As use of limited breast surgery has recently increased, including breast-conserving surgery and SNBs, further studies are needed of patients who undergo limited breast surgery.

CQ33. Is treatment without mastectomy recommended for occult breast cancer?

Recommendation

For authentic occult breast cancer with no primary lesion inside the breast confirmed by MRI, therapy without resection of the breast might be carefully selected, provided that patients undergo radiotherapy to the whole breast (Grade C1).

Occult breast cancer is defined as axillary metastasis of breast cancer cells with no clinically and/or radiologically evident primary tumor in the breast. Basic treatment strategy for occult breast cancer is mastectomy and ALND. MRI identifies the primary breast lesions in about 70 % of patients who had no detectable tumor by mammography. Of 22 patients with positive MRI who had breast surgery, 21 (90 %) had tumors within their surgical specimens. Of 5 patients with negative MRI, only 1 (20 %) had a tumor in her surgical specimen [55]. In a recent study of patients with true occult breast cancer, in whom MRI confirmed absence of any minor primary tumor, 100 % local control by radiotherapy alone without mastectomy was reported [56]. When patients with occult breast cancer received no local treatment but were simply observed, local recurrence occurred in 21–53 % of the patients [57].

Treatment of occult breast cancer only with radiotherapy, without mastectomy, should be cautiously considered as limited data exists for long-term outcomes for this treatment.

CQ34. Is pharmacological therapy effective for postmastectomy pain syndrome (PMPS)?

Recommendation

Although there is no sufficient evidence to demonstrate the usefulness of medical therapy for PMPS, it may be appropriate to use medications for its treatment paying careful attention to adverse events (Grade C1).

PMPS is a neuropathic pain syndrome that may develop after breast surgery, and is believed to be due to injury to the ICBN. Antidepressant drugs [tricyclic antidepressants (SNRI: serotonin noradrenaline re-uptake inhibitors; SSRI: selective serotonin re-uptake inhibitor)], anti-convulsant drugs (gabapentin, pregabalin) and local anesthesia are considered first-line medications for most type of neuropathic pain [58]. Few studies of these drugs for PMPS exist [59]. Efficacy of pharmacological therapy is unclear because these trials did not have enough patients. Furthermore, as these drugs themselves have high rates of adverse events, pharmacological treatment should be considered carefully.

CQ35. Is surgery recommended for phyllodes tumor?

Recommendation

We recommend wide local excision for phyllodes tumors (Grade B).

In a retrospective review of 164 patients, local recurrence rates were 18.9 %, and related to the width of excision margin and tumor size. A surgical approach should include a wide local excision with histologic margins negative for malignant cells [60]. In a retrospective review of 48 women with high-grade malignant phyllodes tumors, the recurrence rate was 60 % for those treated with local excision only (margins <1 cm), compared with 28 % for those treated with wide local excision with appropriate margins (margins ≥1 cm) [61]. ALND is usually not required, as lymph node involvement is only rarely reported, even with malignant tumors.

The difficulty in discriminating phyllodes tumors from fibroadenomas lies in their histologic characteristics and radiologic features. If the needle biopsy results indicate fibroadenoma, but the tumor subsequently exhibits rapid growth or becomes symptomatic, excisional biopsy should be performed.

Conflict of interest The authors declare that they have no conflict of interest.

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CLINICAL TRIAL

Survival outcome and reduction rate of Ki-67 between pre- and post-neoadjuvant chemotherapy in breast cancer patients with non-pCR

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Abstract The research question of this investigation is whether the reduction rate of Ki-67 after neoadjuvant chemotherapy (NAC) could indicate a survival in patients with non-pCR. A total of 455 patients had received NAC, and subsequent surgery was analyzed retrospectively. Patients with non-pCR were divided into three subgroups according to Ki-67 change: High-reduction (the absolute value of Ki-67 was reduced by >80 % compared with that prior to NAC), Low-reduction (the absolute value of Ki-67 was reduced by 0–80 % compared with that prior to NAC), and Increase group (the absolute value of Ki-67 was increased compared with that prior to NAC). The relapse-free survival (RFS) rates were compared among subgroups. pCR was achieved in 93 patients (20.4 %). In patients with non-pCR, the median reduction rate of Ki-67 was 60 %. A total of 15 % of patients were in the High-reduction, 63 % in the Low-reduction, and 22 % in the Increase group. The median follow-up period was 64.5 months. The 5-year RFS rates among the three groups were significantly different ($p < 0.0001$), and the differences were also observed in the HER2 ($p = 0.033$), triple-negative ($p = 0.034$), and luminal-like subtypes ($p = 0.001$). Patients in the High-reduction group showed comparable RFS to that of patients with pCR ($p = 0.363$). In patients with non-pCR, the reduction rate of Ki-67 after NAC significantly predicted RFS regardless of cancer subtypes. Therefore, patients who are non-pCR but who achieve a high reduction of Ki-67 can be expected to have a favorable prognosis similar to that of patients with pCR.

