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ORIGINAL ARTICLE

Long-term influence of adjuvant breast radiotherapy on cognitive function in breast cancer patients treated with conservation therapy

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Abstract

Background The mechanisms underlying cognitive decline after radiotherapy not directed at brain areas remains unclear. We previously suggested that adjuvant breast radiotherapy in breast conservation therapy could lower memory function soon after therapy, and that the process might be partially mediated by plasma interleukin (IL)-6 levels. The present study investigated how that relationship changes longitudinally.

Methods We performed the Wechsler Memory Scale-Revised (WMS-R) test and measured plasma IL-6 levels for 47 breast cancer surgical patients within 1 year after the initial therapy (study 1) and more than 2 years after study 1 (study 2). We also performed 2 × 2 mixed [the radiotherapy group ($n = 25$) or the no-radiotherapy group ($n = 22$) × study 1 or study 2] analysis of covariance on the WMS-R indices and plasma IL-6 levels. The association between changes in plasma IL-6 levels and changes in the WMS-R indices between the two studies was evaluated using Pearson's correlation coefficient.

Results The Immediate Verbal Memory Index was significantly higher in study 2. The Delayed Recall Index was significantly higher in study 2 and significantly lower in the radiotherapy group only in study 1. There was a significant correlation between changes in plasma IL-6 levels and changes only in the Delayed Recall Index of the WMS-R.

Conclusions Memory decline in breast cancer patients soon after adjuvant breast radiotherapy was restored approximately 3 years after treatment, and decreased plasma IL-6 levels might be involved in the recovery process.

Keywords Radiotherapy · Cognitive decline · Interleukin-6 · Breast cancer · Longitudinal study

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Introduction

As therapies for cancer improve patient survival, protracted cognitive decline in patients without tumors in the central nervous system (CNS) or direct CNS therapy has become a focus of attention, because it often has adverse effects on the quality of life of patients and survivors [1–3].

Recent reports have described cognitive decline following radiotherapy not directed at the brain [4–13], and several studies suggest that cognitive decline persists months or even years after radiotherapy [5–8, 11–13]. However, there were some limitations in these studies. First, most did not have control groups consisting of cancer patients [4, 7–12]. Second, many did not perform any objective neuropsychological tests [4, 5, 9, 10]. Finally, some of these studies were cross-sectional and not longitudinal [6, 7, 13]. Moreover, the mechanism of cognitive decline after radiotherapy remains unknown.

We previously demonstrated that breast cancer patients exposed to adjuvant breast radiotherapy in breast conservation therapy 7 months after treatment showed lower scores in some indices of the Wechsler Memory Scale-Revised (WMS-R) test [14–16] than breast cancer patients not exposed to radiotherapy. In addition, we suggested that the decline of memory function was partially mediated by elevated levels of plasma interleukin (IL)-6 [17]. This study investigated longitudinal changes in the relationship between adjuvant breast radiotherapy in breast conservation therapy and memory function among breast cancer patients and whether plasma IL-6 levels were involved in the process.

Patients and methods

This study was approved by the Institutional Review Board (IRB) and the Ethics Committee of the National Cancer Center of Japan (IRB number 11-95) and was performed after obtaining written informed consent from the patients. The study was conducted as a secondary analysis using a database of brain magnetic resonance imaging (MRI) scans from breast cancer survivors [18].

Subjects and procedures

Subjects were recruited during follow-up visits to the Department of Breast Surgery, National Cancer Center Hospital East, after their first breast cancer surgery at the same division. We analyzed their medical charts using continuous sampling and asked patients who met the inclusion criteria to participate in the study within 3–15 months after surgery and within 1 year of completing initial therapy. Patients included in the study were females aged 18–55 years that had no conflicts with the exclusion criteria. Exclusion criteria were as follows: (1) a history of cancer other than breast cancer; (2) bilateral breast cancer; (3) clear evidence of residual, recurrent, or metastatic cancer; (4) current chemotherapy or radiotherapy; (5) a history of any neurological disorders, traumatic brain injury, or psychiatric disorders other than affective and anxiety disorders; (6) psychotropic medication taken within 1 month of participation in the study; (7) a history of substance abuse or dependence; (8) a family history of early dementia; (9) any physical symptoms that interfered with daily life; (10) possible dementia defined as a score of <24 on the Mini-Mental State Examination-Japanese [19, 20]; (11) a history of major depression and/or post-traumatic stress disorder before cancer diagnosis; and (12) any contraindication to undergoing an MRI. Surgeries were performed from March 1998 to August 2001. Patients who agreed to participate in the study were interviewed to screen for exclusion criteria. Patients who were not excluded received neuropsychological tests, blood sampling, the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (SCID) [21], and a brain MRI. Subjects who were not excluded following this second group of tests were considered to have completed the first study (study 1) [17, 18]. After 2 years, patients who had completed study 1 were asked to participate in the second study (study 2). Patients who agreed to participate in study 2 underwent the same procedures performed in study 1. The inclusion and exclusion criteria for study 2 were the same as in study 1. Subjects who completed study 2 were analyzed (Fig. 1) [18].

