recommended as the new standard treatment. The estimated 5-year OS of these patients is commonly 64–88 % [4–6]. A total of 342 patients were needed to detect a prolongation of the 5-year OS from 75 % for patients in the TU arm to 85 % for patients in ACT arm with an 80 % power and a two-sided alpha of 5 %. Considering some patients potentially lost to follow-up, the sample size was set at 400 patients in total. The planned study period was originally 2 years for recruitment and an additional 5 years for follow-up. Due to the slow recruitment, the protocol was revised to extend the recruitment period, and the sample size was revised to 330 patients with a recruitment period of 5 years. OS was analyzed for all randomized patients and RFS for randomized patients excluding a patient with bone metastasis at the registration. OS and RFS were estimated using the Kaplan–Meier method, and curves were compared using a log-rank test. Hazard ratios of treatment effects were estimated by a Cox regression model. All analyses were based on intent to treat. All statistical analyses were performed using SAS release 8.2 (SAS Institute, Cary, NC).

Interim analysis and monitoring plan

An interim analysis was to be performed when half of the total number of patients was enrolled. The JCOG Data and Safety Monitoring Committee (DSMC) independently reviewed the interim analysis report, and premature termination of the trial could be considered at that stage. In-house interim monitoring was performed by the JCOG Data Center to ensure data submission, patient eligibility, protocol compliance, safety, and on-schedule study progress. The monitoring reports were submitted to and reviewed by the DSMC every 6 months.

Results

This study began in 1994. At an interim analysis on June 1999, patient recruitment was so slow that the DSMC recommended terminating patient recruitment or continuing but changing the primary endpoint to RFS. Furthermore, a consensus meeting in St. Gallen in 1997 deemed that administering tamoxifen to hormone receptor-negative patients was ethically unacceptable [7]. Therefore, recruitment of patients was terminated pursuant to suggestions from the JCOG DSMC.

In total, 169 patients were recruited and randomly assigned (Fig. 1). Four patients were ineligible because two were enrolled after starting protocol treatment, one had been diagnosed with bone metastasis, and the other was postmenopausal before recruitment, but these patients were included in the analysis. The two groups had highly similar baseline characteristics (Table 1). The median age was 46 years (30–56 years). One hundred and seventeen patients (69.2 %) had node metastases involving 1–3 nodes, while 52 (30.8 %) had node metastases involving 4–9 nodes. There were 59 patients (34.9 %) with ER- or PR-tumors, including patients with an unknown hormone status. Most patients (95.3 %) underwent total or radical mastectomy. Eighty-seven patients were assigned to the TU arm, and 82 patients were assigned to the ACT arm. Patient's diagram was shown in Fig. 1. The protocol treatment in the TU arm was completed by 75 of 87 patients (86.2 %), and the protocol treatment in the ACT arm was completed by 66 of 82 patients (80.5 %).

Survival

There were no significant differences in OS for patients in the two arms ($p = 0.494$, hazard ratio 0.76, 95 % confidence interval [CI] 0.35–1.66) (Fig. 2a). The 3- and 5-year OS were 90.3 and 79.7 % for patients in the TU arm and 90.6 and 83.0 % for patients in the ACT arm, respectively. There were no significant differences in RFS for patients in the two arms ($p = 0.37$, HR: 0.77, 95 % CI 0.44–1.36) (Fig. 2b). The 3- and 5-year RFS were 74.0 and 66.1 % for patients in the TU arm and 76.7 and 70.6 % for patients in the ACT arm, respectively.

Subgroup analysis was performed according to hormone receptor status. There were 57 patients (65.5 %) who were ER+ and/or PR+ in the TU arm and 52 (63.4 %) in the ACT arm. The OS curve is shown in Fig. 3a. Both ER- and PR-negative patients had a worse prognosis than ER-positive patients. However, patients in the TU and ACT arms had a similar OS, regardless of hormone status. Both ER- and PR-negative patients in the TU arm had a relatively shorter RFS than those in the ACT arm (Fig. 3b). There were no differences in the RFS of ER+ and/or PR+ patients in both arms.

Safety profile

Safety profiles are listed in Table 2A and B. Only one patient was observed grade 4 adverse event (GPT elevation) in the TU arm. This event was diagnosed at 35th day after the start of TU, and once the administration of UFT was halted, GPT decreased to normal levels. A higher proportion of patients in the ACT arm had a lower white blood cell count that was rated grade 3 (0 % in the TU arm, 3.8 % in the ACT arm), and a higher proportion of patients in the TU arm had elevated total bilirubin, GOT, and GPT that were rated grade 3 (12.6, 2.3, and 2.3 % in the TU arm, 0, 1.3, and 1.3 % in the ACT arm) and lower hemoglobin (3.4 % in the TU arm, 0 % in the ACT arm). A non-hematological toxicity (grade 3 nausea) was noted only in patients in the ACT arm (10 %). There was grade 3 rash (1.2 %) in a patient in the TU arm and grade 3 arrhythmia (1.3 %) in a patient in the ACT arm.

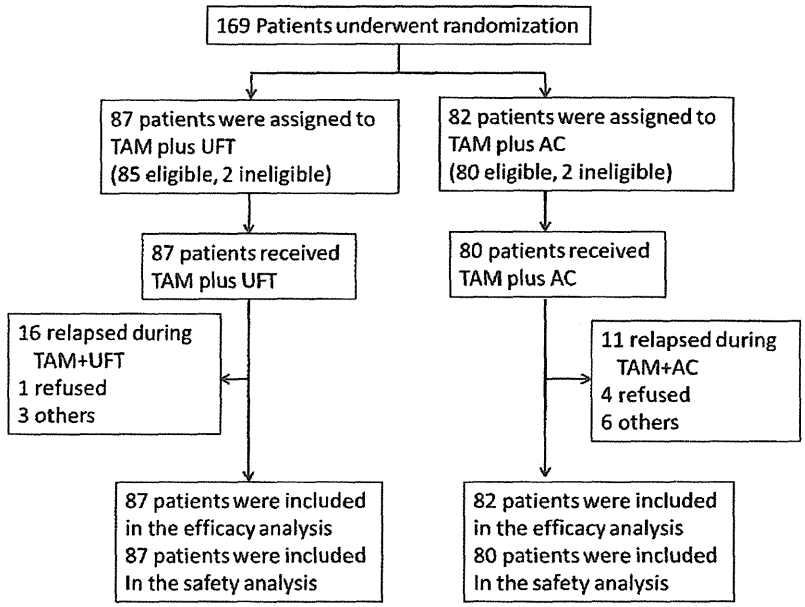

Fig. 1 Trial profile of Japan Clinical Oncology Group study, JCOG 9404

Table 1 Patient characteristics

Characteristics	TU ($n = 87$)	ACT ($n = 82$)
Age (year)		
Median	47	45
Range	31–55	30–56
No. of positive axillary nodes		
1–3	59	58
4–9	28	24
ER and/or PgR		
Negative/unknown	29	30
Positive	58	52
HER2		
Negative/unknown	70	63
Positive	17	19
Stage		
I	12	12
II	58	60
IIIA	17	11
Operation		
Radical mastectomy	1	6
Total mastectomy	81	73
Partial resection	5	3

Discussion

The decision to administer postoperative adjuvant drug therapy, which seeks to inhibit the recurrence of breast cancer, is often currently made based on the primary tumor's subtype. Breast cancer is essentially categorized