Keywords Breast cancer · Neoadjuvant chemotherapy · Ki-67 · Pathological complete response · Prognostic factor

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Introduction

Neoadjuvant chemotherapy (NAC) is now well established as the standard treatment for patients with operable and locally advanced breast cancer [1, 2]. NAC followed by surgery has several clinical benefits compared with surgery alone, for example, higher rate of breast-conservation due to tumor shrinkage and favorable long-term survival outcomes, such as recurrence-free survival (RFS) and overall survival (OS) [3]. In addition, a useful advantage of NAC related to future treatment decisions could be a confirmation of in vivo chemo-sensitivity in individual patients. Biological and pathological analysis differences between biopsy samples before NAC and surgical specimens after NAC could provide new information on predictive and prognostic markers.

A pathological complete response (pCR) after NAC is established as a powerful surrogate marker for long-term oncological outcomes [4, 5]. The achievement of pCR was selected as the primary endpoint of many NAC trials. However, the achievement rate of pCR is usually small, generally reported in only 10–30 % of patients, with standard NAC regimens [3, 6, 7]. For residual patients with

non-pCR, a surrogate marker for survival has not yet been well established. Thus, development of a useful marker for prognosis in patients with non-pCR is highly desirable.

Ki-67 is a nuclear protein with nuclear function that is expressed in all phases of the cell cycle, except G0 [8]. Ki-67 is one of the major markers of tumor proliferation, assessed by immunohistochemistry (IHC) with the anti-Ki-67 antibody called MIB-1 [9]. Many investigations have reported that Ki-67 is an independent predictive and prognostic marker in patients with operable breast cancer [10, 11]. Thus, assessment of Ki-67 is already introduced into daily practice in order to discriminate breast cancer subtypes, predict oncological outcomes, or decide on indications for adjuvant treatment [12].

In the NAC setting, changes of the absolute values of Ki-67 between pre- and post-NAC are often observed [13–15]. Reduction of the absolute value of Ki-67 after NAC compared with the value prior to NAC has been reported to be associated with a favorable prognosis [15–17]. In addition, we previously reported that the significance of this association was dependent on breast cancer subtypes [18]. However, almost all previous investigations, including ours, simply divided patients into two subgroups according to Ki-67 changes, such as Ki-67 increase or Ki-67 decrease. Also, a reduction of the absolute value of Ki-67 after NAC was commonly observed in patients with non-pCR, reported in 60–80 % of patients [18–20].

It is speculated that in patients with non-pCR, the reduction rate of Ki-67, such as High reduction or Low reduction, would affect their long-term oncological outcome. However, to the best of our knowledge, no published investigation has reported an association between the reduction rate of Ki-67 and the oncological outcome in detail. We hypothesized that the reduction rate of Ki-67 has a prognostic significance and has a potential to become a useful biomarker for oncological outcomes in patients with non-pCR. Therefore, we retrospectively analyzed whether the reduction rate of Ki-67 could discriminate oncological outcomes in patients with non-pCR after NAC and predict whether a prognostic significance of the reduction rate of Ki-67 was dependent on breast cancer subtypes.

Materials and methods

Patients and treatment

We retrospectively reviewed the clinical and pathological records of patients who received neoadjuvant anthracycline with or without taxane chemotherapy followed by curative surgery at the National Cancer Center Hospital East (Kashiwa, Japan) between January 2000 and December 2011. Written informed consent for treatment was obtained from all patients before treatment initiation. For inclusion in this analysis, the patients had to be in clinical stage II A to stage III C with histological confirmation of breast cancer by core needle biopsy, according to the American Joint Committee on Cancer staging (7th edition). All chemotherapy regimens were allowed for this analysis, if the chemotherapy was administered as anthracycline with or without taxane. Basically, NAC was administered in four to eight cycles. If HER2 positivity was confirmed by three plus of IHC scoring or c-erbB2 gene amplification by fluorescence in situ hybridization (FISH), then trastuzumab was administered as neoadjuvant treatment for 3 months after 2008. On the other hand, none of the patients with HER2-positive disease received neoadjuvant trastuzumab treatment from 2000 to 2008, because trastuzumab was not approved in Japan as neoadjuvant treatment until 2008.