For this study, we selected subjects aged 55 years or less to minimize variance in cognitive function due to dementia [17]. This study sought to determine the biological mechanism underlying “cancer brain” by assessing the effect of adjuvant breast radiotherapy in breast conservation therapy on memory function and its association with plasma IL-6 levels. Therefore, when choosing subjects, we included age and other restrictions to ensure the study cohort was as uniform as possible.

Adjuvant breast radiotherapy in breast conservation therapy

Radiotherapy was performed on the ipsilateral breast after breast conservation therapy in the Department of Radiation Oncology, National Cancer Center Hospital East. Irradiation for breast conservation therapy followed clinical practice guidelines for breast cancer from the Japanese Breast Cancer Society [22]: patients received 50 Gy in 25 fractions tangential irradiation to remaining breast tissue using a 6 MV X-rays radiation source. In cases where the distance between surgical resection margin and tumor cells was 5 mm or less

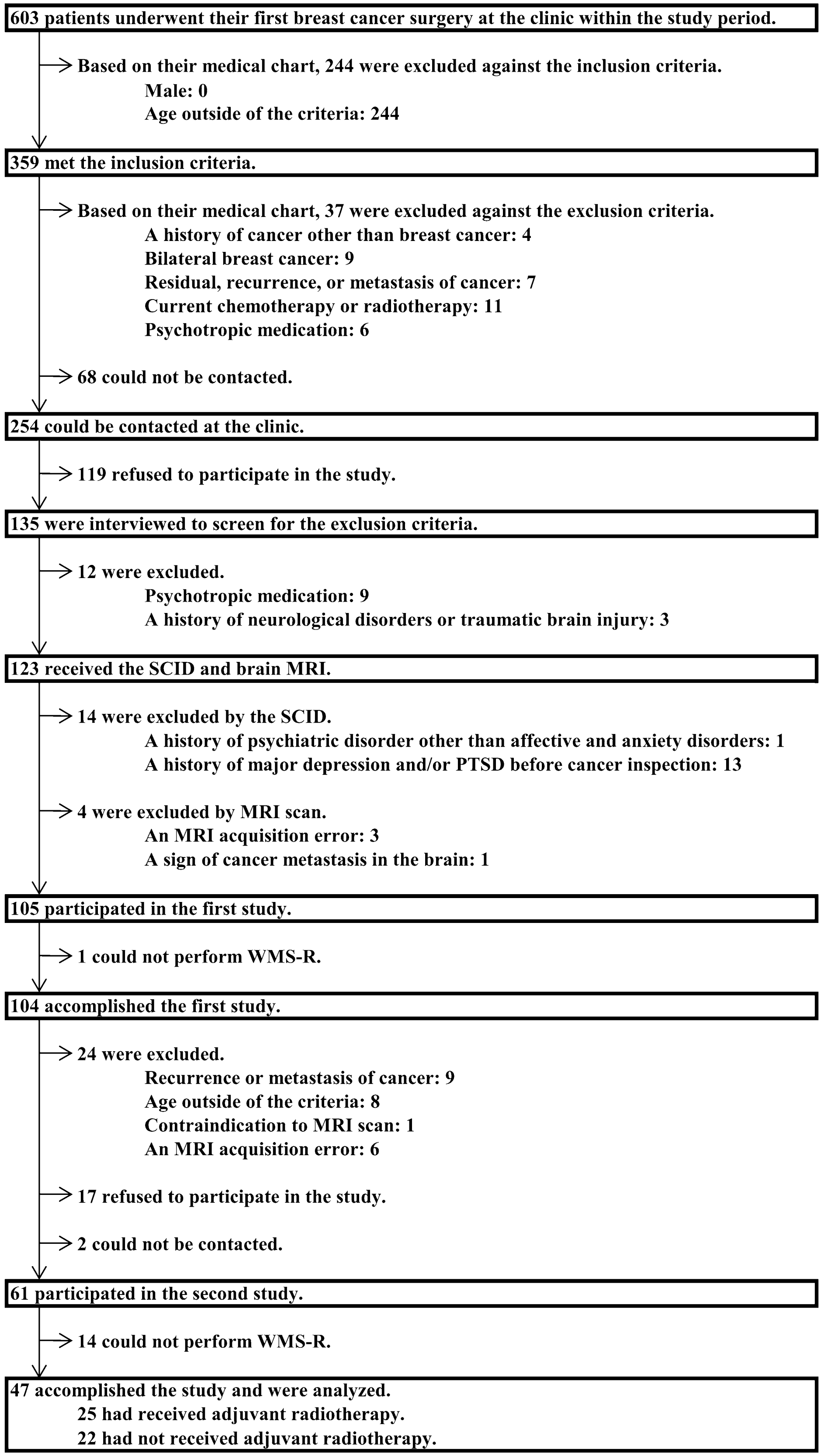

Fig. 1 This flowchart illustrates subject sampling. *SCID* the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, *MRI* magnetic resonance imaging, *PTSD* post-traumatic stress disorder, *WMS-R* the Wechsler Memory Scale-Revised

from the tumor histopathology, the tumor bed received a boost of 10 Gy in 5 fractions using a 6 MeV electron beam.

Neuropsychological tests

The Japanese version of the Wechsler Memory Scale-Revised (WMS-R) [15, 16] was administered to patients. The WMS-R evaluates memory function using indices of Attention/Concentration, Immediate Verbal Memory, Immediate Visual Memory, and Delayed Recall [14]. Because in mild cognitive impairment, memory function is often lower than healthy subjects unlike other cognitive functions [23, 24], we decided to use memory function test for evaluation of cognitive function in this study. WMS-R is the comprehensive memory function test most commonly used internationally.

Plasma IL-6 levels

Blood samples drawn from a peripheral vein were collected in ethylenediaminetetraacetate (EDTA)-2Na-containing tubes and immediately centrifuged at 4 °C and 2300*g* for 10 min. The plasma components were separated and stored at − 80 °C until analysis. Plasma IL-6 levels were analyzed by an automated chemiluminescent enzyme immunoassay (Lumipulse-F, Fujirebio Corporation, Tokyo, Japan). The coefficient of variation for measurements were 2.2–3.8%, and the coefficient of correlation for measurements from a traditional enzyme-linked immunosorbent assay by the same company was 0.99 or above [25].

