

Table 1. Demographics and clinical characteristics of all participants

Characteristics	All		≥65 years		<65 years		P
	N	%	N	%	N	%	
No.	807	100.0	243	30.1	564	69.9	
Age	Mean: 57.6 (SD = 11.6) Median: 57 (range, 23–86)		Mean: 71.3 (SD = 4.7) Median: 71 (range, 65–86)		Mean: 51.7 (SD = 8.3) Median: 52 (range, 23–64)		
Sex							
Male	433	53.7	219	90.1	214	37.9	0.00
Female	374	46.3	24	9.9	350	62.1	
Marital status							
Married	640	79.3	221	90.9	419	74.3	0.00
Education							
>12 years	513	63.5	139	57.2	374	66.3	0.93
Employment status							
Full-time/part-time	365	45.2	49	20.2	316	56.0	0.00
Cancer site							
Breast	237	29.4	8	3.3	229	40.6	0.00
Prostate	126	15.6	102	42.0	24	4.3	
Colon	58	7.2	20	8.2	38	6.7	
Stomach	48	5.9	22	9.1	26	4.6	
Lung	34	4.2	13	5.3	21	3.7	
Bladder	31	3.8	12	4.9	19	3.4	
Uterus	31	3.8	0	0.0	31	5.5	
Hematopoietic system	29	3.6	5	2.1	24	4.3	
Liver	23	2.9	10	4.1	13	2.3	
Rectum	22	2.7	10	4.1	12	2.1	
Esophagus	15	1.9	7	2.9	8	1.4	
Head and neck	12	1.5	1	0.4	11	2.0	
Kidney	10	1.2	5	2.1	5	0.9	
Ovary	10	1.2	0	0.0	10	1.8	
Pancreas	9	1.1	6	2.5	3	0.5	
Biliary system	5	0.6	2	0.8	3	0.5	
Undiagnosed	9	1.1	3	1.2	6	1.1	
Others	98	12.1	17	7.0	81	14.4	
Clinical stage							
Recurrence/metastasis	213	26.4	66	27.2	147	26.1	0.75
History of anti-cancer treatment ^a							
Surgery	678	84.0	175	72.0	503	89.2	0.00
Chemotherapy	384	47.6	94	38.7	290	51.4	0.00
Hormonal therapy	318	39.4	83	34.2	235	41.7	0.05
Radiation therapy	293	36.3	64	26.3	229	40.6	0.00

Continued

Table 1. Continued

Characteristics	All		≥65 years		<65 years		P
	N	%	N	%	N	%	
ECOG performance status							
0	453	56.1	144	59.3	309	54.8	0.44
1	323	40.0	88	36.2	235	41.7	
2	25	3.1	9	3.7	16	2.8	
3	5	0.6	2	0.8	3	0.5	
4	1	0.1	0	0.0	1	0.2	
Duration since diagnosis							
<6 months	45	5.6	19	7.8	26	4.6	0.61
≥6 months to <1 year	112	13.9	32	13.2	80	14.2	
≥1 year to <2 years	190	23.5	50	20.6	140	24.8	
≥2 years to <5 years	288	35.7	92	37.9	196	34.8	
≥5 years	172	21.3	50	20.6	122	21.6	
EORTC QLQ-C30	Mean: 62.2 (SD = 22.7)		Mean: 64.7 (SD = 22.3)		Mean: 61.2 (SD = 22.8)		0.04
Global health status score	Median: 66.7 (range, 0–100)		Median: 66.7 (range, 0–100)		Median: 66.7 (range, 0–100)		

ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.

^aMultiple choice.

symptoms ($P < 0.01$), constipation ($P < 0.01$), psychological symptoms ($P = 0.01$) and daily living ($P = 0.01$), after adjusting for age, sex, marital status, clinical stage, duration since diagnosis, employment status and educational level. As the coefficient of determination (R^2) in this survey was 0.31, we could not sufficiently estimate QOL from the concerns of elderly cancer patients.

DISCUSSION

As to the elderly cancer patients' concerns, about half of them had difficulty with self-management, psychological symptoms and medical information. In terms of self-management, it appears that they would like to decide their own treatment and they are likely to do something on their own without relying on others. As for psychological symptoms and medical information, a previous study reported that the prevalence of unmet needs among cancer patients aged over 70 years was high in the Psychological and Health system and Information domains and slightly >50% of them appeared to be unsatisfied (26), which is consistent with our findings. This indicates that they have not obtained sufficient information for living with medical treatment, even though cancer care support and information service centers play an important role in providing cancer patients and their families with useful information such as how to deal with side effects at home, available treatment or treatment options and interpersonal communication. The reasons for this are that many cancer patients are still not

familiar with the centers (31), or older patients with cognitive dysfunction might not be able to approach the centers because of their inadequate health literacy (32), so it may be necessary to simply remind them about the centers. With regard to psychological symptoms of older cancer patients such as insomnia, medical staff must handle this properly, for example, by regularly making assessments in clinical practices and objectively asking the families or visiting nurses about the patient's home life (33). Moreover, it would be necessary for oncologists to receive training on the primary approach for dealing with psychological symptoms of older cancer patients (34).

With respect to the comparison between elderly and younger cancer patients' concerns, a previous study reported that the elderly had less trouble with psychological symptoms and social functioning than younger cancer patients (25), and another study suggested that the elderly showed lower physical functioning scores in the QOL domains compared with the younger cancer patients (26), and these results are in agreement with our study. The reason for this seems to be that older cancer patients in Japan receive their pension or financial support from their children, which alleviates concerns about money. In addition, since they have finished raising their children and are retired from work, they have fewer demands on their time and resources compared with younger cancer patients (35,36). Since younger individuals still have work and family responsibilities, they seem to have more difficulty with psychosocial problems, financial problems, social functioning and so on (35,36). Regarding QOL, it is generally considered

Table 2. Prevalence of concerns^a and differences between elderly (≥65 years) and younger (<65 years) cancer patients—univariate analysis

Concerns	All		≥65 years		<65 years		P
	n = 807	%	n = 243	%	n = 564	%	
Physical symptoms (having one or more concerns in the following five items)	123	15.2	39	16.0	84	14.9	0.68
Loss of weight	51	6.3	22	9.1	29	5.1	0.04
Loss of appetite	49	6.1	16	6.6	33	5.9	0.69
Dyspnea	43	5.3	9	3.7	34	6.0	0.18
Diarrhea	35	4.3	12	4.9	23	4.1	0.58
Nausea and/or vomiting	21	2.6	6	2.5	15	2.7	0.88
Psychological symptoms (having one or more concerns in the following five items)	391	48.5	114	46.9	277	49.1	0.57
Insomnia	257	31.8	84	34.6	173	30.7	0.28
Being tired and/or feeling sluggish	226	28.0	51	21.0	175	31.0	0.00
Not being insightful	146	18.1	31	12.8	115	20.4	0.01
Feeling down and/or depressed	123	15.2	21	8.6	102	18.1	0.00
Feeling agitated and/or nervous	71	8.8	16	6.6	55	9.8	0.15
Daily living (having one or more concerns in the following six items)	241	29.9	51	21.0	190	33.7	0.00
Concerns about medical fees	179	22.2	35	14.4	144	25.5	0.00
Inability to do job	133	16.5	18	7.4	115	20.4	0.00
Inability to do housework and/or to take care of family	69	8.6	12	4.9	57	10.1	0.02
Concerns about nursing care insurance	66	8.2	24	9.9	42	7.4	0.25
Inability to take care of oneself	58	7.2	11	4.5	47	8.3	0.06
Having no means of going to hospital	37	4.6	7	2.9	30	5.3	0.13
Self-management (having one or more concerns in the following three items)	494	61.2	135	55.6	359	63.7	0.03
Want to know what I can do for curing of disease by myself	423	52.4	110	45.3	313	55.5	0.01
Want to know what I can do in poor health	414	51.3	112	46.1	302	53.5	0.05
Want to know what I can do to take care of myself	334	41.4	85	35.0	249	44.1	0.02
Medical information (having one or more concerns in the following five items)	373	46.2	103	42.4	270	47.9	0.15
Want to know about other treatments	289	35.8	83	34.2	206	36.5	0.52
Want to know about other hospitals	235	29.1	73	30.0	162	28.7	0.71
Unable to understand explanation about disease and/or treatment	149	18.5	54	22.2	95	16.8	0.07
Unable to communicate well with doctor	140	17.3	42	17.3	98	17.4	0.98
Want to know about fertility	66	8.2	15	6.2	51	9.0	0.17
Pain							
Painful	142	17.6	41	16.9	101	17.9	0.72
Constipation							
Constipated	126	15.6	27	11.1	99	17.6	0.02