Patients whose clinical or pathological parameters were not available were excluded from this analysis. Patients who received neoadjuvant hormonal therapy or a combination of chemo-hormonal therapy and who had not undergone curative surgery were also excluded from this analysis.

The indications for the composition of post-surgical treatment (adjuvant treatment) were based on the St. Gallen Consensus Recommendation at that time. In brief, none of the patients received additional chemotherapy after surgery (adjuvant chemotherapy). All patients who underwent breast-conserving surgery had routinely received adjuvant radiotherapy. Adjuvant radiotherapy was also administered to patients with mastectomy who had axillary lymph node metastasis. Patients whose hormonal status was ER and/or PgR positive by IHC underwent adjuvant hormonal therapy for at least 5 years. If HER2 positivity was confirmed by IHC or FISH, trastuzumab was administered as adjuvant treatment for 1 year after 2005. On the other hand, none of the patients with HER2-positive disease received adjuvant trastuzumab treatment between 2000 and 2005, because trastuzumab was not approved in Japan as adjuvant treatment until 2005.

Immunohistochemistry

IHC was routinely performed in our institution using formalin-fixed, paraffin-embedded tissue blocks with both pre-treatment core needle biopsy samples and post-treatment surgical excision specimens. Immunohistochemical staining of tumors for ER (Confirm anti-ER (SP1), rabbit monoclonal antibody, Ventana Medical Systems), PgR (Confirm anti-PGR (1E2), rabbit monoclonal antibody, Ventana Medical Systems), and HER2 (Pathway anti-HER2 (4B5), rabbit monoclonal antibody, Ventana Medical Systems) were performed using the automated

Benchmark XT platform (Ventana Medical Systems) and according to the manufacturer's recommendations. For Ki-67 (Clone MIB1, Dako, Glostrup, Denmark; dilution 1:50), tumors were stained in accordance with the manufacturer's recommendation. All tumor samples were evaluated by two experienced and certificated pathologists belonging to our institution. A cutoff value of ≥ 1 % of positively stained nuclei was used as the definition of ER- and PgR-positive disease. HER2 protein positivity was defined as a score of 3 by IHC or as positive by FISH. The methods and procedures of IHC were unchanged through the study period.

Ki-67 expression was quantified using a visual grading system. Cells stained for Ki-67 were counted and expressed as a percentage. If the staining was homogenous, then the percentage of Ki-67 positive cells among the total number of carcinoma cells counted was determined at a magnification of 400× using an eye-piece graticule and counting 10 randomly selected fields. When hot spots, defined as areas in which Ki-67 staining was particularly prevalent, were present, pathologists assessed the whole section and recorded the overall average score. Each Immunohistochemical staining included an external control to validate the Ki-67 protein expression status of each case. Therefore, the same section was used for the external control.

The subtypes were defined by IHC of core needle biopsy samples as follows. A luminal-like subtype was defined as negative HER2 status, ER positive, and/or PgR positive. The triple-negative subtype was defined as negative HER2 status, ER negative, and PgR negative. The HER2 subtype was defined as positive HER2 status regardless of ER and PgR status.

A pathological complete response (pCR) was defined by the absence of invasive carcinoma in the primary breast tumor regardless of pathological axillary node status. And then, only the presence of residual ductal carcinoma in situ was included in the pCR.

Subgroup assignment according to Ki-67 change in patients with non-PCR

Patients with non-pCR were subdivided into three subgroups according to Ki-67 change after neoadjuvant chemotherapy as follows: High-reduction group (the absolute value of Ki-67 was reduced by >80 % compared with that prior to neoadjuvant chemotherapy), low-reduction group (the absolute value of Ki-67 was reduced by 0–80 % compared with that prior to neoadjuvant chemotherapy), and increase group (the absolute value of Ki-67 was increased compared with that prior to neoadjuvant chemotherapy).

Statistical analysis

The definition of relapse excluded local breast relapse, axillary lymph node relapse, and newly diagnosed contralateral breast cancer. The relapse-free survival (RFS) period was defined as the interval from the date of surgery to that of the first diagnosis of relapse or the last follow-up date without relapse.