Statistical analysis

All analyses were performed using SPSS, version 19 (SPSS Inc., Chicago). The α level was set at $P < 0.05$ (two-tailed).

In study 2, we used the Student *t* test, Mann–Whitney *U* test, χ^2 test, or Fisher's exact test to analyze each of the demographic and medical factors for differences between cancer patients exposed to radiotherapy and those not exposed. When comparing the statistic between the radiotherapy group and the no-radiotherapy group, the Student *t* test was conducted if the homoscedasticity between the two groups was not rejected, and the Mann–Whitney *U* test was performed when rejected. When comparing frequencies using the cross table between the two groups, the χ^2 test was conducted if the proportion of the cell's expected frequency less than 5 was less than 20%, and in the case of not so, the Fisher's exact test was performed.

To determine whether differences in the WMS-R indices between cancer patients exposed to radiotherapy and those not exposed changed between study 1 and study 2, we used 2 × 2 mixed (the radiotherapy group or the no-radiotherapy group × study 1 or study 2) analysis of covariance (ANCOVA). The analysis was adjusted to control for patient education and between-study changes in age, accumulated alcohol consumption, smoking status, and body mass index (BMI), which are associated with impaired cognitive performance [26]. The main effects and group-time interactions were tested by multiple comparisons using the Bonferroni method.

To determine whether differences in plasma IL-6 levels between the cancer patients exposed to radiotherapy and those not exposed changed between study 1 and study 2, we performed a logarithmic transformation of plasma IL-6 levels, because their distribution was non-normal. This was followed by a 2 × 2 mixed [the radiotherapy group or the no-radiotherapy group × study 1 or study 2] ANCOVA. The analysis was adjusted to control for changes between studies in patient age, accumulated alcohol consumption, smoking status, and BMI. The main effects and group-time interactions were tested by multiple comparisons using the Bonferroni method.