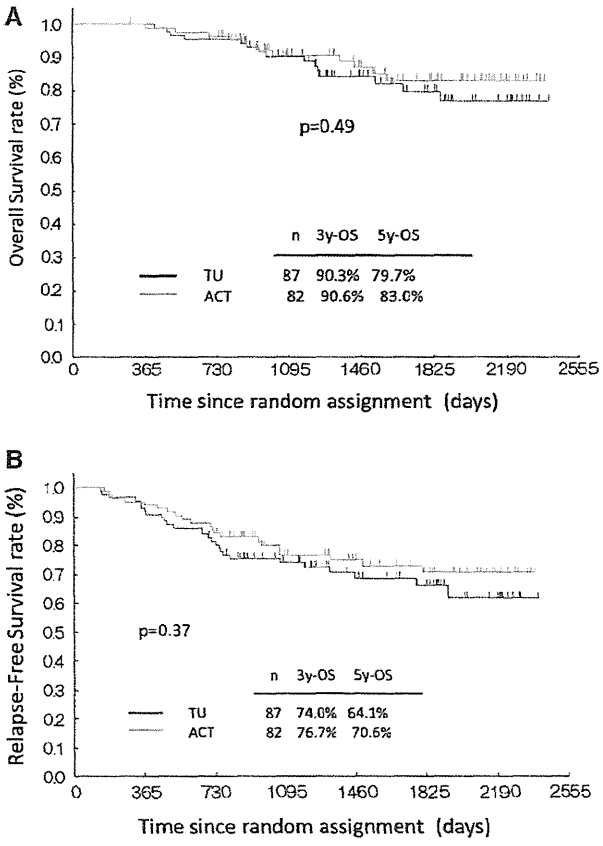

Fig. 2 Kaplan–Meier curves of overall survival (**a**) and relapse-free survival (**b**) for node-positive breast cancer patients treated with tamoxifen plus tegafur-uracil or tamoxifen with anthracycline and cyclophosphamide

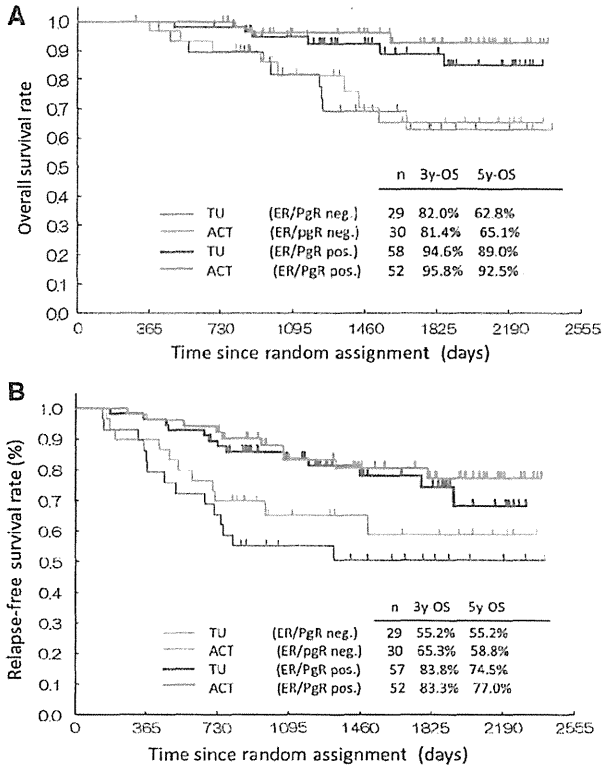

Fig. 3 Kaplan–Meier curves of overall survival (**a**) and relapse-free survival (**b**) for node-positive breast cancer patients treated with tamoxifen plus tegafur-uracil or tamoxifen with anthracycline and cyclophosphamide according to estrogen receptor (ER) and progesterone receptor (PgR) status

into four subtypes depending on the expression of ER, PgR, HER2, and Ki67 [2]. Endocrine drugs are given to patients with ER- and/or PgR-positive luminal tumors. Trastuzumab (a molecular-targeted agent) and an anticancer agent are both administered to HER2-positive patients. These strategies are tailor-made target therapies according to the prediction of efficacy of drugs. In addition to endocrine drugs, anticancer agents are often administered to patients with breast cancer expressing a high level of Ki67 [8, 9]. The individual determination of whether or not a tumor is sensitive to a drug is difficult, and despite this, anticancer agents are administered. Including anticancer agents is considered acceptable when patients have numerous lymph node metastases (irrespective of tumor subtype), if their cancer is ER- and/or PgR-positive and expressing a low level of Ki67. The validity and evaluation of Ki-67 are not definitive [10]. Both anthracycline and taxane are often administered sequentially for these patients despite the possibility that efficacy of these drugs is low. These classifications of breast cancer and administration of taxane and molecular drugs were widely in use after the current trial began.

Table 2 Hematological (A) and non-hematological (B) toxicities

Toxicities	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
(A)			
TU			
WBC	8 (9)	0 (0)	0 (0)
Hb	2 (2)	3 (3)	0 (0)
T-bill	43 (49)	11 (13)	0 (0)
GOT	5 (6)	2 (2)	0 (0)
GPT	9 (10)	2 (2)	1 (1)
ACT			
WBC	12 (14)	3 (3)	0 (0)
Hb	7 (8)	0 (0)	–
T-bill	8 (9)	0 (0)	0 (0)
GOT	1 (1)	1 (1)	0 (0)
GPT	5 (6)	1 (1)	0 (0)
(B)			
TU			
Infection	0 (0)	0 (0)	0 (0)
Nausea/vomiting	7 (0)	0 (0)	–
Diarrhea	2 (0)	0 (0)	0 (0)
Arrhythmia	1 (1)	0 (0)	0 (0)
Thrombosis	0 (0)	0 (0)	0 (0)
Alopecia	0 (0)	–	–
Rush	2 (0)	1 (0)	0 (0)
ACT			
Infection	0 (0)	0 (0)	0 (0)
Nausea/vomiting	29 (36)	8 (10)	–
Diarrhea	1 (1)	0 (0)	0 (0)
Arrhythmia	1 (1)	1 (1)	0 (0)
Thrombosis	0 (0)	0 (0)	0 (0)
Alopecia	37 (46)	–	–
Rush	1 (1)	0 (0)	0 (0)

At the beginning of this study, tamoxifen was administered as the standard therapy even if the patient was ER-negative. In light of current evidence, there is no doubt that tamoxifen has little efficacy in treating ER-negative breast cancer [11], though there are also no data indicating that the efficacy of anticancer agents will diminish if used in combination with tamoxifen. Thus, the results of this trial simply compared taking UFT for 2 years to taking AC to treat node-positive premenopausal breast cancer. Previous meta-analyses clearly revealed data indicating that AC therapy is more effective at preventing recurrence than CMF [12–16], but AC therapy has not been compared to oral fluoropyrimidine. The results of this trial indicated no difference between oral fluoropyrimidine and AC therapy in terms of prolonging survival in patients overall. AC therapy resulted in a longer recurrence-free survival (RFS) in only ER-negative patients. These results do not have a meaning

for recent breast cancer treatment strategy, because of the insufficiency of patients recruitment and old adjuvant treatment design. However, this finding suggests that AC therapy has limited efficacy when treating node-positive breast cancer by administering tamoxifen as a postoperative adjuvant therapy to treat ER-positive breast cancer. This finding also suggests that administration of oral fluoropyrimidine alone may be sufficient in some cases. In fact, OS and PFS were similar between ACT and TU arm with ER-positive breast cancer. A potent anticancer agent, like anthracycline, may not be needed to treat ER-positive breast cancer even if it has lymph node metastasis.

The question of whether UFT is needed or if tamoxifen alone is sufficient remains. Results of the JCOG9401 study [17], which examined patients with postmenopausal breast cancer with lymph node metastasis during the same period as the current trial, may offer an answer. The study compared tamoxifen alone and ACT therapy to treat patients with node-positive breast cancer, and results indicated that ER-positive patients had a 5-year RFS of 59.3 % when given tamoxifen alone versus 76.9 % when given ACT therapy and a 5-year OS of 87.1 % when given tamoxifen alone versus 90 % when given ACT therapy. Patients in this trial who were given UFT+tamoxifen had a 5-year RFS of 74.5 % and a 5-year OS of 89 %. There was possibility of prognostic benefit of additional UFT for ER-positive node-positive patients. Thus, comparison of TU therapy to tamoxifen alone is needed. In Japan, a prospective clinical trial on adding S-1 to treat patients with ER-positive breast cancer after completion of standard chemotherapy is currently enrolling subjects (UMIN000003969).