^aRated 3 or 4 on the four-point Likert scale on each item of the comprehensive concerns assessment tool.

to be lower in elderly compared with younger cancer patients, because the physical functions of elderly patients are weakened and they tend to have more comorbidities than younger patients (37), and the severity of comorbidities adversely affects QOL (38). In a previous study, however, the QOL of elderly cancer patients was the same degree as in younger cancer patients after adjustment for PS (39), and another study reported that QOL was not significantly different between

elderly and younger cancer patients (26). In our study, QOL was higher in the elderly than in the younger cancer patients. One of the reasons for this seems to be that older cancer patients are better able to adapt to severe situations compared with younger patients, although the elderly are more strongly affected by cancer itself or the treatment (40,41).

Regarding the association between concerns and QOL of elderly cancer patients, we found that there is a significant

Table 3. Association between elderly cancer patients' concerns and quality of life^a—multiple regression analysis^b

Concerns	Coefficient (<i>B</i>)	Standardizing coefficient (β)	<i>T</i>	<i>P</i>	Partial <i>R</i> ²
Physical symptoms	-11.77	-0.19	-3.23	0.00	0.14
Psychological symptoms	-6.70	-0.15	-2.53	0.01	0.11
Daily living	-8.34	-0.15	-2.53	0.01	0.11
Self-management	-4.67	-0.10	-1.61	0.11	0.08
Medical information	-3.44	-0.08	-1.20	0.23	0.06
Pain	-12.23	-0.21	-3.64	0.00	0.11
Constipation	-11.96	-0.17	-3.07	0.00	0.05
					Total <i>R</i> ² = 0.31

^aGlobal health status score of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.

^bAdjusted for age, sex, marital status (two groups), clinical stage (two groups), duration since diagnosis (three groups), employment status (two groups) and educational level (two groups).

association, but self-management and medical information, which are highly prevalent concerns among the elderly subjects, do not significantly contribute to QOL. Nevertheless, elderly subjects have great difficulty with these two subscales. On the other hand, the other five subscales that are significantly associated with QOL do not pose much difficulty for the elderly cancer patients. Therefore, we consider it important to comprehensively intervene in their multiple concerns. Several previous studies have suggested that the more adequate information cancer patients obtain, the more satisfied they are (20), and the more able they are to adapt to their psychological and emotional states (42); therefore the QOL of elderly cancer patients is expected to improve with multifaceted intervention and the provision of sufficient information about their concerns.

The present study has several limitations. First, there was the potential for selection bias in that the subjects were outpatients, over 90% of them were diagnosed >6 months earlier, ~90% of them were male and 40% were prostate cancer, and moreover, they were all able to participate in this internet survey. Based on these factors, it was estimated that most of the subjects were physically and mentally stable, and they had little cognitive dysfunction and high health literacy because they were capable enough to use the internet. As more men than women use the internet in general, it is believed that most subjects in this study were men. That is to say, subjects in this study were not representative elderly cancer patients in Japan. Further investigations need to be conducted other than through the internet, such as by interviews with not only outpatients but inpatients in clinical sites, in the future. In addition, we should point out that there was a possibility that most of the study subjects had normal cognitive function. In fact, the number of cognitive deficit patients in Japan was estimated to be 4 620 000 in 2013 (43), and many elderly cancer patients have cognitive impairment. Therefore, we should evaluate the cognitive function of elderly cancer patients first, positively detect their concerns including concerns of patients with cognitive dysfunction by using assessment tool like

comprehensive geriatric assessment (CGA) after that, and examine whether we can clarify their concerns.

Second, the CCAT questionnaire for cancer patients' concerns proved to be valid and reliable in a previous study, but it is not specific to elderly cancer patients (28). Finally, since our investigation was cross-sectional in design, we cannot conclude the causal relationship between patients' concerns and their QOL. This problem needs further investigation in a longitudinal study; for example, we should reinvestigate after an interval of several months. In addition, further research needs to focus on various patients and clinical characteristics such as age, sex, cancer type, PS and so forth.

Despite these limitations, this study has several strengths. To our knowledge, it is the first study to comprehensively assess elderly cancer patients' concerns in Japan; in doing so, we could understand the characteristics of elderly cancer patients' concerns in detail. The response rate of this study was 80%, which was considered to be relatively high.

In today's aging society, multidisciplinary intervention and training for healthcare professionals will be required to deal with different and complex concerns of elderly patients with cancer. We should also make an active effort to investigate concerns of elderly cancer patients who do not complain, predict their possible problems such as upset, and intervene in them. This will make it possible to provide them with optimal oncological care to improve their QOL.

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Conflict of interest statement

None declared.

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Comprehensive Assessment of Cancer Patients' Concerns and the Association with Quality of Life

Minori Yokoo¹, Tatsuo Akechi², Tomoko Takayama³, Atsuya Karato⁴, Yuki Kikuuchi⁵, Naoyuki Okamoto⁶, Kayoko Katayama⁶, Takako Nakanotani¹ and Asao Ogawa^{1,*}

¹Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center East Hospital, Kashiwa, Chiba, ²Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City Graduate School of Medical Sciences, Nagoya, Aichi, ³Cancer Information Service Division, Center for Cancer Control and Information Service, National Cancer Center, Tsukiji, Tokyo, ⁴Patient Support Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Ariake, Tokyo, ⁵Department of Patient and Family Support, Shikoku Cancer Center, Matsuyama, Ehime and ⁶Cancer Prevention and Cancer Control Division, Kanagawa Cancer Center Research Institute, Yokohama, Kanagawa, Japan

*For reprints and all correspondence: Asao Ogawa, Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center East Hospital, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan.
E-mail: asogawa@east.ncc.go.jp, asogawa.ncche@gmail.com

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Objective: Comprehensive assessment of perceived concerns can be used to guide supportive care appropriate to individual cancer patients. This study sought to determine the prevalence of cancer patients' concerns and the degree to which these concerns contribute to patients' quality of life.

Methods: Participants were patients with all types of cancer, who completed an Internet survey questionnaire regarding comprehensive concerns about physical, psychological, psychosocial and economic aspects of having cancer. The questionnaire was based on the newly developed Comprehensive Concerns Assessment Tool and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

Results: We obtained complete data from 807 patients. Factors related to 'self-management' concerns were the most common (61.2%), followed by concerns about 'psychological symptoms' (48.5%), 'medical information' (46.2%), 'daily living' (29.9%), 'pain' (17.6%), 'constipation' (15.6%) and other 'physical symptoms' (15.2%). Multiple regression analysis revealed that all concerns except those about 'medical information' significantly contributed to quality of life.