In the present study, the type of surgery had a strong correlation with radiotherapy. Therefore, the type of surgery was excluded from the nuisance parameters because of multicollinearity (see Table 1).

The association between the amount of change in plasma IL-6 levels and that of each of the WMS-R indices between the two studies was tested using Pearson's correlation coefficient.

Results

Demographic or medical background

Table 1 shows the demographic and medical background data of each group in study 2. The study included 25 breast cancer patients exposed to adjuvant radiotherapy and 22 no-radiotherapy patients (Fig. 1). Because patients exposed to radiotherapy all chose breast conservation therapy, there was a significant difference in the type of surgery between the two groups. In addition, the proportion of smokers was significantly higher in the group exposed to radiotherapy.

Radiotherapy and changes in the WMS-R indices between the two studies

The difference in changes of each of the WMS-R indices between the two studies were compared between the radiotherapy group and the no-radiotherapy group controlling for age, education, accumulated alcohol consumption, smoking status, and BMI.

Analysis of the main effects revealed that the Attention/Concentration Index tended to be higher in study 2 ($P = 0.054$). However, there were no other significant

Table 1 Demographic or medical background information in the group of patients exposed to their radiotherapy and in the group of patients unexposed in study 2

	Received radiotherapy ($n=25$)	Not received radiotherapy ($n=22$)	P
Age, mean ± SD, years	48.8 ± 5.4	47.9 ± 4.6	0.511
Handedness: right-handedness, no. (%)	23 (92.0)	22 (100.0)	0.491
Hight, mean ± SD, cm	158.2 ± 7.0	156.6 ± 5.8	0.429
Weight, mean ± SD, kg	58.4 ± 10.4	54.6 ± 7.4	0.159
BMI, mean ± SD, kg/m^2	23.3 ± 3.3	22.2 ± 2.7	0.244
Education, mean ± SD, years	13.1 ± 1.5	13.4 ± 1.9	0.626
Smoking, no. (%)	9 (36.0)	2 (9.1)	0.041†
Accumulated alcohol consumption, mean ± SD, kg	42.4 ± 70.4	14.0 ± 27.1	0.198
Postmenopausal, no. (%)	13 (52.0)	12 (54.5)	1.000
PS: 0, no. (%)	22 (88.0)	21 (95.5)	0.611
Clinical stage: 0–I, no. (%)	13 (52.0)	8 (36.4)	0.434
Lymphnode metastasis: positive, no. (%)	4 (16.0)	7 (31.8)	0.303
Histological type, no. (%)			
Carcinoma in situ	2 (8.0)	0 (0.0)	0.491
Invasive carcinoma	19 (76.0)	20 (90.9)	0.253
Special type	4 (16.0)	2 (9.1)	0.670
Histological grade: poor, no. (%)	6 (24.0)	3 (13.6)	0.470
Surgical type: partial mastectomy, no. (%)	25 (100.0)	3 (13.6)	0.000†††
Axillary lymphadectomy, no. (%)	13 (52.0)	17 (77.3)	0.135
Days after surgery, mean ± SD, days	1257 ± 169	1222 ± 185	0.494
Radiotherapy: boost irradiation, no. (%)	10 (40.0)	NA	NA
Days after radiotherapy, mean ± SD, days	1180 ± 170	NA	NA
Chemotherapy, no. (%)	10 (40.0)	13 (59.1)	0.311
Hormonal therapy, no. (%)	5 (20.0)	9 (40.9)	0.213
Days after the first study, mean ± SD, days	959 ± 135	972 ± 158	0.763

NA not applicable, *BMI* body mass index, *PS* performance status

†Significant difference ($P<0.05$) between radiotherapy group and no-radiotherapy group

†††Significant difference ($P<0.001$) between radiotherapy group and no-radiotherapy group

findings for the main effects, group-time interactions, and the multiple comparisons analysis using the Bonferroni method (data not shown).

The Immediate Verbal Memory Index was significantly higher in study 2 ($P<0.001$), and it had a tendency to be lower in the radiotherapy group ($P=0.060$) in the main effects analysis. The index was significantly higher in study 2 for both the radiotherapy group and the no-radiotherapy group ($P=0.003$ and 0.013, respectively) and had a tendency to be lower in the radiotherapy group for study 1 ($P=0.073$) in a multiple comparisons analysis using the Bonferroni method (Fig. 2a).