No major differences were noted in ER-negative patients in either arm of this trial. That said, ER-negative patients had a 5-year OS and a 5-year RFS that was about 30 % shorter than the 5-year OS and 5-year RFS of ER-positive patients. Trastuzumab tends to be administered to patients with ER-negative breast cancer if they are HER2-positive [18], and taxane tends to be administered along with anthracycline if they are HER2-negative [14]. The regimens in this trial were inadequate to evaluate the appropriate adjuvant drugs for ER-negative patients with node metastases.

In terms of adverse events, a hematological event in the form of a grade 3 decline in the white blood cell count was noted only in patients in the ACT arm. In terms of nonhematological events, abnormal liver function was noted in patients in the TU arm and nausea was often noted in patients in the ACT arm. Results of this trial revealed numerous adverse events in patients in the ACT arm as a whole. Since the current dose of AC is higher than that used in this trial, UFT may be less damaging. However, results suggested that sufficient caution in abnormal liver function is necessary to use UFT for long time as adjuvant therapy. The current trial did not administer both endocrine therapy and chemotherapy concurrently. Previous data on such chemoendocrine therapy have highlighted the enhancement of adverse events and an increase in thrombosis in particular [19–21]. Neither group of patients in this trial had thrombosis/embolism. Existing data are from the USA and Europe, where thrombosis is more prevalent. These conditions may pose far less of a problem in Japan because of their different physique. Chemoendocrine therapy is ruled out based on current data from Europe and the USA, but there may be leeway for therapy selection depending on the patient.

This trial prospectively studied the usefulness of ACT therapy to treat patients with node-positive premenopausal breast cancer. This trial began prior to 2000, and modern standard adjuvant therapy was established during collecting patients for this trial. There were some issues with trial design and trial enrollment since the standard therapy changed substantially during trial enrollment. However, the times changed from an era of actively administering anticancer agents to every patient with breast cancer with lymph node metastasis to an era of selecting therapy by predicting drug efficacy. Postoperative adjuvant therapy with oral FU was the standard therapy in this trial, and a new appreciation for the efficacy of that therapy is developing. In this trial, ACT did not significantly prolong survival compared to TUFT, especially in ER-positive patients. Without a doubt, these findings pose clinical questions that should be answered when formulating a treatment strategy for postoperative adjuvant therapy. Further studies via prospective trials (which include those currently underway) are needed.

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Psychometric Properties of the Japanese Version of the Concerns About Recurrence Scale (CARS-J)

Kanae Momino[1,2], Tatuo Akechi[3,4,*], Toshinari Yamashita[5,6], Takashi Fujita[5], Hironori Hayahi[5,7], Nobuyuki Tsunoda[5,8], Mitsunori Miyashita[2,9] and Hiroji Iwata[5]

[1]Nagoya City University Graduate School of Nursing, Nagoya, [2]Department of Adult Nursing/Palliative Care Nursing, School of Health Sciences and Nursing, Graduate School of Medicine, The University of Tokyo, Tokyo, [3]Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, [4]Division of Palliative Care and Psycho-oncology, Nagoya City University Hospital, Nagoya, [5]Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, [6]Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, [7]Department of Breast and Endocrine Surgery, Nagoya University Hospital, Nagoya, [8]Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya and [9]Division of Palliative Nursing, Health Sciences, Tohoku University Graduate School of Medicine, Sendai, Japan

*For reprints and all correspondence: Tatsuo Akechi, Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya, Aichi, 467-8601 Japan. E-mail: takechi@med.nagoya-cu.ac.jp

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Objective: Although the fear of recurrence is a major concern among breast cancer survivors after their surgery, there are no instruments to evaluate their distress in Japan. This study examines the psychometric properties of the Japanese version of the concerns about recurrence scale, which was originally developed in the USA.

Methods: The forward and backward translation method was used to develop Concerns About Recurrence Scale. Randomly selected ambulatory female patients with breast cancer participated in this study. They were asked to complete Japanese version of the concerns about recurrence scale and Hospital Anxiety and Depression Scale. The validity and reliability of Japanese version of the concerns about recurrence scale were evaluated statistically.

Results: Data were obtained from 375 patients. A novel four-factor solution was found (Health and Death Worries, Womanhood Worries, Self-valued Worries and Role Worries) that accounted for 59.2% of the total variance. Correlation coefficients between the Japanese version of the concerns about recurrence scale subscale scores and the anxiety score measured by Hospital anxiety and depression scale ranged from 0.39 to 0.60. Cronbach's alpha coefficients, which are measures of the internal consistency of the subscales, ranged from 0.86 to 0.94.

Conclusions: The results suggest that Japanese version of the concerns about recurrence scale is a reliable and valid clinical research tool to evaluate the fear of recurrence among patients with breast cancer in Japan, although there may be cross-cultural differences regarding factor structures between Western and Japanese breast cancer patients.

Key words: fear of recurrence – breast cancer – validity – scale

INTRODUCTION

Breast cancer is currently the most common malignant neoplasm among females, and both mortality and incidence have increased during the past decade in Japan. Advances in early detection and individualized medical treatment have improved the survival of breast cancer patients and enabled them to live with the disease for prolonged periods of time.

Breast cancer survivors experience considerable distress. Their most prevalent unmet needs are psychological (1,2), where the most common is the fear of recurrence and/or spread of the cancer (1–3). A previous Japanese study that investigated cancer patients' perceived difficulties in their daily life found that the most common problem is psychological distress (4). The study also indicated that nearly half of the cancer survivors experience psychological distress, particularly, anxiety about recurrence or metastases of their cancer (4). Our previous study indicated that approximately one in four Japanese breast cancer survivors experience clinical anxiety and depression, and that the most common unmet need among ambulatory breast cancer patients is the 'fear of cancer spread'; 63% of the patients reported a need for help to alleviate this fear (5,6). It has also been reported that the fear of recurrence decreases the quality of life of breast cancer survivors (7).

Thus, the fear of cancer recurrence is one of the most common distressing symptoms for cancer survivors, and appropriate interventions are needed. Although certain recent studies have proposed potential interventions to reduce this fear (7,8), there are no standard strategies to alleviate this distress. To clarify the biomedical and clinical factors underlying the fear of recurrence and to develop novel interventions, appropriate instruments to evaluate patients' fear are needed. While there are some instruments that evaluate patients' fear of cancer recurrence (9), no brief measures have been validated in Japan. Among several instruments which can assess fear of cancer recurrence including Cancer Worry Scale (10), Fear of Recurrence Scale (11), Fear of Recurrence Questionnaire (12) and so on, we have selected the Concerns About Recurrence Scale (CARS) because this instrument has multi-dimensional nature and good validity and reliability (13). CARS, originally developed in the USA is a multidimensional instrument that addresses different domains of patients' fear as well as the overall fear of tumor recurrence (13). This study examines the psychometric properties of the Japanese version of CARS (CARS-J).

PATIENTS AND METHODS

Participants

The participants were ambulatory females with breast cancer visiting the outpatient department of Aichi Cancer Center Hospital in Japan.

The following were the eligibility criteria for the study: women (i) with a diagnosis of invasive breast cancer and who were informed of the cancer diagnosis, (ii) who were disease-free survivors after mastectomy or partial mastectomy and (iii) 20 years or older. The exclusion criteria were (i) severe mental or cognitive disorders, (ii) inability to understand the Japanese language and (iii) patients considered by their oncologists as physically or mentally incapable of participating in the study.

Procedure

Oncologists consecutively identified all eligible patients at their ambulatory clinic and briefly explained them the survey when they visited the hospital during 3 weeks in October 2008. If they were interested in the study, the oncologists provided them with the questionnaires. Patients who agreed to participate in the study, after reading an explanatory document on it, were asked to complete the questionnaire anonymously at home and send them back by mail, instead of obtaining a written consent. Patients who did not wish to participate in the survey returned the questionnaires that were checked 'no participation.'