Conclusions: Cancer patients' concerns were shown to be multidimensional and significantly associated with quality of life. Thus, assessment of patients' concerns should be multidimensional in nature, and a multidisciplinary care team should help patients improve their quality of life.

Key words: quality of life – patient care team – social support – needs assessment

INTRODUCTION

Cancer patients face various symptoms and problems in daily life that involve the physical, psychological and socio-economic effects of treatment complications and extended survival.

Numerous symptoms and problems must be managed, including pain (1), distress (2), insufficient social support (3)

and treatment location (4). Almost all of these are reported to be factors significantly related to quality of life (QOL) (5–8). Recent studies have also dealt with a wide range of cancer patients' care needs, and having many needs is one of the factors reported to worsen cancer patients' QOL (9,10). These findings suggest that medical professionals should focus on the various symptoms and problems that cancer patients face in order to better support them.

However, past studies have shown that patients' symptoms and problems are often not appropriately addressed by medical professionals (11–13). Also, patients frequently report that they have not received the support they needed during treatment and follow-up (14–16). These problems result in part from a lack of appropriate, brief assessment tools of symptoms and problems, which leads to insufficient guidance for effective and efficient care. Cancer patients experience one or more symptoms and several problems simultaneously, and how they feel and respond to these symptoms and problems differs between individuals. Therefore, their symptoms and problems must be assessed comprehensively from the patient's viewpoint as 'perceived concerns'. The comprehensive assessment of perceived concerns can offer some advantages. First, patient-important outcomes can be directly assessed. Second, it can help with the prioritization of necessary care by more specifically indicating the support resources needed to improve the patient's QOL. However, as mentioned above, few tools are available for such assessment.

The framework of this study is based on the premise of appropriate supportive care, which is defined as care based on patients' perceived concerns to improve QOL. The study objectives were 3-fold: to develop a questionnaire that comprehensively assesses cancer patients' concerns; to examine the prevalence of concerns in cancer patients; and to explore the contribution of concerns to cancer patients' QOL.

PATIENTS AND METHODS

SUBJECTS

Subjects were patients on the registered cancer patient list of Intage Inc., Tokyo, Japan, a company that specializes in Internet surveys and recruits monitors from among Internet users by advertisements placed on various websites in Japan. From the registered monitors, we selected patients that matched the eligibility criteria of this study. Inclusion criteria were persons aged 20 years or older, who were diagnosed with cancer (any primary cancer site, all stages and at any time point after diagnosis) and had visited a hospital for cancer treatment within the past year. Exclusion criteria were patients who were either healthcare professionals or who worked in the areas of media, advertisement or web investigation. The reward for responding to the questionnaire was given according to a point system. Respondents could save points if they completed all questions. They could then exchange points for money or save their accumulated points.

This study was approved by the Institutional Review Board and Ethics Committee of the National Cancer Center, Japan. Because this was an Internet survey, responding to the survey constituted informed consent to participate in this study.

PROCEDURE

In this cross-sectional study, the survey was conducted over the Internet between 22 and 24 October 2012. In total, 1009

eligible cancer patients were asked to complete the self-administered questionnaires.

We excluded data when answers were transmitted repeatedly from the same terminals, when attributes were different from those of the answer or when the answer time was inappropriate. Missing values were not possible because the web investigation was structured to require participants to answer all of the questions.

INSTRUMENTS

CANCER PATIENTS' CONCERNS

We developed a self-reported questionnaire, which we named the Comprehensive Concerns Assessment Tool (CCAT), to comprehensively assess the concerns of patients across all types of cancer throughout all phases of the cancer experience. After reviewing existing patient and family support sheets compiled by the National Cancer Center Japan and a needs assessment tool [Short-form Supportive Care Needs Survey Questionnaire: SCNS-SF34-J (17)], we selected 50 items encompassing physical, psychological and psychosocial concerns of cancer patients. We then selected 26 of these items using a focus group of experts that included psycho-oncologists, nurses and medical social workers. We explored subcategories by factor analysis and examined the internal consistency of each subscale.

On the CCAT, respondents were asked to indicate the level or frequency of their concerns over the last week. The four response options were (i) no concern, (ii) mild concern (1 or 2 days a week), (iii) moderate concern (more than half the week) and (iv) serious concern (every day).

The CCAT will be published on the homepage (<http://pod.ncc.go.jp>).

QUALITY OF LIFE

We assessed patient QOL using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C 30 (18). The EORTC QLQ-C 30 consists of 30 items on self-reported aspects of QOL in cancer patients. The validity and reliability of the Japanese version of the EORTC QLQ-C 30 had been confirmed (17). In this study, we used the Global Health Status score ranging from 0 to 100, with higher scores representing higher QOL.

SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

We used an *ad hoc* self-administered questionnaire to obtain data on the patients' socio-demographic status, including marital status, employment status and educational level. We also obtained other medical information, including primary cancer site, time since diagnosis and presence of recurrence or metastasis from this questionnaire.

STATISTICAL ANALYSIS

First, we evaluated factor validity of the CCAT using factor analysis with Promax rotation. The number of factors was determined by Keiser's criterion (eigenvalue of 1.0 or greater). To evaluate the internal consistency of each factor, we calculated Cronbach's alpha coefficients. We calculated the prevalence of each subscale and each item to clarify the prevalence of concerns. We defined 'presence of each concern subscale' as the presence of one or more items receiving a score of 3 or 4 on each factor, and 'presence of each concern item' as an item receiving a score of 3 or 4.

Next, to explore the contribution of each concern to cancer patients' QOL, we conducted multiple regression analysis, where the dependent variable was the Global Health Status score of the EORTC QLQ-C 30 and the independent variables were the presence of each concern subscales. In this analysis, age, sex, marital status (married or other), occupation (employed or unemployed), educational level (college graduate or other), time since diagnosis (<6 months, 6 months to <5 years and >5 years) and presence of recurrence or metastasis were entered as independent variables for adjustment, with reference to past studies.

A *P* value of <0.05 was considered statistically significant, and all reported that *P* values were two tailed. All statistical analysis was conducted using SPSS 21 version software for Windows (IBM Inc., 2012).

RESULTS

PATIENT CHARACTERISTICS

Complete data were available for 807 patients. The response rate was 80.0%. Table 1 shows the participants' socio-demographic and clinical characteristics. Mean (\pm SD) and median age of the study population were 57.6 (\pm 11.6) and 57.0 years, respectively. The male–female ratio was about 1 : 1. Approximately 80% were married, and ~60% had a graduate education. As for cancer site, most had breast cancer (~30%), followed by prostate cancer (15.6%) and colorectal cancer (9.9%). A few subjects had lung, stomach or liver cancer. Most subjects were survivors whose time since diagnosis fell within 2–5 years, and 5.6% of participants were in the early stages of cancer treatment. Mean (\pm SD) and median (range) of the Global Health Status score of EORTC QLQ-C 30 were 62.2 (\pm 22.7) and 66.7 (0–100), respectively.

FACTOR STRUCTURE OF PERCEIVED CONCERNS

Factor analysis indicated a five-factor solution. Table 2 shows the final factor pattern, factor name and internal consistency of each factor (Cronbach's alpha coefficient).