There was no significant finding for the Immediate Visual Memory Index in main effects, group-time interactions, and multiple comparisons analyses using the Bonferroni method (data not shown).

The Delayed Recall Index was significantly higher in study 2 ($P<0.001$) and significantly lower in the radiotherapy group ($P=0.032$) in the main effects analysis. The index was significantly higher in study 2 for both the radiotherapy group and the no-radiotherapy group ($P<0.001$ and 0.004, respectively), significantly lower in the radiotherapy group for study 1 ($P=0.026$), and had a tendency to be lower in the radiotherapy group for study 2 ($P=0.079$) in a multiple comparisons analysis using the Bonferroni method (Fig. 2b).

Radiotherapy and changes in plasma IL-6 levels between the two studies

When the difference in changes of logarithmic-transformed plasma IL-6 levels between the two studies were compared between the radiotherapy group and the no-radiotherapy group while controlling for age, accumulated alcohol consumption, smoking status, and BMI, the levels were significantly lower in study 2 ($P<0.001$) in the main effects analysis. Furthermore, the levels were significantly lower in study 2 for the radiotherapy group ($P<0.001$) and had a tendency to be lower in study 2 for the no-radiotherapy group ($P=0.050$) in a multiple comparisons analysis using the Bonferroni method (Fig. 3).