This study was approved by the Institutional Review Board and Ethics Committee of Aichi Cancer Center and was conducted in accordance with the principles laid down in the Helsinki Declaration.

Instruments

Japanese Version of the Concerns About Recurrence Scale

CARS is a 30-item breast cancer-specific self-report scale, originally developed in the USA. It assesses the overall fear of breast cancer recurrence and four domains of specific fear of recurrence (13). Overall fear consists of four items including questions on frequency, potential for upset, consistency and intensity of fear. The four domains are Health Worries (11 items that refer to concern about future treatment, emotional upset, physical heath, planning activities and loss of breast), Womanhood Worries (seven items referring to femininity, sexuality, womanhood, body image, romantic relationships, identity and spirituality or faith), Role Worries (six items pertaining to roles and responsibilities at work and home, relationships with friends and family, physical ability to complete daily activities, financial problems and self-confidence), and Death Worries (two items pertaining to the possibility that recurrence of breast cancer could lead to death). The reliability and validity of CARS have been confirmed among American and Dutch breast cancer patients (13,14).

After obtaining permission to develop CARS-J from the original author, the forward and backward translation method was used to develop the Japanese version. The CARS items were first translated into Japanese by two independent translators, and then translated back into English by another translator, who is fluent in English and Japanese and had not seen the original English version. Next the English back-translated items were compared with the original version. If a back-translated item

did not agree with the original, the first translator performed a second translation and the second translator performed a second back-translation; this process was repeated until a satisfactory agreement was reached. CARS-J is available with the authors.

Hospital Anxiety and Depression Scale

Hospital anxiety and depression scale (HADS) is a 14-item self-report questionnaire that was developed to evaluate psychological distress, including anxiety and depression, in medically ill patients and does not contain any questions regarding physical symptoms (15). Participants are asked to rate their feelings during the previous week using a four-point Likert scale. HADS includes an anxiety and a depression subscale (0–21 points each), and the total score ranges from 0 to 42. Higher scores indicate a more severe degree of depression and anxiety. The Japanese version of HADS has been validated for cancer populations (16).

Sociodemographic and Clinical Factors

An *ad hoc* self-administered questionnaire was used to obtain information on sociodemographic status such as age, marital status, employment status, educational level, types of treatments received and time since the operation.

Statistical Analysis

The psychometric properties of CARS were evaluated statistically.

Factor validity was evaluated using factor analysis with varimax rotation. The number of subscales was identified by Kaiser's criterion (eigenvalue of 1.0 or greater).

Convergent validity was explored by calculating Pearson's correlation between the CARS-J domains and HADS subscales. We hypothesized that all scores of the CARS-J domains would be significantly related to the anxiety subscale of HADS.

Discriminant validity, i.e. the ability of each CARS-J domain to discriminate between subgroups of patients, was investigated. We hypothesized that patients who were younger (<50 years), with experience of anticancer treatment (chemotherapy, radiotherapy and hormone therapy), suffering from any physical symptoms that cause impairment in daily activities, and who had more recent operations would experience higher fear of recurrence. With regard to the period since operation, the analysis of variance was conducted to compare scores among the three different groups of patients (<1 year vs. 1–3 years vs. ≥3 years).

The reliability of the scale was evaluated by calculating Cronbach's alpha coefficient, a measure of the internal consistency of responses to a group of items. The minimum acceptable value for internal consistency is thought to be 0.70 (17).

Item non-response rates were <10% for all study variables. To preserve a complete study sample, missing data were replaced by the mean of that variable for all other cases (single imputation technique).

A P value of <0.05 was adopted as the significance level in all statistical analyses and all P values reported were two-tailed. All statistical procedures were conducted using the SPSS 17.0J software for Windows.

RESULTS

Among the 432 patients who met the eligibility criteria, a total of 377 patients (87%) returned the questionnaires. Two of these patients were excluded, one for not having undergone operation and the other because of missing data. Data from the remaining 375 patients were analyzed.

Patient Characteristics

Participants' characteristics are shown in Table 1. The median age of the study population was 56 years. A majority of the women were married (79%), and approximately half of them had a full- or part-time job (45%). More than half of the

Table 1. Characteristics of the study participants ($n = 375$)

Characteristics	*N*	(%)
Age	Mean: 56 (SD = 11) median: 56 (range, 31–80)	
Sex		
Female	375	100
Marital status		
Married	295	79
Others	81	21
Job		
Full-time	88	23
Part-time	84	22
Others	190	51
Unknown	14	4
Education		
High school	212	56
College/university	155	41
Unknown	9	2
Anticancer treatment		
Chemotherapy	206	55
Radiation therapy	149	40
Hormone therapy	241	64
Duration since operation		
<1 year	82	22
≥1 to <3 years	128	34
≥3 years	160	43
Unknown	5	1.3

participants reported experience of either chemotherapy or hormonal therapy. Among the participants, 22 and 34% of the participants had undergone operation <1 and 1–3 years earlier, respectively.

Factor Validity

Factor analysis indicated a four-factor solution, which accounted for 59.2% of the total variance (Table 2). The factor structure obtained was similar to, but differed from, the original study. The first factor, which comprised Health and Death Worries items of the original CARS and accounted for ~24.8% of the variance, was named Health and Death Worries (13 items). The second factor mainly comprised Womanhood Worries items of the original CARS and accounted for 15.3% of the variance. Therefore, it was named Womanhood Worries (six items), similar to the original version. The third factor mainly comprised some Womanhood Worries items and the Role Worries items of the original version, accounting for ~10.7% of the variance. This factor was named Self-valued Worries (five items). The fourth factor, which comprised the Role Worries subscale of the original version and accounted for 8.4% of the variance, was named Role Worries (two items).

Table 2. Factor pattern for the items of CARS-J

Original items[a]		Factor loading[b]			
		1	2	3	4
DW	Threaten my life (Item 14)	0.82	0.13	0.28	0.18
DW	Cause me to die (Item 27)	0.72	0.21	0.17	0.23
HW	Threaten my physical health	0.72	0.15	0.33	0.14
HW	Be more serious than the first diagnosis	0.71	0.22	0.27	0.16
HW	Cause me pain and suffering	0.71	0.24	0.06	0.34
HW	Upset me emotionally	0.67	0.15	0.33	0.01
HW	Require further surgery	0.66	0.42	−0.01	0.15
HW	Require chemotherapy	0.63	0.22	0.05	0.20
RW	Interfere with my physical ability to perform daily activities	0.58	0.19	0.33	0.34
HW	Keep me from doing planned things	0.57	0.13	0.34	0.19
HW	Interfere with my ability to plan for the future	0.53	0.22	0.38	0.39
HW	Require radiation treatment	0.46	0.43	−0.02	0.15
RW	Cause financial problems for me	0.36	0.18	0.07	0.32
WW	Lead me to feel less feminine	0.19	0.73	0.28	0.10
WW	Make me feel less of a woman	0.15	0.67	0.32	−0.08
HW	Mean losing my breast(s)	0.43	0.62	0.03	0.08
WW	Make me feel bad about how my body looks or feels	0.36	0.60	0.22	0.22
WW	Interfere with my sense of sexuality	0.17	0.60	0.19	0.19
WW	Damage my romantic relationship(s)	0.02	0.52	0.25	0.30
WW	Threaten my identity (how I see myself)	0.24	0.50	0.65	0.16
HW	Make me feel that I do not have control over my life	0.43	0.28	0.63	0.23
RW	Harm my self-confidence	0.31	0.49	0.54	0.11
WW	Threaten my spirituality or faith	0.33	0.38	0.48	0.24
RW	Hurt my relationships with friends and family	0.10	0.32	0.45	0.23
RW	Keep me from fulfilling my responsibilities (in my job or at home)	0.39	0.18	0.22	0.75
RW	Keep me from fulfilling important roles (in my job or at home)	0.42	0.17	0.28	0.69
	Variance	24.8	15.3	10.7	8.4
	Eigenvalue	12.2	2.3	1.3	1.1

[a]DW, Death Worries; HW, Health Worries; RW, Role Worries; WW, Womanhood Worries.
[b]Factor loadings for each item for main loading and for the items where cross-loading >0.4 were demonstrated.