The first six items comprising concerns related to daily living during cancer treatment showed significant loading onto Factor 1. The next five items related to concerns about

Table 1. Characteristics of the study participants (*n* = 807)

Characteristics	No. of participants	%
Age (years)		
Mean: 57.6 (SD = 11.6), median: 57.0, range: 23–86		
Sex		
Man	433	53.7
Woman	374	46.3
Marital status		
Married	640	79.3
Unmarried	90	11.2
Separated/divorced	55	6.8
Widow/widower	22	2.7
Occupation		
Unemployed	442	54.8
Employed	365	45.2
Educational level		
Junior high school	13	1.6
High school	281	34.8
Technical school	60	7.4
Junior college	97	12.0
College	331	41.0
Graduate school	25	3.1
Primary cancer site		
Breast	237	29.4
Prostate	126	15.6
Colon	58	7.2
Stomach	48	5.9
Lung	34	4.2
Urinary bladder	31	3.8
Uterus	31	3.8
Hematologic cancer	29	3.6
Liver	23	2.9
Rectum	22	2.7
Esophagus	15	1.9
Head and neck	12	1.5
Kidney	10	1.2
Ovary	10	1.2
Pancreas	9	1.1
Gall bladder	5	0.6
Not yet diagnosed	9	1.1
Others	98	12.1
Time since diagnosis		
<6 months	45	5.6
6 months to <1 year	112	13.9

Continued

Table 1. Continued

Characteristics	No. of participants	%
1 year to <2 years	190	23.5
2 years to <5 years	288	35.7
>5 years	172	21.3
Recurrence/metastasis		
Yes	213	26.4
No	594	73.6

medical information loaded onto Factor 2. Five items including ‘being tired and/or feeling sluggish’ related to concerns about psychological symptoms loaded onto Factor 3. Three items related to concerns about self-management loaded onto Factor 4, and five other items related to concerns about physical symptoms loaded onto Factor 5. Items for ‘pain’ and ‘constipation’ did not belong to any factor. ‘Pain’ might reflect not only physical symptoms but also various aspects of cancer patients’ concerns. ‘Constipation’ might not have been a symptom related to the kind of cancer and cancer treatment found in this study population. However, pain and constipation are very common and important symptoms for all cancer patients so we included these two items as individual subscales in the other analysis in this study. Factors 1–4 showed good internal consistency ($\alpha > 0.70$), and Factor 5 showed moderate internal consistency ($\alpha = 0.67$).

PREVALENCE OF PERCEIVED CONCERNS

Table 3 shows the prevalence of each subscale and item. The subscale related to concerns about ‘self-management’ was the most common (61.2%), followed by ‘psychological symptoms’ (48.5%), ‘medical information’ (46.2%), ‘daily living’ (29.9%), ‘pain’ (17.6%), ‘constipation’ (15.6%) and ‘physical symptoms’ (15.2%). Among the items, ‘Want to know what I can do for curing the disease by myself’ was the most common, followed by ‘Want to know what I can do in poor health’, and ‘Want to know what I can do to take care of myself’. The prevalence of these items was over 40% and all of them belonged to the ‘self-management’ subscale. Half of the subjects had ‘psychological concerns’ and one-third of subjects suffered from ‘insomnia’ and ‘being tired and/or feeling sluggish’. About half of the subjects also had some difficulties with ‘medical information’ and wanted to know about other treatments and hospitals. However, the prevalence of items about communication with medical staff, such as being ‘unable to communicate well with doctor’, was <20%. About one-third of subjects had some concerns about ‘daily living’. Comparatively, more subjects had economic concerns such as ‘concerns about medical costs’ and an ‘inability to work’. The prevalence of the subscale related to concerns about ‘physical symptoms’ was <20% as was those for ‘pain’ and ‘constipation’.

Table 2. Factor pattern for the questionnaire items and reliability data

	Item number in the questionnaire and item	Factor loadings ^a
Factor 1	Daily living (six items); Cronbach’s $\alpha = 0.84$	
	C5 Concerns about nursing care insurance	0.78
	C3 Inability to take care of oneself	0.73
	C2 Inability to do housework and/or to take care of family	0.72
	C6 Having no means of going to hospital	0.72
	C4 Concerns about medical costs	0.66
	C1 Inability to do job	0.62
Factor 2	Medical information (five items); Cronbach’s $\alpha = 0.85$	
	D2 Unable to communicate well with doctor	0.94
	D1 Unable to understand explanation about disease and/or treatment	0.92
	D3 Want to know about other hospitals	0.63
	D8 Want to know about fertility	0.47
	D4 Want to know about other treatments	0.44
Factor 3	Psychological symptoms (five items); Cronbach’s $\alpha = 0.79$	
	B2 Feeling down and/or depressed	0.98
	B3 Feeling agitated and/or nervous	0.72
	B4 Being not insightful	0.68
	B1 Insomnia	0.47
	A3 Being tired and/or feel sluggish	0.37
Factor 4	Self-management (three items); Cronbach’s $\alpha = 0.91$	
	D6 Want to know what I can do for curing the disease by myself	0.96
	D7 Want to know about what I can do in poor health	0.85
	D5 Want to know what I can do to take care of myself	0.71
Factor 5	Physical symptoms (five items); Cronbach’s $\alpha = 0.67$	
	A2 Loss of appetite	0.66
	A8 Loss of weight	0.55
	A5 Nausea and/or vomiting	0.50
	A7 Dyspnea	0.50
	A6 Diarrhea	0.47
Factor 6	Pain (one item) ^b	
	A1 Painful	
Factor 7	Constipation (one item) ^b	
	A4 Constipated	

Loading after Promax rotation ($n = 807$).

^aFactor loadings for the items where a cross-loading of >0.30 were demonstrated.

^b[Pain] and [constipation] belonged to neither factor in the first factor analysis.

ASSOCIATION BETWEEN PERCEIVED CONCERNS AND QOL

The seven subscales are considered to be independent of each other as multicollinearity was ruled out because tolerances were sufficiently large (0.77–0.93) and variance inflation

Table 3. The prevalence of concerns of the study participants (*n* = 807)

Concerns ^a	No. of participants	%
Physical symptoms		
Having one or more concerns in the following items	123	15.2
1 Loss of weight	51	6.3
2 Loss of appetite	49	6.1
3 Dyspnea	43	5.4
4 Diarrhea	35	4.4
5 Nausea and/or vomiting	21	2.6
Psychological symptoms		
Having one or more concerns in the following items	391	48.5
1 Insomnia	257	31.9
2 Being tired and/or feeling sluggish	226	28.1
3 Being not insightful	146	18.1
4 Feeling down and/or depressed	123	15.2
5 Feeling agitated and/or nervous	71	8.8
Daily living		
Having one or more concerns in the following items	241	29.9
1 Concerns about medical costs	179	22.2
2 Inability to work	133	16.5
3 Inability to do housework and/or to take care of family	69	8.5
4 Concerns about nursing care insurance	66	8.2
5 Inability to take care of oneself	58	7.1
6 Having no means of going to hospital	37	4.6
Self-management		
Having one or more concerns in the following items	494	61.2
1 Want to know what I can do for curing the disease by myself	423	52.4
2 Want to know what I can do in poor health	414	51.3
3 Want to know what I can do to take care of myself	334	41.4
Medical information		
Having one or more concerns in the following items	373	46.2
1 Wanting to know about other treatments	289	35.8
2 Wanting to know about other hospitals	235	29.1
3 Unable to understand explanation about disease and/or treatment	149	18.4
4 Unable to communicate well with doctor	140	17.3
5 Wanting to know about fertility	66	8.2
Pain		
1 Painful	142	17.6
Constipation		
1 Constipated	126	15.6

^aRated three or more on the four-point Likert scale on each questionnaire item.

factors were sufficiently small (1.07–1.30). Except for the subscale related to concerns about ‘medical information’, each subscale contributed to QOL with meaningful variables

Table 4. Concerns associated with the participant's quality of life (QOL)^a in the multiple regression analysis^b

Participant's concerns ^c	Coefficient (<i>B</i>)	Standardized coefficient (<i>β</i>)	<i>t</i>	<i>P</i>	Partial <i>R</i> ² (rank)
Physical symptoms	−11.07	−0.18	−5.46	0.00	0.06 (2)
Psychological symptoms	−10.69	−0.24	−7.25	0.00	0.09 (1)
Daily living	−6.84	−0.14	−4.14	0.00	0.05 (4)
Self-management	−3.72	−0.08	−2.39	0.02	0.03 (5)
Medical information	−2.03	−0.05	−1.35	0.18	0.02 (7)
Pain	−10.77	−0.18	−5.87	0.00	0.06 (2)
Constipation	−5.07	−0.08	−2.67	0.01	0.03 (5)
					Total <i>R</i> ² = 0.34

^aGlobal QOL score of the EORTC QLQ-C30.