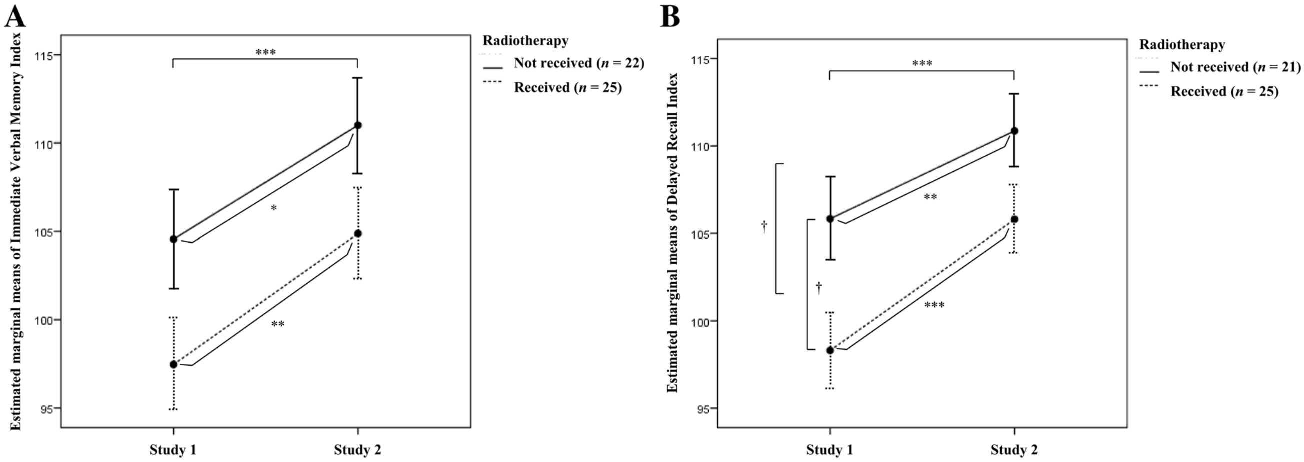

Fig. 2 Changes in the Immediate Verbal Memory Index (**a**), and in the Delayed Recall Index (**b**) of the Wechsler Memory Scale-Revised (WMS-R) test between study 1 and study 2 in patients exposed to radiotherapy and those unexposed. The dotted line indicates the radiotherapy group; the solid line indicates the no-radiotherapy group; the error bar indicates the standard error of the estimated marginal means. In **b**, one missing value in the no-radiotherapy group was excluded, because a survivor refused to perform the test domain needed for the Delayed Recall Index in the study 1. The 2×2 mixed (the radiotherapy group or the no-radiotherapy group × study 1 or study 2) analysis of covariance (ANCOVA) was controlled for education and changes between the studies in age, accumulated alcohol consumption, smoking status, and body mass index (BMI). The main effects and group-time interactions were evaluated by multiple comparisons using the Bonferroni method. **a** Index was significantly higher in study 2 ($P<0.001$) and had a tendency to be lower in the radiotherapy group ($P=0.060$) in the main effects. The index was significantly higher in study 2 for both the radiotherapy group and the no-radiotherapy group ($P=0.003$ and 0.013, respectively) and had a tendency to be lower in the radiotherapy group for study 1 ($P=0.073$) based on multiple comparisons analyses using the Bonferroni method. There was no significant difference in the index between the two groups in study 2 based on multiple comparisons analysis using the Bonferroni method or in group–time interactions. **b** Index was significantly higher in study 2 ($P<0.001$) and significantly lower in the radiotherapy group ($P=0.032$) in the main effects. The index was significantly higher in study 2 for both the radiotherapy group and the no-radiotherapy group ($P<0.001$ and 0.004, respectively), significantly lower in the radiotherapy group for study 1 ($P=0.026$), and had a tendency to be lower in the radiotherapy group for study 2 ($P=0.079$) based on multiple comparisons analyses using the Bonferroni method. There was no significant finding in group-time interactions. *Significant difference ($P<0.05$) between study 1 and study 2. **Significant difference ($P<0.01$) between study 1 and study 2. ***Significant difference ($P<0.001$) between study 1 and study 2. †Significant difference ($P<0.05$) between the radiotherapy group and the no-radiotherapy group

Change in plasma IL-6 levels and in the WMS-R indices between the two studies

When evaluating the amount of change in plasma IL-6 levels and that in the WMS-R indices between the two studies, there was a significant negative correlation between the amount of change in plasma IL-6 levels and that only in the Delayed Recall Index (Pearson's correlation coefficient = −0.327, $P=0.028$, Table 2).

Discussion

This study showed that the Immediate Verbal Memory Index of the WMS-R had a tendency to be lower and the Delayed Recall Index of the WMS-R was significantly lower in breast cancer patients exposed to adjuvant breast radiotherapy in breast conservation therapy 7 months after treatment than in breast cancer patients not exposed to radiotherapy. Most importantly, the Immediate Verbal Memory Index and the Delayed Recall Index improved significantly, and between-group differences in these two indices had nearly disappeared 3 years after treatment. Furthermore, plasma IL-6 levels decreased significantly after treatment, especially in patients exposed to radiotherapy, and the extent of improvement in the Delayed Recall Index of the WMS-R was correlated with the decrease in plasma IL-6 levels. These results suggest that after approximately 3 years, memory decline in patients treated with adjuvant breast radiotherapy in breast conservation therapy recovered to the point, where there was almost no influence of the therapy, and that a part of the improvement was associated with a decrease in plasma IL-6 levels.

As shown in Fig. 2a, b, improvement in the WMS-R indices occurred in patients not exposed to radiotherapy as well as patients exposed to radiotherapy. If our hypothesis that circulating IL-6 plays an important role in cognitive decline among cancer patients treated with radiotherapy [17] is correct, then the tendency of plasma IL-6 levels to decrease in the no-radiotherapy group (Fig. 3) could be the mechanism for this improvement.