Table 3. Internal consistency of CARS-J ($n = 375$)

CARS domain	Items included	Cronbach's alpha coefficient	Mean (SD)
Factor 1 (Health and Death Worries)	13	0.94	27.3 (12.5)
Factor 2 (Womanhood Worries)	6	0.86	7.6 (5.6)
Factor 3 (New: Self-valued Worries)	5	0.88	5.9 (4.7)
Factor 4 (Role Worries)	2	0.91	3.8 (2.5)

Table 4. Convergent validity[a]: correlation coefficients between CARS-J and HADS

HADS[b]	Factor 1 (Health and Death Worries)	Factor 2 (Womanhood Worries)	Factor 3 (New: Self-valued Worries)	Factor 4 (Role Worries)	Overall Worries CARS 1–4
Anxiety	*0.50*	*0.43*	*0.59*	*0.39*	*0.60*
Depression	*0.35*	*0.42*	*0.55*	*0.29*	*0.38*
Total	*0.46*	*0.47*	*0.62*	*0.37*	*0.52*

[a]Only the statistical results corresponding to previously hypothesized results are shown. All correlations between the scales were statistically significant. The italicized values indicate that the hypothesis was supported.
[b]Hospital anxiety and depression scale

Reliability

All Cronbach's alpha coefficients for the subscales were over 0.85; they ranged from 0.86 for Womanhood Worries to 0.94 for Health and Death Worries (Table 3).

Convergent Validity

Pearson correlations between CARS-J subscales and the corresponding HADS scores are shown in Table 4. All correlations of each domain of CARS-J and the anxiety subscale of HADS were statistically significant. In addition, significant correlation between each domain of CARS-J and the depression subscale and total score of HADS were observed.

Discriminant Validity

The observations of discriminant validity are shown in Table 5. Patients who were younger, had a history of chemotherapy, and experienced any physical symptoms showed higher scores for Overall Worries and most other subscales of CARS-J. The presence of previous or current radiotherapy and the period since operation were significantly associated with several subscales of CARS-J, including Health and Death Worries and Womanhood Worries, but not with Overall Worries. Previous or current hormone therapy was not significantly associated with any subscale of CARS-J or Overall Worries.

DISCUSSION

The development of appropriate interventions to address the fear of recurrence is essential to enhance cancer patients' quality of life, and an appropriate assessment instrument is needed to achieve this goal. The present study demonstrated that CARS-J is a reliable and valid tool to assess the fear of recurrence experienced by Japanese breast cancer patients, although there seemed to be several cultural differences between Western and Asian patients.

The findings of factor analysis, which obtained a four-factor structure, are slightly different from the original study, suggesting some cross-cultural differences with regard to the construct validity of the fear of recurrence. In particular, Health and Death Worries in CARS-J, which consisted of both the Health Worries and Death Worries items of the original CARS, may reflect the influence of Japanese culture on patients' view of life and death, namely continuity, wherein not only the soul but also person's individuality continues after death (18). In addition, Self-valued Worries was newly identified. This novel factor showed a strong relationship with anxiety and depression, as evaluated by HADS, and may be a relevant domain when considering novel interventions for ameliorating the fear of recurrence among Japanese cancer patients.

The observation that all Cronbach's alpha coefficients for the subscales were over 0.85 demonstrates that CARS-J has sufficient internal consistency. Convergent validity was demonstrated by the significant correlation between each domain of CARS-J and the anxiety subscale of HADS. The discriminant validity results supported our hypothesis that younger patients and patients with a history of chemotherapy and experiencing physical symptoms would more likely experience the fear of recurrence. However, previous and current hormone therapies were not significantly associated with any type of fear of recurrence. Although further investigation of factors clinically associated with patients' fear of recurrence is beyond the scope of the present study, future studies to address these themes are important and promising for the development of novel interventions to ameliorate patients' fear of recurrence.

The present study has several limitations. First, because the fear of recurrence seems to be influenced by the patients' cultural backgrounds, the findings might not be applicable to patients of other cultures. Second, since the present study was conducted at one institution, an institutional bias might exist. Finally, because this study focused on ambulatory breast cancer patients and relatively few patients with low physical functioning or advanced cancer were enrolled, the results might not be applicable to patients with other types and/or advanced stages of cancer.

Table 5. Discriminant validity[a]: differences in CARS-J scores between patient subgroups.

Group	*N*	CARS domain													
		Factor 1 (Health and Death Worries)			Factor 2 (Womanhood Worries)			Factor 3 (New: Self-valued Worries)			Factor 4 (Role Worries)			Overall Worries CARS 1–4		
		Mean (SD)	*t*	*P* value	Mean (SD)	*t*	*P* value	Mean (SD)	*t*	*P* value	Mean (SD)	*t*	*P* value	Mean (SD)	*t*	*P*
Age (years)																
>50	115	31.4 (11.8)	4.47	0.00	8.7 (5.7)	2.50	0.01	6.3 (4.8)	0.87	0.38	6.3 (4.8)	5.45	0.00	14.3 (5.2)	2.28	0.02
≤50	259	25.3 (12.3)			7.1 (5.5)			5.8 (4.7)			5.8 (4.7)			12.9 (5.4)		
History of chemotherapy																
None	206	23.6 (13.0)	−4.94	0.00	6.9 (5.8)	−2.31	0.02	5.1 (4.7)	−3.21	0.00	3.2 (2.6)	−4.23	0.00	12.0 (5.2)	−3.92	0.00
Some	144	30.2 (11.4)			8.3 (5.5)			6.7 (4.7)			4.3 (2.3)			14.2 (5.3)		
RT																
None	202	25.9 (13.2)	−2.70	0.00	7.1 (5.7)	−2.29	0.02	5.8 (4.8)	−1.00	0.32	3.6 (2.6)	−2.00	0.05	12.9 (5.6)	−1.78	0.08
Some	149	29.5 (11.3)			6.3 (4.6)			6.3 (4.6)			4.1 (2.3)			13.9 (4.9)		
Hormone therapy																
None	118	26.8 (12.6)	−0.73	0.47	7.6 (5.8)	−0.34	0.73	6.0 (4.7)	0.02	0.98	3.6 (2.25)	−1.45	0.15	13.7 (5.8)	0.91	0.37
Some	241	27.8 (12.3)			7.8 (5.6)			6.0 (4.8)			3.9 (2.4)			13.1 (5.1)		
Symptom																
None	283	25.5 (12.3)	−4.89	0.00	7.1 (5.4)	−3.10	0.00	5.3 (4.4)	−3.95	0.00	3.4 (2.4)	−4.67	0.00	12.7 (5.3)	−3.37	0.00
Some	86	32.8 (11.3)			9.2 (5.9)			7.6 (5.2)			4.8 (2.3)			15.0 (5.2)		
Period since operation																
<1 year	82	31.7 (11.6)	F	P	9.0 (5.8)	F	P	7.2 (5.0)	F	P	4.5 (2.3)	F	P	14.0 (5.4)	F	P
≥1 to <3 years	128	28.2 (11.7)	9.88	0.00	7.6 (5.4)	3.18	0.04	6.1 (4.8)	4.19	0.02	4.0 (2.4)	7.31	0.00	14.0 (5.4)	2.63	0.07
≥3 years and more	160	24.5 (12.5)			7.1 (5.6)			5.4 (4.4)			3.3 (2.5)			12.7 (5.2)		

[a]Only the statistical results corresponding to previously hypothesized results are shown.