^bAdjusted for age, sex, marital status (two groups), educational level (two groups), occupation (two groups), time since diagnosis (three groups) and presence of recurrence/metastasis.

^cIndependent variables are presence of concerns; having one or more items rated three or more on the four-point Likert scale of each subscale.

(*P* < 0.05), and explained 33.8% of patients' QOL (*R*² = 0.34). The subscale related to concerns about ‘psychological symptoms’ most contributed to QOL (*β* = −0.24), followed by ‘physical symptoms’ (*β* = −0.18), ‘pain’ (*β* = −0.18), ‘daily living’ (*β* = −0.14), ‘self-management’ (*β* = −0.08) and ‘constipation’ (*β* = −0.08) after adjusting for age, sex, marital status, occupation, educational level, time since diagnosis and presence of recurrence/metastasis (Table 4).

DISCUSSION

We began this study by developing a questionnaire to comprehensively assess cancer patients' concerns. The findings support the validity and reliability of the CCAT developed and revealed that patients' concerns are multidimensional (e.g. physical, psychological and social).

In regard to examining the prevalence of concerns as a next step, we found that cancer patients can experience a wide range of perceived concerns. In particular, more than half of our ambulatory cancer patients were concerned about ‘self-management’. Indeed, cancer treatment has expanded to include the home setting because of longer survival, the increased number of ambulatory patients treated with chemotherapy and shortened hospital stays. Because cancer patients are primarily responsible for managing their treatment, ‘self-management’ has become an important factor in cancer self-care. Thus, self-management skills and information on beneficial exercise (19,20) and appropriate nutrition and meal planning should be provided to help patients manage their cancer. The second most prevalent concern was

'psychological symptoms'. About half of the subjects had psychological concerns, and 30% suffered from 'insomnia'. Because insomnia is a common problem in cancer patients (1,21), medical personnel should routinely ask them whether they are suffering from insomnia. Providing information on sleep hygiene (22) is especially recommended as part of a routine care for patients with insomnia. In addition to medication, psychotherapy including cognitive behavioral therapy (23,24) and relaxation therapy (22,25) could offer alternative support if these services are available. Many subjects also had concerns about medical and socio-economic information. Information demand is not limited to the early stages of disease but continues throughout cancer treatment (26,27). Therefore, this information should be easy for patients to obtain and easy to understand. More medical personnel having sufficient knowledge and good communication skills are needed to settle the concern about information. We found a relatively low prevalence of concern about 'physical symptoms', including 'pain' and 'constipation', which might reflect the large majority of participants who were at relatively earlier stage of cancer. It might also reflect concern about 'current' physical symptoms, not about possible 'future' symptoms. Based on our findings, we conclude that there is a need to improve support for cancer patients' self-management, psychiatric concerns and access to information on medical care and daily living.

In relation to our third objective of identifying which concerns contribute to patients' QOL, our findings indicate that all concerns except those related to 'medical information' significantly contributed to QOL. These results suggest that addressing patients' multidimensional concerns can help them effectively improve their QOL. On the other hand, considering the multidimensionality of patients' concerns, intervention would ideally involve multidisciplinary team support for each patient. Multidisciplinary care teams have recently been operating in various contexts of cancer care, including nutrition support teams, rehabilitation and palliative care (28,29). With the aim of improving the quality of cancer treatment that includes QOL, the multidisciplinary care team could consist of, for example, an oncologist, palliative care specialist, psycho-oncologist, expert nurse, pharmacist, dietitian and medical social worker. Because patients' concerns and sense of values have become more diverse with the advancement and diversification of cancer treatment, patients' problems should be screened comprehensively and efficiently, with subjects prioritized, and the right persons placed in the right positions to support them. The Cochrane Database Systematic Review revealed that each psychosocial intervention had only a small effect on QOL of cancer patients, and therefore suggested the need to select the most effective interventions and assign the most appropriate support staff (30).

This study has several limitations. First, patients were recruited over the internet. It was based on relatively little data from patients diagnosed with common cancers (e.g. stomach, colon, lung and liver) and those in the early stages of cancer treatment. The CCAT was only conducted at the website,

namely not face to face. Therefore, our results included the availability of CCAT might not be applicable to patients with all types and all stages of cancer treatment in actual critical scenes. However, data were obtained from patients across the country, minimizing institutional bias. Second, the investigation was cross-sectional in design, which precludes any conclusions about causality between concerns and QOL. Third, the contribution rate of the factor analysis was not extremely high. Thus, other factors might be associated with cancer patients' improved QOL. Future studies are warranted to extend our findings to other cancer sites and cancer treatment stages in actual critical scenes. Also, concrete intervention plans must be prepared when we use this tool and longitudinal study is needed to investigate whether intervention based on the results of cross-sectional studies will affect patients' QOL. Because CCAT is only Japanese version, English version will require future research in order to confirm its utility.

In conclusion, through comprehensive assessment, we have demonstrated the prevalence of cancer patients' concerns. The questionnaire developed in this study can serve as a screening tool to identify cancer patients' concerns. Concerns about psychological symptoms, physical symptoms, daily living, self-management and medical information contributed to patients' QOL directly or indirectly. Intervention by multidisciplinary care teams would be ideal, and experts on these teams should work closely together to support cancer patients.

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Conflict of interest statement

None declared.

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ORIGINAL RESEARCH

Association between adjuvant regional radiotherapy and cognitive function in breast cancer patients treated with conservation therapy

Osamu Shibayama¹, Kazuhiro Yoshiuchi¹, Masatoshi Inagaki², Yutaka Matsuoka³, Eisho Yoshikawa⁴, Yuriko Sugawara⁵, Tatsuo Akechi⁶, Noriaki Wada⁷, Shigeru Imoto⁸, Koji Murakami⁹, Asao Ogawa¹⁰, Akira Akabayashi¹ & Yosuke Uchitomi¹¹

¹Department of Stress Sciences and Psychosomatic Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

²Department of Neuropsychiatry, Okayama University Hospital, Okayama, Japan

³Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology and Psychiatry, Tokyo, Japan

⁴Department of Neuropsychiatry, Toshiba General Hospital, Tokyo, Japan

⁵NISSAN Motor Health Insurance Society, Kanagawa, Japan

⁶Department of Psychiatry and Cognitive-Behavior Medicine, Nagoya City University Graduate School of Medical Sciences, Aichi, Japan

⁷Department of Breast Surgery, National Cancer Center Hospital East, Chiba, Japan

⁸Department of Breast Surgery, Kyorin University Hospital, Tokyo, Japan

⁹Department of Diagnostic Radiology, School of Medicine, Keio University, Tokyo, Japan

¹⁰Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Chiba, Japan

¹¹Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

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Correspondence

Yosuke Uchitomi, Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kitaku, Okayama 700-8558, Japan.
Tel: +81-86-235-7242; Fax: +81-86-235-7246;
E-mail: uchitomi@md.okayama-u.ac.jp