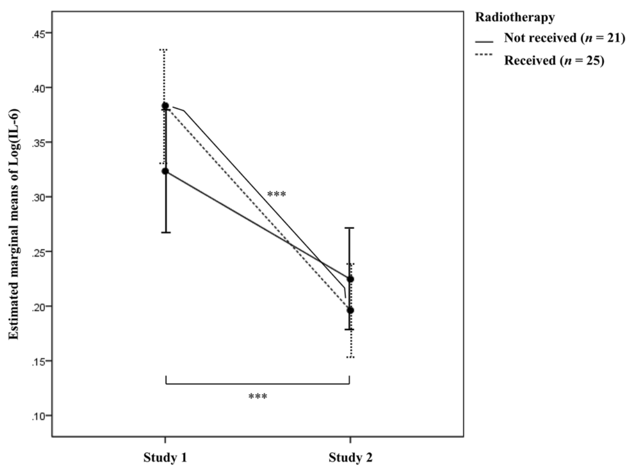

Fig. 3 Changes in logarithmic-transformed plasma interleukin (IL)-6 levels (pg/ml) between study 1 and study 2 in the radiotherapy and no-radiotherapy groups. The dotted line indicates the radiotherapy group; the solid line indicates the no-radiotherapy group; the error bar indicates the standard error of the estimated marginal means. One missing value in the no-radiotherapy group was excluded, because the blood sample of one survivor in the group was not collected in study 1. The 2×2 mixed (the radiotherapy group or the no-radiotherapy group × study 1 or study 2) analysis of covariance (ANCOVA) controlling for the changes between studies in age, accumulated alcohol consumption, smoking status, and body mass index (BMI) was used. The main effects and group-time interactions were evaluated by multiple comparisons using the Bonferroni method. The level was significantly lower in study 2 ($P<0.001$) in the main effect. The level was significantly lower in study 2 for the radiotherapy group ($P<0.001$), and had a tendency to be lower in study 2 for the no-radiotherapy group ($P=0.050$) based on multiple comparisons analyses using the Bonferroni method. There were no significant findings in other comparisons of levels, such as in the main effect between the two groups, in the multiple comparisons analyses of study 1 and 2 using the Bonferroni method, or in the group-time interaction analyses. ***Significant difference ($P<0.001$) between study 1 and study 2

Table 2 Relationship between the amount of change of the plasma IL-6 levels and that of each of the indices of WMS-R between study 1 and study 2

	Pearson's correlation coefficient	*P*
WMS-R index		
Attention/concentration[a]	− 0.198	0.187
Verbal memory[a]	− 0.191	0.204
Visual memory[a]	0.159	0.292
Delayed recall[b]	− 0.327	0.028[†]

IL-6 interleukin-6, *WMS-R* Wechsler Memory Scale-Revised

[†]Significant correlation ($P<0.05$) between the amount of change of the index and that of plasma IL-6 levels

[a]One missing value was excluded ($n=46$)

[b]Two missing values were excluded ($n=45$)

Chemotherapy and hormonal therapy may affect cognitive function [1, 3], which may have influenced the results of this study. However, it is unlikely, because Table 1 shows there was no significant difference in the proportion of patients who received chemotherapy (or hormonal therapy) between the radiotherapy and no-radiotherapy groups. Furthermore, in study 1, there was no significant difference in the WMS-R indices between patients who received chemotherapy (or hormonal therapy) and those who did not (data not shown).

Two studies have investigated long-term cognitive function in cancer patients who had radiotherapy in areas other than the brain and cancer patients who did not have radiotherapy. One cross-sectional study assessed the cognitive function of testicular cancer patients approximately 3 years after treatment using several neuropsychological tests. They found no significant difference between the average scores of patients who had undergone only surgery and patients exposed to adjuvant radiotherapy [6]. A longitudinal study showed that breast cancer patients treated with and without adjuvant breast radiotherapy all showed improvements in immediate memory and delayed memory based on the measurement of several cognitive functions 18 and 36 months after diagnosis [27]. These finding are generally consistent with results of the present study. However, the second study showed no significant differences in memory indices between the radiotherapy and no-radiotherapy groups at the first assessment [27], which differs from this study. This may be because subjects in the study from Zheng et al. [27] included more elderly people than this study. Thus, variances in the memory indices in their study might be larger than in our study, where subject selection was limited to a younger patient population to minimize factors other than cancer therapy that might affect memory function, such as the effect of aging on the brain.

A cross-sectional study used a battery of neuropsychological tests to assess the cognitive function of breast cancer survivors 65 years or older more than 10 years after the completion of treatment. They showed that survivors who had received local therapy with or without radiotherapy scored lower than survivors who received adjuvant chemotherapy on several cognitive domains, including verbal learning and short-term retention [13]. A longitudinal study over at least 10 years may be needed to explore the association between radiotherapy and cognitive function more deeply.

Studies that investigated levels of proinflammatory cytokines after radiotherapy have suggested that the elevation of proinflammatory cytokines could persist for up to 1 year after treatment [17, 28, 29]. However, our study is the first to investigate levels of proinflammatory cytokines more than 2 years after radiotherapy. Our study suggests that the elevation of proinflammatory cytokines might not persist more than 3 years after adjuvant breast radiotherapy in breast cancer survivors.

In this study, changes in the Delayed Recall Index of the WMS-R were correlated with changes in plasma IL-6 levels between the two studies. This is consistent with our previous cross-sectional study of breast cancer survivors approximately 7 months after treatment, which showed that radiotherapy exerted a significant indirect effect on the Delayed Recall Index of the WMS-R through plasma IL-6 levels [17]. These results strengthen our hypothesis that the association between radiotherapy and memory decline might be explained partially by hippocampal inflammation caused by elevated plasma IL-6 levels [17]. As we mentioned before [17], it has been suggested that delayed recall memory is associated with the hippocampus [30, 31]. Furthermore, an animal study suggested that peripheral IL-6 signaled the brain and induced inflammation in the hippocampus [32].