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Conflict of interest statement

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EPIDEMIOLOGY

Contribution of problem-solving skills to fear of recurrence in breast cancer survivors

Tatuo Akechi · Kanae Momino · Toshinari Yamashita · Takashi Fujita · Hironori Hayashi · Nobuyuki Tsunoda · Hiroji Iwata

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Abstract Although fear of recurrence is a major concern among breast cancer survivors after surgery, no standard strategies exist that alleviate their distress. This study examined the association of patients' problem-solving skills and fear of recurrence and psychological distress among breast cancer survivors. Randomly selected, ambulatory, female patients with breast cancer participated in this study. They were asked to complete the Concerns about Recurrence Scale (CARS) and the Hospital Anxiety and Depression Scale. Multiple regression analyses were used to examine their associations. Data were obtained from 317 patients. Patients' problem-solving skills were significantly associated with all subscales of fear of recurrence and overall worries measured by the CARS. In addition, patients' problem-solving skills were significantly associated with both their anxiety and depression. Our findings warrant clinical trials to investigate effectiveness of psychosocial intervention program, including enhancing patients' problem-solving skills and reducing fear of recurrence among breast cancer survivors.

Keywords Breast cancer · Survivors · Problem-solving skills · Fear of recurrence

T. Akechi (✉)
Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan
e-mail: takechi@med.nagoya-cu.ac.jp

T. Akechi
Division of Palliative Care and Psycho-oncology, Nagoya City University Hospital, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan

K. Momino
Nagoya City University Graduate School of Nursing, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan

T. Yamashita · T. Fujita · H. Hayashi · N. Tsunoda · H. Iwata
Department of Breast Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

T. Yamashita
Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 18-22,Honkomagome 3chome, Bunkyo-ku, Tokyo 113-8677, Japan

H. Hayashi · N. Tsunoda
Department of Breast and Endocrine Surgery, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan

Introduction

Breast cancer is one of the most common cancers among women all over the world; in particular, in Japan its incidence is continually increasing. At present, approximately 60,000 women develop breast cancer annually in Japan. Advances in early detection and individualized medical treatment have improved the survival of breast cancer patients and enabled them to live with the disease for prolonged periods of time.

Breast cancer survivors experience considerable distress. Their most prevalent unmet needs are psychological [1, 2], where fear of recurrence and spread of cancer are the most common [1–3]. Moreover, according to a previous Japanese study on cancer patients' perceived difficulties in daily life, the most common problem is psychological distress [4]. The study also indicated that nearly half of the cancer survivors experience psychological distress—in particular, anxiety about recurrence or metastases of their cancer [4]. Our previous study indicated that approximately one in four Japanese breast cancer survivors experience clinical anxiety and depression, and that the most common

unmet need among ambulatory breast cancer patients is the "fear of cancer spread"; 63 % of the patients reported the need for help to alleviate this fear [5, 6]. It has also been reported that fear of recurrence decreases the quality of life of breast cancer survivors [7].

Thus, fear of cancer recurrence is one of the most common distressing symptoms for cancer survivors, and appropriate interventions are needed. Although certain recent studies have proposed potential interventions to reduce this fear [7, 8], standard strategies to alleviate this distress do not exist. In addition, although Western studies have systematically reviewed the effectiveness of psychosocial interventions for cancer patients, demonstrating that cognitive behavioral therapy is recommended [9], our clinical experience suggests that most cancer patients do not have extreme distortions of cognition and that traditional cognitive therapeutic interventions are often not appropriate for cancer patients [10]. Our experience also suggests that problem-solving therapy (PST) may be useful for reducing fear of recurrence among breast cancer survivors, although PST does not directly deal with fear or anxiety itself, instead focuses on daily problems [10]. PST is a brief intervention program to help patients to use their own skills and resources to solve their problems by using structured strategy.

Thus, we plan to establish a novel psychosocial intervention program, including PST, for reducing fear of recurrence in breast cancer survivors. However, to the best of our knowledge, there have been no findings about the contribution of patients' problem-solving skills to fear of recurrence among breast cancer survivors. Our study investigated the association between problem-solving skills and psychological distress including fear of recurrence among breast cancer survivors. Our hypothesis was that patients' problem-solving skills are significantly associated with fear of recurrence, anxiety, and depression.

Methods

Participants

The participants were ambulatory females with breast cancer visiting the outpatient department of Aichi Cancer Center Hospital, Japan.

The following were the eligibility criteria for the study: women (a) with a diagnosis of invasive breast cancer and who were informed of the cancer diagnosis, (b) who were disease-free survivors after mastectomy or partial mastectomy, and (c) above 20 years. The exclusion criteria were (a) severe mental or cognitive disorders, (b) inability to understand the Japanese language, and (c) patients considered by their oncologists as physically or mentally incapable of participation.

Procedure

Oncologists consecutively identified all eligible patients in their ambulatory clinic and briefly explained the survey to them when they visited the hospital. If they were interested in the study, the oncologists provided them with the questionnaires. Instead of a written consent, patients who agreed to participate in the study, after reading an explanatory document on it, were asked to complete the questionnaire anonymously at home and send them back by mail. Patients who did not wish to participate in the survey returned the questionnaires stating "no participation."

This study was approved by the Institutional Review Board and Ethics Committee of Aichi Cancer Center and was conducted in accordance with the principles laid down in the Helsinki Declaration.

Instruments

Japanese version of the Concerns about Recurrence Scale (CARS-J)

CARS-J is a 26-item, self-report scale, originally developed in the USA [11]. The reliability and validity of CARS-J has been confirmed among Japanese breast cancer patients, although factor structure is slightly different from the original study, suggesting some cross-cultural differences with regard to the construct validity of fear of recurrence [12]. CARS-J assesses the overall fear of breast cancer recurrence and four domains of specific fear of recurrence. Overall fear consists of four items: questions on frequency, potential for upset, consistency, and intensity of fear. The four domains are Health and Death Worries (13 items that refer to concern about future treatment, emotional upset, physical heath, planning activities, loss of breast, and the possibility that recurrence of breast cancer could lead to death); Womanhood Worries (6 items referring to femininity, sexuality, womanhood, body image, and romantic relationships); Self-valued Worries (5 items referring to identity, spirituality or faith, self-confidence, and relationships with friends and family); and Role Worries (2 items pertaining to roles and responsibilities at work and at home).

Japanese version of the Social Problem-Solving Inventory-Revised Short Form (SPSI-R:S)

SPSI-R:S is a 25-item, self-report scale that was developed to assess problem-solving skills [13–15]. It includes five scales: Positive Problem Orientation (PPO, 4 items); Negative Problem Orientation (NPO, 5 items); Rational Problem Solving (RPS, 5 items); Impulsivity/Carelessness

style (IPC, 5 items); and Avoidance Style (AS, 5 items). The PPO scale assesses general cognitive skills, such as the tendency to view problems in a positive light, to see them as challenges rather than as threats, and to be optimistic regarding the existence of a solution and one's ability to detect and implement effective solutions. In contrast, the NPO scale assesses the presence of maladaptive problem-solving approaches and cognitive-emotional tendencies that prevent effective problem solving. The RPS scale assesses an individual's tendency to use effective problem-solving techniques systematically and deliberately. The ICS scale evaluates a tendency to solve problems by making overly quick decisions in an impulsive, incomplete, and haphazard manner. The AS scale measures maladaptive patterns of problem solving characterized by general passivity or putting the problem off and waiting for problems to resolve by themselves [16, 17]. Social problem-solving score (SPS) is calculated as PPO/4+ (20− NPO)/5 + RPS/5+ (20− ICS)/5+ (20− ACS)/5; a higher score indicates better problem-solving skills.

Hospital anxiety and depression scale (HADS)

HADS is a 14-item, self-report questionnaire that was developed to evaluate psychological distress, including anxiety and depression, in medically ill patients and does not contain questions regarding physical symptoms [18]. Participants are asked to rate their feelings during the previous week using a four-point Likert scale. HADS includes an anxiety and a depression subscale (0–21 points each), and the total score ranges from 0 to 42. Higher scores indicate a more severe degree of depression and anxiety. The Japanese version of HADS has been validated for cancer populations [19].