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Abstract

Although protracted cognitive impairment has been reported to occur after radiotherapy even when such therapy is not directed to brain areas, the mechanism remains unclear. This study investigated whether breast cancer patients exposed to local radiotherapy showed lower cognitive function mediated by higher plasma interleukin (IL)-6 levels than those unexposed. We performed the Wechsler Memory Scale-Revised (WMS-R) and measured plasma IL-6 levels for 105 breast cancer surgical patients within 1 year after the initial therapy. The group differences in each of the indices of WMS-R were investigated between cancer patients exposed to adjuvant regional radiotherapy ($n = 51$) and those unexposed ($n = 54$) using analysis of covariance. We further investigated a mediation effect by plasma IL-6 levels on the relationship between radiotherapy and the indices of WMS-R using the bootstrapping method. The radiotherapy group showed significantly lower Immediate Verbal Memory Index and Delayed Recall Index ($P = 0.001$, $P = 0.008$, respectively). Radiotherapy exerted an indirect effect on the lower Delayed Recall Index of WMS-R through elevation of plasma IL-6 levels (bootstrap 95% confidence interval = -2.6626 to -0.0402). This study showed that breast cancer patients exposed to adjuvant regional radiotherapy in conservation therapy might have cognitive impairment even several months after their treatment. The relationship between the therapy and the cognitive impairment could be partially mediated by elevation of plasma IL-6 levels.

Introduction

As therapies for cancers improve survival time of patients with cancers, protracted cognitive impairment in cancer patients, who do not have tumors in the central nervous system (CNS) and have not had direct therapy to the CNS, has received growing interest in recent years because such impairment often imposes an adverse impact on the quality of life (QOLs) of cancer patients and survivors [1, 2].

Recently, cognitive impairment accompanied by radiotherapy not directed to brain areas has been reported. Although Browall et al. found no association between such radiotherapy and cognitive function [3], several studies suggested some association between such radiotherapy and cognitive impairment. While some of these studies suggested that cognitive function recovered during radiotherapy or shortly after radiotherapy [4–6], others suggested that cognitive impairment persisted several months or even several years after radiotherapy [7–12]. There were problems with the data interpretation in some of the previous studies. First, many of these studies did not have control groups [3–6, 9], or the control groups were not cancer patients [7, 10, 11]. In addition, most previous studies did not perform any objective neuropsychological tests [3–6, 8].

With regard to the mechanism of cognitive impairment associated with radiotherapy, several studies suggested that even local radiotherapy induced inflammation and elevated circulating levels of proinflammatory cytokines [13–21]. The association of proinflammatory cytokines and cognitive impairment is often referred to in the context of “sickness behavior,” which is a constellation of physiological, behavioral, and neuropsychological symptoms accompanied by conditions which induce inflammation, such as infection and cancer [22, 23]. In this connection, two clinical studies suggested an association between circulating proinflammatory cytokines and cognitive impairment in cancer patients, and they indicated that only the level of interleukin (IL)-6, among proinflammatory cytokines, including IL-1 and tumor necrosis factor- α , had a negative correlation with either cognitive function [24] or cognitive functioning QOL [25], while other proinflammatory cytokine levels had no correlation with it [24, 25]. Therefore, the elevation of circulating IL-6 levels may be one of the factors important in cognitive impairment in cancer patients treated with radiotherapy.

Accordingly, we hypothesized that one of the mechanisms of cognitive impairment accompanied by radiotherapy not directed to brain areas was that irradiation induces inflammation and elevates circulating levels of proinflammatory cytokines, and among these cytokines, IL-6 plays an important role and leads to cognitive impairment.

The aims of this study were to evaluate whether among non-CNS cancer patients, patients who had undergone local radiotherapy to areas other than brain showed lower cognitive function as assessed by objective neuropsychological tests than patients who had not undergone radiotherapy, and whether elevation of plasma IL-6 levels mediated the cognitive function decline in those patients receiving radiotherapy.

Material and Methods

This study was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center of Japan and was performed after obtaining written informed consent from patients.

This study was conducted as a secondary analysis using a database of brain magnetic resonance imaging (MRI) scans from breast cancer survivors [26].

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 in continuous sampling and asked the patients who met the inclusion criteria to participate in the study within 3–15 months after their surgery and 1 year after the end of their initial therapy. The patients chosen were (1) women and (2) aged between 18 and 55 years, and did not conflict with the exclusion criteria of (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 before 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 [27, 28], (11) a history of major depression and/or posttraumatic stress disorder before inspection for cancer diagnosis, and (12) any contraindication to undergoing an MRI scan. The surgeries were performed from March 1998 to August 2001. Among them, the patients who could be contacted and agreed to participate in the study were interviewed to screen for the exclusion criteria, and the 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) [29],

and a brain MRI. The subjects who were not excluded by the exclusion criteria on the SCID and by the MRI data were analyzed (Fig. 1) [26].

The reason why the age for the inclusion criteria was 55 years or under is as follows: a meta-analysis indicated that the prevalence of dementia increases sharply after the age of 65 years [30], and a 14-year follow-up study indicated that the first decline in cognitive performance appears as early as about 10 years before dementia [31]. Therefore, in order to exclude the variance of cognitive function associated with dementia as much as possible, we decided that the age of the subjects for this study was 55 years or under.

Adjuvant regional radiotherapy in breast conservation therapy

Radiotherapy was performed on the remaining breast after breast conservation therapy in the Department of Radiation

Oncology, National Cancer Center Hospital East. The method of irradiation for breast conservation therapy followed the clinical practice guideline of breast cancer published by the Japanese Breast Cancer Society [32]: 50 Gy tangential irradiation given in 25 treatments to the remaining breast tissue was performed with a radiation source 6 MV X-ray, and in the cases where the resection margin was 5 mm or under from the tumor histopathology, a boost of 10 Gy irradiation was given in five treatments to the tumor bed with a radiation source 6 MeV electron beam.

Neuropsychological tests

The Japanese version of the Wechsler Memory Scale-Revised (WMS-R) [33, 34] was performed. WMS-R consists of indices of Attention/Concentration, Immediate Verbal Memory, Immediate Visual Memory, and Delayed Recall to evaluate memory function [35].