Associations between prognostic factors and RFS were analyzed using Chi-square test or Fisher's exact test, where appropriate. The Cox proportional hazards model was used for the estimation of multivariate analysis. Survival distributions were estimated using the Kaplan–Meier method for RFS, and the Log-rank test was used to compare survival in different strata. All statistical tests were two sided and had a 95 % confidence interval (CI), with the level of significance established at $p < 0.05$. Statistical analyses were performed using PASW (Predictive Analysis Software) 18.0 for Windows (SPSS, IBM, Chicago, Ill., USA). This study was carried out in accordance with Declaration of Helsinki and Japanese ethical guidelines for epidemiological research. We obtained the National Cancer Center institutional review board (NCC-IRB) waiver from the NCC-IRB chairperson to conduct this study.

Results

Patient characteristics

A total of 455 patients were eligible and analyzed in this investigation. Table 1 shows the baseline characteristics of all patients. The median and mean numbers of NAC cycles were 8.0 and 6.2 (range 2–8 cycles), respectively. Over 80 % of patients received NAC with anthracycline followed by taxane, and the residual patients received only the anthracycline-containing regimen. The median Ki-67 value before NAC was 20.0 % (range 1.0–80.0 %). The patients were subdivided into three subtypes according to IHC pattern. A total of 195 patients (42.8 %) were classified as Luminal-like, 126 (27.7 %) were Triple-negative, and 134 (29.5 %) were HER2 subtype. Baseline characteristics between subtypes showed no significant differences, except for the median Ki-67 value before NAC ($p < 0.001$). More details of baseline characteristics are shown in Table 1.

Response and pathological outcome after neoadjuvant chemotherapy

pCR was observed in 20.4 % of all patients. The pCR rate was highest for HER2 (35.8 %) followed by Triple-negative (25.8 %) and Luminal-like subtypes (6.7 %), and the differences in pCR rates were significantly different between subtypes ($p < 0.001$). The residual 362 patients having non-pCR were subdivided into three subgroups according to their Ki-67 change status after NAC. Of 362 patients, 53 (14.6 %), 179 (49.5 %), and 130 patients

Table 1 Baseline characteristics

	Total (%)	Luminal (%)	TN (%)	HER2 (%)	*p*
No. of patients (%)	455 (100)	195 (42.8)	126 (27.7)	134 (29.5)	
Median age (range)	53 (25–71)	52 (25–70)	53 (28–71)	53 (31–71)	0.69
Menstrual status					0.74
Premenopausal	209 (45.9)	86 (44.1)	55 (43.7)	47 (35.1)	
Postmenopausal	246 (54.1)	109 (55.9)	71 (56.3)	87 (64.9)	
Clinical tumor status					0.16
cT1	16 (3.5)	8 (4.1)	4 (3.2)	4 (3.0)	
cT2	254 (55.8)	112 (57.4)	74 (58.7)	68 (50.7)	
cT3	96 (21.1)	35 (18.0)	23 (18.3)	38 (28.4)	
cT4	89 (19.6)	40 (20.5)	25 (19.8)	24 (17.9)	
Clinical nodal status					0.084
cN positive	308 (67.7)	125 (64.1)	87 (69.0)	96 (71.6)	
cN negative	147 (32.3)	70 (35.9)	39 (31.0)	38 (28.4)	
ER status					
Positive	235 (51.6)	193 (98.9)	0	42 (31.3)	
Negative	220 (48.4)	2 (1.1)	0	92 (68.7)	
PgR status					
Positive	194 (42.6)	165 (84.6)	0	29 (21.6)	
Negative	261 (57.4)	30 (15.4)	0	105 (78.4)	
HER2 status					
Positive	134 (29.5)	0	0	134 (100)	
Negative	321 (70.5)	195 (100)	126 (100)	0	
Median Ki-67 Pre-chemotherapy (range)					<0.001
	20.0 (1–80)	9.0 (1–14)	30.0 (2–80)	20.0 (4–70)	
Neoadjuvant chemotherapy regimen					0.45
Anthracycline → Taxane	380 (83.5)	164 (84.1)	101 (80.2)	115 (85.8)	
Anthracycline only	75 (16.5)	31 (15.9)	25 (19.8)	19 (14.2)	

(35.9 %) were in High-reduction, Low-reduction, and Increase groups, respectively. The proportions of the different subtypes in these subgroups were not significantly different ($p = 0.794$), but the median Ki-67 values after NAC were significantly different among the subtypes ($p < 0.001$). The details of response and pathological outcome after NAC are shown in Table 2.