Sociodemographic and clinical factors

An *ad hoc* self-administered questionnaire was used to obtain information on sociodemographic status such as age, marital status, employment status, educational level, types of treatments received, and time since the operation.

Statistical analysis

First, to investigate the association between patients' problem-solving skills and fear of recurrence and psychological distress in univariate analysis, Pearson's correlation coefficients between SPS and subscales of CARS-J and SPS and anxiety and depression scores of the HADS were calculated. Second, to investigate the association between problem-solving skills and fear of recurrence and psychological distress after adjusting for potential confounding factors in multivariate analysis, multiple regression analyses were conducted, including age, marital status, and education as independent variables.

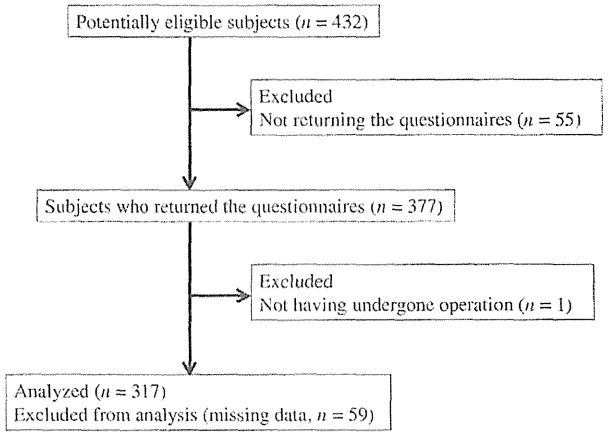

Fig. 1 Flow diagram of the analyzed subjects

A p value of less than 0.05 was adopted as the significance level in all statistical analyses, and all p-values reported were two-tailed. All statistical procedures were conducted using IBM SPSS Statistics version 19 software for Windows (SPSS Inc., 2010).

Results

Among the 432 patients who met the eligibility criteria, a total of 377 patients (87 %) returned the questionnaires. A total of 60 patients were excluded because of not having undergone operation and missing data. Data from the remaining 317 patients (73 %) were analyzed. Flow diagram of the analyzed subjects is shown in Fig. 1.

Patients' characteristics

Participants' characteristics are shown in Table 1. The median age of the study population was 55 years. A majority of the women were married (79 %), and approximately half of them had a full- or part-time job (47 %). More than half the number of participants reported experience of either chemotherapy or hormonal therapy. In addition, 23 and 33 % of the participants had undergone operation less than 1 year and 1–3 years earlier, respectively.

Association between problem-solving skills and fear of recurrence and psychological distress

The results of univariate analyses are shown in Table 2. SPS were significantly associated with all dimensions of fear of recurrence, except for Role Worries and

Table 1 Characteristics of the study participants ($n = 317$)

Characteristics		*N*	(%)
Age	Mean: 55 (*SD* = 10) Median: 55 (range, 31–80)		
Sex	Female	317	100
Marital status	Married	251	79
	Others	66	21
Job	Full-time	75	24
	Part-time	73	23
	Others	159	50
	Unknown	10	3
Education	High school	172	54
	College/university	139	44
	Unknown	6	2
Anticancer treatment	Chemotherapy	206	55
	Radiation therapy	149	40
	Hormone therapy	241	64
Duration since operation	<1 year	72	23
	≥1 to <3 years	105	33
	≥3 years	135	43
	Unknown	5	2

psychological distress. Correlation coefficients between problem-solving skills and the subscales of fear of recurrence ranged from −0.10 to −0.30. Correlation coefficients between problem-solving skills and anxiety and depression were −0.29 and −0.33, respectively. The results of multivariate analyses are shown in Table 3. SPS were significantly associated with all dimensions of fear of recurrence and psychological distress. Among adjusted variables, younger age were significantly associated with Overall Worries, Health and Death Worries, Womanhood Worries, and Role Worries, while age was not significantly associated with Self-valued Worries.

Discussion

The present findings support the hypothesis that patients' problem-solving skills contributed to the development of fear of recurrence, anxiety, and depression among breast cancer survivors. These results suggest that a psychosocial intervention program enhancing patients' problem-solving skills can ameliorate patients' psychological distress, including fear of recurrence.

As mentioned earlier, PST is a brief intervention program to help patients use their own skills and resources to solve their problems by using structured strategy. In addition, PST program specifically for cancer patients is already available [10, 20–22], while appropriate modification for addressing fear of recurrence experienced by breast cancer survivors should be needed. In addition, since association between patients' problem-solving skills and fear of recurrence are not so strong (e.g., correlation coefficients between problem-solving skills and subscales of fear of recurrence ranged from −0.10 to −0.30), only brief PST may not be a strong intervention to reduce patients' fear of recurrence. Novel intervention program including other therapeutic techniques such as group therapy and behavioral activation as well as PST can be more appropriate to effectively ameliorate patients' fear of recurrence. However, our findings warrant clinical trials to investigate effectiveness of psychosocial intervention program, including enhancement of patients' problem skills, on patients' fear of recurrence among breast cancer survivors.

We would like to comment on patients' demographic factors that are associated with fear of recurrence. In particular, our findings demonstrate that younger age is an important factor that contributes to developing patients' fear of recurrence. Many previous studies have suggested that younger breast cancer patients can experience stronger psychological distress; [23–25] these findings suggest that target population should include younger breast cancer patients.

The present study has several limitations. First, the investigation was cross-sectional in design, precluding any conclusions with regard to causality. Second, because fear of recurrence seems to be influenced by the patients' cultural backgrounds, the findings might not be applicable to patients of other cultures. Finally, since the present study

Table 2 Associations between problem-solving skills and fear of recurrence and psychological distress—correlation coefficients

	Fear of recurrence					Psychological distress	
	Overall worries	Health and death worries	Womanhood worries	Self-valued worries	Role worries	Anxiety	Depression
Problem-solving skills	−0.15*	−0.16*	−0.19*	−0.30*	−0.10	−0.29*	−0.33*

* $p < 0.01$

Table 3 Associations between problem-solving skills and fear of recurrence and psychological distress—multiple regression analyses

Dependent variables	Independent variables	Coefficient (B)	Standardized coefficient (Beta)	t	p	R^2
Overall worries	Problem-solving skills	−0.11	−0.19	−3.23	<0.01	0.06
	Age	−0.02	−0.16	−2.72	<0.01	
	Marital status	0.19	0.06	1.06	0.29	
	Education	0.09	0.03	0.59	0.56	
Health and death worries	Problem-solving skills	−0.09	−0.20	−3.57	<0.01	0.13
	Age	−0.03	−0.26	−4.69	<0.01	
	Marital status	0.22	0.09	1.69	0.09	
	Education	0.25	0.13	2.27	0.02	
Womanhood worries	Problem-solving skills	−0.09	−0.21	−3.78	<0.01	0.09
	Age	−0.02	−0.24	−4.14	<0.01	
	Marital status	−0.08	−0.03	−0.59	0.55	
	Education	0.02	0.01	0.20	0.84	
Self-valued worries	Problem-solving skills	−0.14	−0.32	−5.84	<0.01	0.11
	Age	−0.01	−0.10	−1.72	0.09	
	Marital status	0.16	0.07	1.29	0.20	
	Education	0.18	0.09	1.64	0.10	
Role worries	Problem-solving skills	−0.09	−0.16	−2.84	<0.01	0.10
	Age	−0.03	−0.21	−3.71	<0.01	
	Marital status	0.34	0.11	2.09	0.04	
	Education	0.34	0.14	2.41	0.02	
Anxiety	Problem-solving skills	−0.46	−0.31	−5.45	<0.01	0.10
	Age	−0.03	−0.10	−1.75	0.08	
	Marital status	0.03	0.003	0.06	0.95	
	Education	0.45	0.06	1.10	0.27	
Depression	Problem-solving skills	−0.52	−0.31	−5.65	<0.01	0.13
	Age	−0.04	−0.12	−2.18	0.03	
	Marital status	−1.25	−0.14	−2.58	0.01	
	Education	0.28	0.04	0.66	0.51	

was conducted at one institution, an institutional bias might exist.