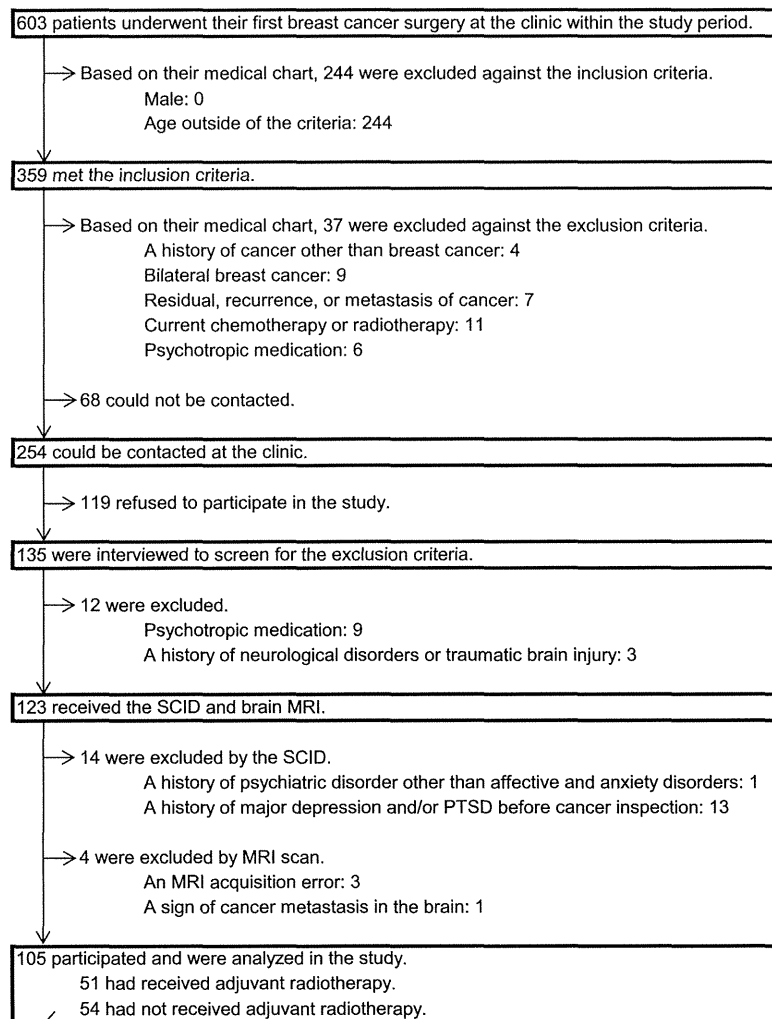


Figure 1. This flowchart illustrates subject sampling in this study. SCID, the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV; MRI, magnetic resonance imaging; PTSD, posttraumatic stress disorder.

Plasma IL-6 levels

Blood samples were collected from a peripheral vein into ethylenediaminetetraacetate-2Na tubes and immediately centrifuged at 4°C and 2300g for 10 min, and the plasma components were separated and stored at -80°C until analyses. Plasma IL-6 levels were analyzed by automated chemiluminescent enzyme immunoassay (Lumipulse-F, Fujirebio Corporation, Tokyo, Japan). Coefficients of variation in measurements were 2.2–3.8%, and the coefficient of correlation with measurements by traditional enzyme-linked immunosorbent assay by the same company was 0.99 or above [36].

Statistical analysis

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

The group differences in each of the demographic or medical factors were compared between the cancer patients exposed to radiotherapy and those not exposed, by using either the Student *t* test, Mann–Whitney *U* test, χ^2 test or the Fisher's exact test.

The group differences in each of the indices of WMS-R were compared between the cancer patients exposed to radiotherapy and those not exposed, using analysis of covariance (ANCOVA) controlling for age, education, accumulated alcohol consumption, smoking status, and body mass index (BMI), which were reported to be associated with impaired cognitive performance [37].

In order to investigate a mediation effect by plasma IL-6 levels on the relationship between radiotherapy and the indices of WMS-R, the sizes of the indirect effects of receiving radiotherapy on the indices of WMS-R through plasma IL-6 levels were estimated, using a bias-corrected bootstrapping method [38] with 5000 replications, and bootstrap 95% confidence intervals (CIs) were obtained. The outcome variable was each of the indices of WMS-R, the independent variable was whether the patient was exposed to radiother-

apy or not, and the mediator was the plasma IL-6 levels. We further controlled for age, education, accumulated alcohol consumption, smoking status, and BMI (see Fig. 2).

In this study, because clinical stage, surgical type, and lymphadectomy had strong correlations with radiotherapy, they were excluded from nuisance values because of multicollinearity (see Table 1).

Results

Demographic or medical background

Table 1 shows the demographic and medical background data of each group. The subjects consisted of 51 exposed to adjuvant radiotherapy and 54 no-radiotherapy patients (Fig. 1). Because the patients who were exposed to radiotherapy had all chosen breast conservation therapy, their clinical stage was significantly less advanced, and the proportion of patients who underwent axillary lymphadectomy was significantly smaller than that in the no-radiotherapy group. In addition, accumulated alcohol consumption was significantly greater in the group exposed to radiotherapy.

Radiotherapy and WMS-R

When the difference in each of the indices of WMS-R was compared between the radiotherapy group and the no-radiotherapy group controlling for age, education, accumulated alcohol consumption, smoking status, and BMI, the radiotherapy group showed a significantly lower Immediate Verbal Memory Index and a Delayed Recall Index (radiotherapy group vs. the no-radiotherapy group: 94.9 ± 12.4 vs. 103.6 ± 13.9 , $P = 0.001$; 98.5 ± 10.6 vs. 104.3 ± 11.4 , $P = 0.008$, respectively. Table 2).

Indirect effect of radiotherapy on WMS-R through plasma IL-6 levels

When the size of the indirect effect of receiving radiotherapy on each of the indices of WMS-R through plasma

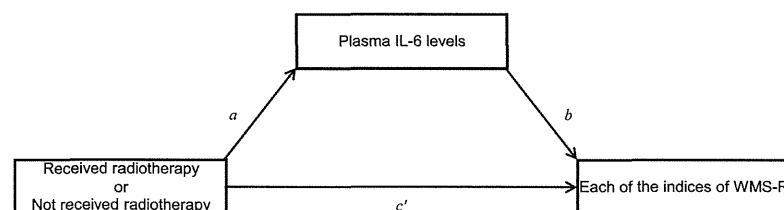


Figure 2. Illustration of a mediation model [38], which hypothesizes that radiotherapy exerts an indirect effect on each of the indices of the Wechsler Memory Scale-Revised (WMS-R) through plasma interleukin (IL)-6 levels. Path *a* represents the effect of radiotherapy on plasma IL-6 levels, the proposed mediator. Path *b* represents the effect of plasma IL-6 levels on each of the indices of WMS-R partialling out the effect of radiotherapy. Path *c'* is the direct effect of radiotherapy on each of the indices of WMS-R partialling out the effect of plasma IL-6 levels. The indirect effect of radiotherapy on each of the indices of WMS-R through plasma IL-6 levels is the product of *a* and *b*, which is tested with the bootstrap confidence interval (CI) obtained through the bootstrapping method.

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

	Received radiotherapy (n = 51)	Not received radiotherapy (n = 54)	P
Age, mean ± SD, year	47.0 ± 5.2	46.6 ± 6.2	0.755
Handedness: right-handedness, no. (%)	49 (96.1)	53 (98.1)	0.611
Hight, mean ± SD, cm	156.9 ± 6.5	156.0 ± 5.2	0.432
Weight, mean ± SD, kg	56.9 ± 9.0	54.9 ± 6.3	0.196
BMI, mean ± SD, kg/m ²	23.1 ± 3.4	22.5 ± 2.4	0.333
Education, mean ± SD, year	13.1 ± 1.9	13.2 ± 1.8	0.797
Smoking, no. (%)	8 (15.7)	3 (5.6)	0.116
Accumulated alcohol consumption, mean ± SD, kg	38.4 ± 60.4	27.9 ± 84.6	0.043 [‡]
Postmenopausal, no. (%)	29 (56.9)	31 (57.4)	1.000
PS: 0, no. (%)	35 (71.4) ¹	38 (70.4)	1.000
Clinical stage: 0–I, no. (%)	25 (49.0)	13 (24.1)	0.014 [†]
Lymphnode metastasis: positive, no. (%)	15 (29.4)	18 (33.3)	0.824
Histological type, no. (%)			
Carcinoma in situ	4 (7.8)	2 (3.7)	0.428
Invasive carcinoma	39 (76.5)	44 (81.5)	0.696
Special type	8 (15.7)	8 (14.8)	1.000
Histological grade: poor, no. (%)	14 (27.5)	14 (25.9)	1.000
Surgical type: partial mastectomy, no. (%)	51 (100.0)	6 (11.1)	0.000 ^{†††}
Axillary lymphadectomy, no. (%)	26 (51.0)	44 (81.5)	0.002 ^{††}
Days after surgery, mean ± SD, day	304 ± 101	270 ± 105	0.102
Radiotherapy: boost irradiation, no. (%)	20 (39.2)	NA	NA
Days after radiotherapy, mean ± SD, day	226 ± 100	NA	NA
Chemotherapy, no. (%)	25 (49.0)	26 (48.1)	1.000
Hormonal therapy, no. (%)	17 (33.3)	15 (27.8)	0.685

NA, not applicable; BMI, body mass index; PS, performance status.