Survival according to Ki-67 change

The median follow-up period was 64.5 months and ranged from 7 to 160 months. In the non-pCR population, disease relapse was observed in 114 patients (31.5 %) during the follow-up period. Figure 1 shows the RFS curves according to Ki-67 change in all non-pCR patients. The 5-years RFS rate was 86.2 % in the High-reduction group, 75.5 % in the Low-reduction group, and 46.9 % in the Increase group. The difference in 5-year RFS among the three subgroups was statistically significant (Log-rank $p < 0.001$). We re-analyzed the 5-year RFS separately in relation to subtypes (Luminal-like, Triple negative, and HER2). The significant RFS differences shown above were also observed for all subtypes, such as Luminal-like (Log-rank $p = 0.003$, Fig. 2), Triple-negative (Log-rank $p = 0.040$, Fig. 3), and HER2 subtype (Log-rank $p = 0.034$, Fig. 4).

Figure 5 shows the RFS curves for the pCR group and the High-reduction group of non-pCR patients. There was no significant difference in the 5-year RFS between the two groups (Log-rank $p = 0.363$).

Multivariate analysis

The prognostic factors that have been well established by previous investigations and Ki-67 change status were analyzed for association with unfavorable RFS by multivariate analysis as shown in Table 3. The multivariate analysis identified several independent prognostic factors, such as pT status (Hazard ratio (HR) 2.24, 95 % CI

Table 2 Treatment outcomes of neoadjuvant chemotherapy

	Total (%) $n = 455$	Luminal (%) $n = 195$	TN (%) $n = 126$	HER2 (%) $n = 134$	p
pCR	93 (20.4)	13 (6.7)	32 (25.4)	48 (35.8)	<0.001
non-pCR	362	182	94	86	
Subgroups according to Ki-67 change					0.794
High reduction	53 (14.6)	28 (15.4)	14 (14.9)	11 (12.8)	
Low reduction	228 (63.0)	124 (68.1)	53 (56.4)	51 (59.3)	
Increase	81 (22.4)	30 (16.5)	27 (28.7)	24 (27.9)	
Median Ki-67 post-chemotherapy (range)					<0.001
	5.0	4.0	20.0	10.0	
	(0–80.0)	(0–50.0)	(0–80.0)	(1.0–70.0)	

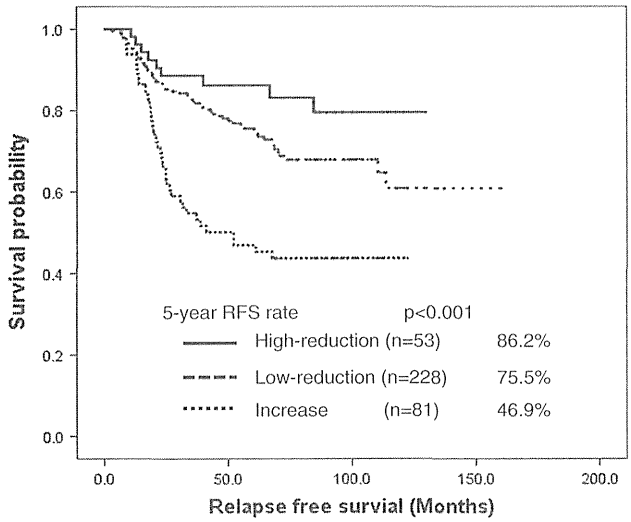

Fig. 1 RFS curves according to Ki-67 change subgroup

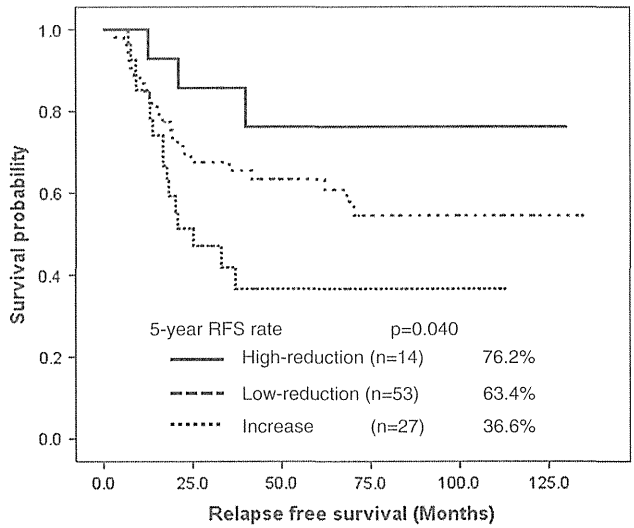

Fig. 3 RFS curves according to Ki-67 change subgroup in patients with Triple-negative subtype

