165	2.83	0.097
Baseline	9.55(1.08)	9.15(1.53)						
Week 4	9.74(0.80)	9.28(1.38)						
FACT-G			0.11	0.738	1.10	0.297	0.26	0.612
Baseline	75.29(15.76)	74.30(14.27)						
Week 4	77.47(14.01)	75.42(15.42)						

SD, standard deviation.

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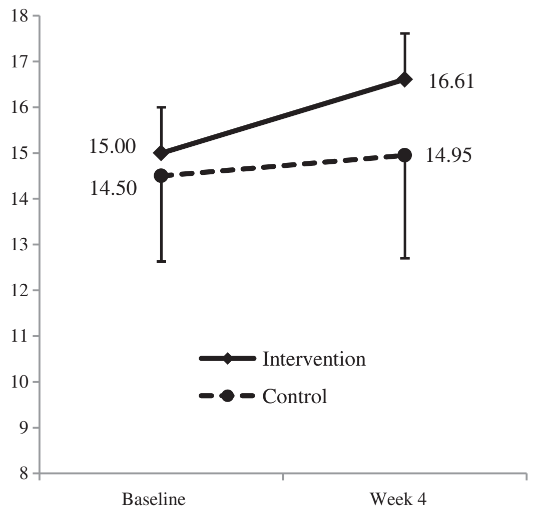

Figure 3. Change between the two groups in Frontal Assessment Batteryn (FAB) scores

addition, we found age as another independent factor ($p = 0.018$, beta = −0.264).We found no significant effect of the stage of cancer or the treatment regimen employed on the changes of the FAB scores.

Discussion

Circumstances of the conduct of speed-feedback therapy with a bicycle ergometer

During the conduct of the program, there were no dropouts from the intervention group for any reason, either refusal to participate or deterioration of the subject's condition after the start of the program, and all of the four sessions could be completed in all of the subjects. Also, many positive comments, such as "it was fun, like a game" were heard from the participants. Therefore, we believe that the program is highly feasible. Furthermore, all of the subjects of the intervention group were able to accomplish the program without any abnormal changes of physical condition either before or after the speed-feedback therapy, and none of the patients complained of any pain or distress. The former findings reveal that the speed-feedback therapy with a bicycle ergometer undertaken in this study was associated with very little risk of adverse events, even when applied to elderly cancer patients, and that it is a safe program.

In addition, we found that there are many cancer patients in Japan who continue to live with an uneasy feeling about some changes that they have noticed in their cognitive abilities without consulting anyone. To our regret, few patients could be informed about the potential adverse effects of cancer therapy on the cognitive function in Japan. We think that it would be beneficial to provide the patients themselves or their families with information about the possible cognitive decline that can occur in elderly cancer patients receiving cancer treatment and about the possibility of rehabilitation to counter such decline, in terms of improving the quality of lives of the patients undergoing cancer treatment.

Efficacy of the intervention

In the current randomized controlled study, we successfully achieved improvement of the score on the FAB by intervention using speed-feedback therapy with a bicycle ergometer. We observed a significant difference in the change of the score on the FAB between the intervention and control groups using the two-way ANOVA. Although the amount of change of FAB scores was small, it is reported that only a small increase of FAB scores can lead to an improvement of IADL [19]. Moreover, we confirmed the independent efficacy of our intervention using stepwise multiple regression analysis, including various possible confounding factors, such as previous or ongoing treatment. However, we cannot completely rule out the possibility that other confounding factors may have influenced the results. On the other hand, we found younger age as another independent factor associated with greater improvement of the FAB score, maybe suggesting easier reversibility in these patients.

In regard to the mechanism underlying the improvement in cognitive function by speed-feedback therapy with a bicycle ergometer, Ootani et al [15] deduced that sustained attention and improved concentration, which are linked to the improvement of cognitive functions, are responsible for the improvement in the attention span of the subjects. Rowe [23] reported that the brain activity increases significantly during motor attention tasks, which may be one of the mechanisms explaining the improvement of the cognitive functions in elderly cancer patients following speed-feedback therapy with a bicycle ergometer, which includes an attention-sustaining element. Moreover, Winocur *et al*. [24] stated that it is possible to reverse the decline of cognitive functions in elderly cancer patients by undertaking rehabilitation focused on attention, which lends support to our contention in the present study that the attention-sustaining element of speed-feedback therapy with a bicycle ergometer was responsible for the improvement of the cognitive function in elderly cancer patients.

On the other hand, no improvement in the results of evaluation by the BI, IADL, or FACT-G was observed in the present study. The subject sample size may be one of the factors responsible for this. Because we computed the sample size in this study based on the changes in the FAB score, the sample size may have been insufficient to detect significant differences in the scores on the other evaluation scales. Another possible factor is the good functional state of the subjects. Because we used a performance status of 1 or higher as an eligibility criterion for this study, the mean

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scores on the BI and IADL at baseline were 99.87 (SD 1.13) and 9.35 (SD 1.34), respectively, that is, almost perfect scores. Thus, the ceiling effect may have come into play preventing the appearance of any significant changes.

Expectations of holistic rehabilitation to maintain the patients' QOL to the greatest possible degree during protracted cancer therapy have increased [25]. In such background, assessment of the efficacy in this study of a rehabilitation intervention for cognitive decline in elderly cancer patients represents a new dimension in the rehabilitation of cancer patients. We also believe that the finding of this study that a physical exercise task involving a sustained-attention element can bring about an improvement of cognitive function will serve as a valuable material for future research on the rehabilitation of cancer patients. Moreover, our observation during the course of this study that there are significant numbers of elderly cancer patients who feel uneasy about their cognitive abilities and need to talk to someone about it is a matter that needs to be addressed with some urgency in clinical settings. It is hoped that other rehabilitation approaches for these patients, such as occupational therapy, are also adopted in the future. Further elucidation of the actual situation in regard to cognitive decline in cancer patients and how to deal with this problem will be necessary in order to provide appropriate support for such patients in the future.

Limitations and perspectives

Because the intervention group in this study was required to come to the hospital and talk with the therapist once a week, whereas the control group was not, it is difficult to rule out the possibility that the greater number of opportunities for the intervention group to go out and to talk to someone about their condition may have affected the results. However, because no significant differences in the subjects' occupations, exercise habits or functional status were observed between the two groups at baseline; it is hard to imagine that the intervention group just having the additional opportunity to go to the hospital and talk with the therapist once a week would have greatly affected the results. Nevertheless, it will be necessary to verify the efficacy of speed-feedback therapy with a bicycle ergometer after eliminating the potential influence of this factor on the results. Additionally, it should be examined whether speed-feedback therapy is more effective than other treatments that also sustain attention and improve concentration. Another limitation of this study is that we demonstrated the efficacy of this therapy by evaluations repeated twice. We should have repeated the follow-up evaluations after the intervention several times in order to examine the long-term effectiveness of this therapy. Furthermore, only breast and prostate cancer patients from a single institution were enrolled in this study, and we cannot deny the possibility of selection bias as a limitation of the study. Therefore, it is impossible at this time to generalize the results of our study. Also, although speed-feedback therapy with a bicycle ergometer has been shown to be effective in improving the frontal lobe function in elderly cancer patients, the underlying mechanism, duration of efficacy, and the effects on the daily life, including on the decision-making abilities of the subjects, have not yet been clarified Therefore, it will be necessary to expand the number of subjects and conduct a long-term study for further clarification of the efficacy of this therapy.

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Conflict of interest

The authors have declared no conflict of interest.

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