¹Two missing values were excluded.

[‡]Significant difference ($P < 0.05$) between radiotherapy group and no-radiotherapy group.

^{††}Significant difference ($P < 0.01$) between radiotherapy group and no-radiotherapy group.

^{†††}Significant difference ($P < 0.001$) between radiotherapy group and no-radiotherapy group.

IL-6 levels was estimated controlling for age, education, accumulated alcohol consumption, smoking status, and BMI, the bootstrap 95% CI of Delayed Recall Index only

Table 2. Each of the indices of WMS-R in the group of patients exposed to their radiotherapy and in the group of patients unexposed.

	Received radiotherapy (n = 51)	Not received radiotherapy (n = 54)	P
WMS-R index, mean ± SD			
Attention/concentration	97.4 ± 13.2	101.4 ± 10.3 ¹	0.238
Verbal memory	94.9 ± 12.4	103.6 ± 13.9 ¹	0.001 ^{†††}
Visual memory	102.2 ± 9.9	102.4 ± 13.3 ²	0.989
Delayed recall	98.5 ± 10.6	104.3 ± 11.4 ³	0.008 ^{‡††}

WMS-R, Wechsler Memory Scale-Revised.

¹One missing value was excluded.

²Two missing values were excluded.

³Three missing values were excluded.

^{††}Significant difference ($P < 0.01$) between radiotherapy group and no-radiotherapy group.

^{†††}Significant difference ($P < 0.001$) between radiotherapy group and no-radiotherapy group.

Table 3. Regression coefficients between each pair of variables in the mediation models through which indirect effects of receiving radiotherapy on each of the indices of WMS-R through plasma IL-6 levels were estimated (Fig. 2), and bootstrap 95% CIs obtained through the bootstrapping method evaluating these indirect effects.

WMS-R index	a ¹	b ¹	c ¹	Bootstrap 95% CI
Attention/ concentration ²	0.8174 [‡]	−1.0133	−1.4550	−3.2207 to 0.1191
Verbal memory ²	0.8174 [‡]	−0.5331	−7.2741 ^{††}	−2.1231 to 0.3055
Visual memory ³	0.8173 [‡]	−0.3765	1.3768	−1.7209 to 0.3672
Delayed recall ⁴	0.8138 [†]	−1.1678	−4.6102 [†]	−2.6626 to −0.0402 [‡]

WMS-R, Wechsler Memory Scale-Revised; IL-6, interleukin-6; CI, confidence interval.

¹Regression coefficient between each pair of variables corresponding with each symbol representing each path in Figure 2.

²The plasma IL-6 levels and the index of WMS-R of 96 patients (received radiotherapy 49 and not received 47) were available for analysis.

³The plasma IL-6 levels and the index of WMS-R of 95 patients (received radiotherapy 48 and not received 47) were available for analysis.

⁴The plasma IL-6 levels and the index of WMS-R of 94 patients (received radiotherapy 47 and not received 47) were available for analysis.

[†] $P < 0.05$.

^{††} $P < 0.01$.

[‡]The indirect effect mentioned was significant at α level $P < 0.05$.

did not include zero (bootstrap 95% CI = −2.6626 to −0.0402), which indicated that the indirect effect was significant (Table 3).

Discussion

This study showed that breast cancer patients exposed to adjuvant regional radiotherapy in breast conservation therapy at 7 months after treatment showed a significantly lower Immediate Verbal Memory Index and a Delayed Recall Index of WMS-R than breast cancer patients not exposed to radiotherapy. We also found that radiotherapy exerted an indirect effect on the lower Delayed Recall Index of WMS-R through elevation of plasma IL-6 levels. These results suggested that adjuvant regional radiotherapy in breast conservation therapy could impair memory function some months after completion of the therapy, and that the influence of the therapy on the impairment of memory function is partially mediated by elevation of plasma IL-6 levels.

There have been three studies on the relationship between radiotherapy and cognitive function by objective neuropsychological tests in breast cancer patients. One study was cross-sectional showing significantly lower attention and complex cognition in the Trail Making Test in the patient group exposed to radiotherapy than that in the non-cancer control group [7]. Another study was longitudinal from before and up to 3 months after radiotherapy and showed a decline from baseline in verbal memory in the Rey Auditory Verbal Learning Test [11]. The third study was longitudinal at 6 months and at 36 months after radiotherapy showing a significantly smaller improvement in processing speed and significantly lower executive function on a subtest of the Wechsler Adult Intelligence Scale III at both time points in the patient group exposed to radiotherapy than that in the non-cancer control group [10]. The results of this study using WMS-R (Table 2) generally support these findings. However, this study had an advantage over these previous studies because the previous studies did not have a control group consisting of breast cancer patients who had not been exposed to radiotherapy. Therefore, this study provided more compelling evidence that cognitive impairment was caused by radiotherapy, not by cancer itself and/or by treatments other than radiotherapy.

This study suggested that adjuvant regional radiotherapy in breast conservation therapy might elevate plasma IL-6 levels as a byproduct of the analysis of the indirect effect of radiotherapy on the indices of WMS-R through plasma IL-6 levels (Table 3), although the relation between radiotherapy for cancer patients and the levels of circulating proinflammatory cytokines after radiotherapy has been inconsistent in previous studies, that is, some studies showed elevated levels after irradiation [16, 20], but others showed the opposite results [4, 14, 21, 39]. The mechanism for the elevation of plasma IL-6 levels is not known and should be investigated in future studies. It may be added

that the clinical stage was significantly less advanced in the radiotherapy group than that in the no-radiotherapy group in this study (Table 1). Thus, the possibility that advanced clinical stages influenced prolongation of high level of plasma IL-6 after radiotherapy seems to be low in this study.

This study showed that radiotherapy exerted a significant indirect effect through plasma IL-6 levels only on the Delayed Recall Index of WMS-R (Table 3). It has been suggested that delayed recall memory is associated with the hippocampus [40, 41]. Furthermore, an animal study suggested that peripheral IL-6 signaled the brain and induced inflammation in the hippocampus [42]. Therefore, the association between radiotherapy and memory function impairment might be explained partially by hippocampal inflammation caused by the elevation of plasma IL-6 levels, while adjuvant chemotherapy did not influence the hippocampal volume in breast cancer survivors [26, 43].

There were some limitations to this study. (1) This study was not an interventional study, and was a cross-sectional study. Therefore, the causality between variables was not guaranteed. (2) Because there was a considerable length in time span between the end of the therapies and the search points, the variance of measurements may be larger than if all searches had been performed at the same time after the therapies ended. This can reduce the power of the tests in this study. (3) The number of subjects was small. Therefore, the power of the tests might be reduced. (4) Because the subjects in this study were restricted to comparatively young breast cancer patients, the results should be generalized with caution. (5) The influence of residual cancer on inflammation could not be excluded. (6) Neuropsychological tests other than WMS-R were not conducted in this study. (7) Some factors other than plasma IL-6 that might be associated with cognitive impairment accompanied by radiotherapy, such as other proinflammatory cytokines, fatigue, anemia, chronic pain, etc., were not considered in this study. (8) Biological factors which might have elevated plasma IL-6 levels, such as medication, infection, etc., were not considered in this study.

Conclusion

Breast cancer patients exposed to adjuvant regional radiotherapy could have cognitive impairment, which might be partially mediated by the elevation of plasma IL-6 levels.

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Conflict of Interest

None declared.

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