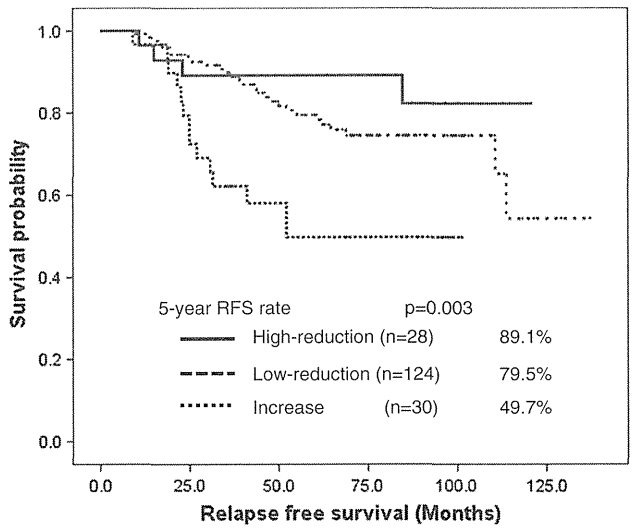

Fig. 2 RFS curves according to Ki-67 change subgroup in patients with Luminal-like subtype

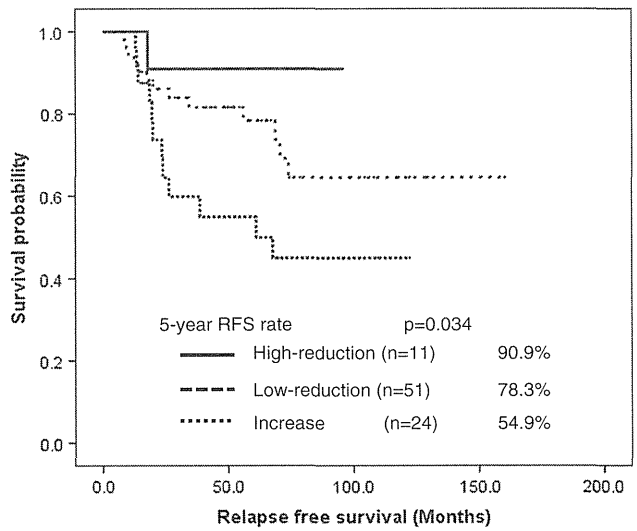

Fig. 4 RFS curves according to Ki-67 change subgroup in patients with HER2 subtype

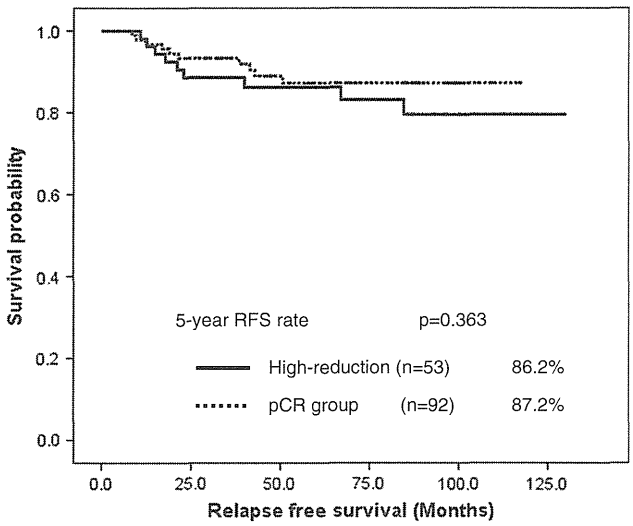

Fig. 5 RFS curves in patients with pCR and high-reduction group

Table 3 Multivariate analysis for factors related to recurrence

	Hazard ratio	95 % CI	*p* value
pT status			
pT1–2	1		
pT3–4	2.24	1.54–3.28	<0.001
pN status			
pN negative	1		
pN positive	3.51	2.16–3.28	<0.001
NAC regimen			
Anthracycline → Taxane	1		
Anthracycline only	1.24	0.79–1.93	0.339
Ki-67 changes after NAC			
High reduction	1		
Low reduction	2.18	0.94–5.06	0.071
Increase	5.26	2.23–12.4	<0.001

1.54–3.28), pN status (HR 3.51, 95 % CI 2.16–3.28), and Ki-67 increase after NAC (HR 5.26, 95 % CI 2.23–12.4).