It is pointed out that a reduction in a neurocognitive test does not necessarily mean clinically meaningful cognitive decline [33]. Certainly, since the WMS-R indices are 100 on average and standard deviation 15 [14, 15], differences of each index between the two groups in this study can be regarded as not clinically meaningful differences if they are taken only by numerical values. However, according to McDonald et al.'s functional MRI study [34], significant frontal lobe hyperactivation to support working memory was found in breast cancer patients compared to healthy subjects, although there was no significant difference in n-back task performance between the two groups. Even though the numerical differences of each index between the radiotherapy group and the no-radiotherapy group are small, there may be clinically meaningful cognitive decline at overloading beyond daily living activities in the patients soon after adjuvant breast radiotherapy, because their reserve memory capacity has declined.

This study shows that cognitive decline might be caused by adjuvant breast radiotherapy and that cognitive recovery occurs within a few years of treatment, which could influence cancer patients' decisions on treatment options: that is, after radiotherapy, a temporary decrease in memory function is observed, so it is necessary to consider support for patients received radiotherapy, but after 3 years, a significant difference in memory function between patients received radiotherapy and not received disappears, so breast cancer patients can receive radiotherapy with relative confidence. In combination with our previous study [17], these results suggest that peripheral IL-6 is involved in cognitive decline associated with adjuvant breast radiotherapy and its recovery process. These findings contribute to clarifying the mechanisms of cognitive decline associated with adjuvant breast radiotherapy and to the development of intervention and prevention for cognitive decline.

There were some limitations to the present study. (1) Because this was not an interventional study, the causality between variables is not guaranteed. There is no indication that the difference in cognitive function between the two groups is due to the difference in the plasma IL-6 concentration, nor is there indication that radiation therapy raises the plasma IL-6 concentration. (2) Because this study did not include data before or during treatment, the relationship between the dynamics of variables and the course of cancer, including its treatment, remains unclear. (3) Because there was considerable variance in time span between the end of therapy and data collection points, the variance of measurements may be larger than if all searches had been performed at the same time after the end of therapy. This reduced the power of tests in the study. (4) The sample size was small, which might reduce the power of tests. (5) Because the follow-up period was short, the long-term influence of radiotherapy is unknown. (6) Because subjects in the present study were restricted to comparatively young breast cancer patients, results should be generalized with caution. (7) Similarly, we should be careful about generalizing results to patients who were excluded by the exclusion criteria. (8) Neuropsychological tests other than the WMS-R were not conducted. (9) Factors other than plasma IL-6 that might be associated with cognitive decline after radiotherapy, such as other proinflammatory cytokines, fatigue, anemia, and chronic pain, were not considered. (10) We selected patient education and between-study changes in age, accumulated alcohol consumption, smoking status, and BMI as confounding factors. However, factors that might have elevated plasma IL-6 levels, such as medication, infection, and residual cancer, were not considered in the present study. (11) Because data were collected a long time ago, this study may be slightly outdated. (12) The clinical meaning of the differences of the WMS-R indices between the two groups in this study is unknown.

Conclusions

The decline of memory in breast cancer patients soon after adjuvant breast radiotherapy had largely recovered by approximately 3 years after treatment, and a decrease of plasma IL-6 levels might be involved in the recovery process.

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Compliance with ethical standards

Conflict of interest Author Uchitomi Y. received research grants from the Japanese Ministry of Health, Labour and Welfare for the submitted work. Author Inagaki M. declares that he has received grants from The Ministry of Health, Labour and Welfare, Japan, the Ministry of Education, Science, and Technology, Japan, Novartis Pharma, and Okayama Health Foundation. Author Inagaki M. received lecture fees from Pfizer Japan Inc., Mochida Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Daiichi-Sankyo Co., Ltd., Meiji Seika Pharma Co. Ltd., and Takeda Pharmaceutical Co., Ltd. outside the submitted work. Author Inagaki M. received royalties from Nippon Hyoron Sha Co., Ltd., Nanzando Co., Ltd., Seiwa Shoten Co., Ltd., Igaku-shoin Ltd., and Technomics, Inc., outside the submitted work. Author Matsuoka Y. received lecture fees from Morinaga Milk Industry Co. Ltd., Eli Lilly Japan K. K., and Takeda Pharmaceutical Company Ltd.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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