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ORIGINAL ARTICLE

Tamoxifen versus tamoxifen plus doxorubicin and cyclophosphamide as adjuvant therapy for node-positive postmenopausal breast cancer: results of a Japan Clinical Oncology Group Study (JCOG9401)

Tadahiko Shien · Hiroji Iwata · Kenjiro Aogi · Takashi Fukutomi · Kenichi Inoue · Takayuki Kinoshita · Masato Takahashi · Akira Matsui · Taro Shibata · Haruhiko Fukuda

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Abstract
Background Cancer subtype has recently become an increasingly important consideration when deciding the treatment strategy for breast cancer. For the estrogen receptor positive (ER+) subtype, the efficacy of adjuvant endocrine therapy is definitive, but that of adjuvant chemotherapy is controversial.
Methods In order to evaluate the effect of adding doxorubicin (A) and cyclophosphamide (C) to tamoxifen (TAM) (ACT) on the overall survival (OS) of node-positive postmenopausal breast cancer (PMBC) patients, we conducted a randomized trial. Eligibility criteria included pathologically node-positive (n = 1–9) PMBC, stage I–IIIA disease. Patients were randomized to receive either TAM (20 mg daily) for 2 years or A (40 mg/m^2) and C (500 mg/m^2) plus TAM (ACT) as adjuvant therapy following surgery.
Results One hundred twenty-nine patients were recruited (TAM 64, ACT 65) between October 1994 and July 1999. The hazard ratios for OS and relapse-free survival (RFS) were 0.58 (95 % CI 0.24–1.39; log-rank p = 0.22) and 0.45 (95 %CI 0.24–0.86; log-rank p = 0.013), respectively, in favor of ACT. The 5-year OS and RFS were 76.9 % (ER+ 87.1 %, ER− 53.3 %) and 54.9 % (ER+ 59.3 %, ER− 42.9 %) for TAM and 85.0 % (ER+ 90.0 %, ER− 77.1 %) and 76.7 % (ER+ 76.9 %, ER− 76.0 %) for ACT. A higher proportion of the patients receiving ACT than those receiving TAM experienced grade 3 decreased white blood cell count and grade 2–3 nausea.
Conclusion The efficacy of adding AC to TAM was not high for ER+, node-positive PMBC. However, adjuvant ACT therapy was considered to be effective for ER−, node-positive PMBC.

Keywords Breast cancer · Adjuvant treatment · Node-positive · Postmenopausal women

On behalf of the JCOG Breast Cancer Study Group. The 22 institutions that belong to the JCOG Breast Cancer Study Group are listed in Appendix.

T. Shien (✉)
Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama 700-8558, Japan
e-mail: tshien@md.okayama-u.ac.jp

H. Iwata
Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya 464-8681, Japan

K. Aogi
Department of Surgery, National Shikoku Cancer Center, Matsuyama 791-0280, Japan

T. Fukutomi · T. Kinoshita
Department of Breast Surgery, National Cancer Center Hospital, Tokyo 104-0045, Japan

K. Inoue
Department of Medical Oncology, Saitama Cancer Center, Saitama 362-0806, Japan

M. Takahashi
Department of Breast Surgery, Hokkaido Cancer Center, Sapporo 003-0800, Japan

A. Matsui
Department of Surgery, National Hospital Organization Tokyo Medical Center, Tokyo 152-8902, Japan

T. Shibata · H. Fukuda
JCOG Data Center, Multi-institutional Clinical Trial Support Center, National Cancer Center, Tokyo 104-0045, Japan

Introduction

Tamoxifen (TAM) is an effective drug used as adjuvant therapy for postmenopausal breast cancer (PMBC) patients. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found, through a meta-analysis, that adjuvant TAM produced better disease-free survival (DFS) and overall survival (OS) in 1990, regardless of the patient's hormone receptor status [1]. Adjuvant chemotherapy for PMBC patients has otherwise been regarded as effective for improving prognosis. The EBCTCG suggested that an anthracycline-containing regimen could improve the breast cancer death ratio and recurrence rate ratio by 16 and 11 %, respectively, compared to a cyclophosphamide, methotrexate, and fluorouracil regimen [2]. At a National Institutes of Health conference, it was proposed that an anthracycline-containing regimen should be the standard adjuvant therapy for resected breast cancer [3]; therefore, an anthracycline-containing regimen has since become the standard adjuvant therapy for node-positive breast cancer patients. However, the efficacy of TAM plus chemotherapy for PMBC was not evaluated in the 1990s.

At a conference at St. Gallen in 1992, chemotherapy was recommended for postmenopausal, node-negative, estrogen receptor (ER) negative (ER−) patients [4]. Fisher et al. [5] reported that TAM plus chemotherapy was more effective than TAM alone for node-positive PMBC in a subgroup analysis of data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-16 trial. Meanwhile, the EBCTCG meta-analysis also showed that chemotherapy alone contributed little to the prolongation of the survival of breast cancer patients over 50 years of age [2]. Thus, TAM plus chemotherapy was expected to be promising as an adjuvant therapy for postmenopausal, node-positive breast cancer patients.

In 1994, to elucidate the efficacy of adding an anthracycline-containing chemotherapy to TAM used as an adjuvant therapy for PMBC, the Breast Cancer Study Group of the Japanese Clinical Oncology Group (JCOG) designed a prospective randomized clinical trial of a regimen of doxorubicin (A) and cyclophosphamide (C) plus TAM (ACT) compared to TAM alone.

Patients and methods

Patients

Postmenopausal female patients who were younger than 70 years and had clinical stage I–IIIa breast cancer were eligible for this study. All patients had to have undergone curative mastectomy with axillary node dissection, and the involvement of 1–9 axillary nodes had to have been detected upon histological examination. Additional eligibility criteria were a World Health Organization performance status of 0–1 and adequate bone marrow, liver, and kidney function. Patients who received previous treatment for breast cancer were excluded. Informed consent was obtained from each patient before study participation.

Planned treatment schedules

All patients were randomly assigned to either of the following two regimens: the TAM arm (only TAM was administered at 20 mg/day until relapse or for a maximum of 2 years), and the ACT arm (A was administered at 40 mg/m^2 intravenously and C was administered at 500 mg/m^2 intravenously on day 1 every 28 days for 6 cycles, while TAM was administered at 20 mg/day for a maximum of 2 years in the absence of relapse, regardless of hormone receptor status).

The target recruitment for each study arm was 110 patients. Randomization was conducted using the minimization method, and the arms were balanced in terms of ER and progesterone receptor (PR) status (positive, i.e., >10 %, versus negative or unknown), HER2 status (positive versus negative or unknown), number of metastatic nodes (1–3 versus 4–9), age (≤60 versus 61–70 years), and institution.

Patient assessment

Initial workup included medical history, tumor assessment, physical examination, routine hematology and chemistry analyses, chest radiography, liver ultrasonography, and bone scan. Hematology and chemistry analyses, tumor marker measurements, and urinalysis were repeated monthly. To check for distant metastasis, chest radiography and liver ultrasonography were performed every 6 months, a bone scan was performed every year, and bilateral mammography was performed every 2 years. Hematological disorders and toxicity were evaluated according to the toxicity grading criteria of the Japan Clinical Oncology Group [6], and were recorded in case report forms.

Endpoint

As per the study design, the primary endpoint was OS and the secondary endpoint was RFS. OS was defined as the time from randomization to death from any cause, and it was censored at the final follow-up date. RFS was defined as the time from randomization to either the first event of recurrence or death from any cause, and it was censored on the date that recurrence-free status was verified. OS and RFS were evaluated according to hormone receptor status (either ER+ or PR+ versus both ER− and PR− or unknown) in subgroup analyses. In addition, the safety of the treatment was evaluated.