Discussion

We assumed that in patients with non-pCR, the reduction rate of Ki-67 might affect their long-term oncological outcome. However, to the best of our knowledge, no published papers have investigated this presumption in detail. In the present investigation, we found that in patients with non-pCR after NAC, a high rate of Ki-67 reduction was associated with a better survival than that of patients who showed a low reduction or increase of Ki-67 regardless of their breast cancer subtypes. Surprisingly, in addition, patients with a high rate of Ki-67 reduction after NAC showed a comparable long-term oncological outcome to that of patients with pCR. Our findings suggested that the monitoring of changes in Ki-67 between pre- and post-NAC could be used to not only classify patients with non-pCR according to chemo-sensitivity but also to predict their survival.

Many previous investigations have shown that pCR after NAC is a powerful surrogate marker for long-term oncological outcome [4, 5]. However, it is a major drawback of this marker that the population that achieves pCR is small [3, 6, 7]. On the other hand, residual patients with non-pCR have been indiscriminately regarded as constituting a group with a high potential for disease relapse. The conventional prognostic factors, such as clinical and/or pathological response, pathological tumor size, axillary lymph node status, and histological grade, are still used to predict survival in patients with non-pCR [21, 22]. However, these conventional factors are not quite sufficient and are not satisfactory in daily practice. Another new approach, gene expression profiling, is already commercially available; however, it cannot be extrapolated to include the NAC setting because of lack of evidence in this setting. Therefore, a new biomarker that reflects the sensitivity to NAC in patients with non-pCR would be very useful and highly desirable.

We hypothesized that the reduction rate of Ki-67 has the potential to become a biomarker for survival in patients with non-pCR. Several previous investigations have already reported that changes in Ki-67 or the post-treatment absolute value of Ki-67 are associated with survival [16–19]. Also, previous investigations revealed that patients with Ki-67 reduction have better survival than those with Ki-67 increase. However, in general, a reduction of the absolute value of Ki-67 after NAC compared with that prior to NAC is widely observed, reported in 60–80 % of patients [18–20]. Nevertheless, the clinical courses in patients with non-pCR and with Ki-67 reduction are heterogeneous. The association between the reduction rate of Ki-67 and prognosis has not previously been investigated in detail. Our results revealed for the first time that the reduction rate of Ki-67 is more important for the long-term oncological outcome than a simple Ki-67 change status in patients with non-pCR.

The standard IHC methods and routine measurements of Ki-67 have not been firmly established and are now under construction [23]. Because it seems to be difficult to measure and compare the correct absolute values of Ki-67, a simple comparison of Ki-67 changes, such as High-reduction, Low-reduction, or Increase group, would be easy to introduce in clinical practice, until a reliable assay method became available. In the future, a nomogram will be constructed for patients with non-pCR to predict the

oncological outcome based on conventional prognostic factors and the reduction rate of Ki-67.

Another meaningful finding from this investigation is that RFS of patients with High reduction of Ki-67 was comparable to the RFS of patients with pCR. To the best of our knowledge, this finding is reported here for the first time. In general, patients and physicians with non-pCR are disappointed with this result of NAC treatment. However, according to our results, patients with non-pCR should not have to worry more about recurrence than those with pCR, if a high reduction of Ki-67 was achieved. Previous investigations have already reported that there were small non-pCR populations that had favorable outcomes comparable to those of pCR patients [24]. Measuring residual cancer burden, as a continuous variable derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary node burden, could divide patients with non-pCR into four categories according to oncological outcome [24]. However, this method seems to be a little too intricate for daily use. On the other hand, our method of Ki-67 change might be simpler and easier to introduce in daily practice.

The patient population with High reduction of Ki-67 in our study comprised only 14.6 % of all non-pCR patients, and we acknowledge that this is a small population. There is no previous reference for the optimal cutoff level of Ki-67 reduction defined as High reduction. We analyzed the cases in this investigation using different cutoff levels for Ki-67 reduction, such as 70, 60, and 50 %, but we found that the 80 % cutoff level provided the best prognostic significance, so we adopted that. Nevertheless, in order to confirm this finding and establish the optimal cutoff level for Ki-67 reduction, further observational or validation studies with a larger sample size will be needed.

The strengths of this investigation are the following: The sample size was large, the follow-up period had adequate length, and the methods for IHC and assessment of Ki-67 were unchanged during the study period. On the other hand, there are several limitations in this investigation. It was a retrospective, single-institution analysis, there was no central pathological review of Ki-67, it included plural chemotherapy regimens, and not all patients with HER2 subtype received trastuzumab as neoadjuvant and/or adjuvant treatment. Perioperative treatment with or without trastuzumab might influence not only the Ki-67 change but also survival status. Despite these limitations, however, the simple strategy of recording Ki-67 change is useful for predicting long-term oncological outcome in patients with non-pCR.

Conclusions

This investigation revealed that the reduction rate of Ki-67 after NAC significantly predicted long-term oncological outcome in patients with non-pCR. This finding could apply to all subtypes of breast cancer. Patients who are non-pCR but who achieved a High reduction of the Ki-67 can be expected to have a favorable prognosis similar to that of patients with pCR. In order to introduce these findings into daily practice, not only larger validation studies but also optimal cutoff levels of Ki-67 reduction defined as High reduction are needed.

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Ethical standards The study was carried out in accordance with the Declaration of Helsinki and Japanese ethical guidelines for epidemiological research.

Conflict of interest The authors declare that they have no conflict of interest.

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Cancer Medicine

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ORIGINAL RESEARCH

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

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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].

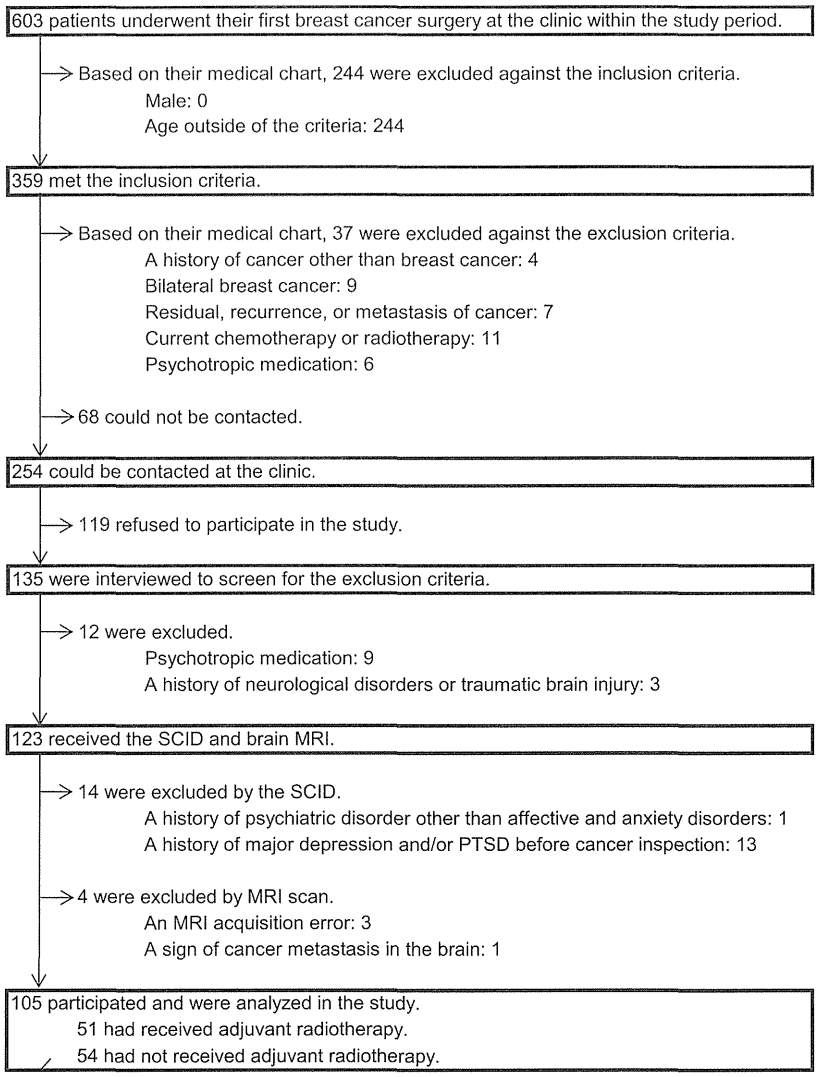

Figure 1. This flowchart illustrates subject sampling in this study. SCID, the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV; MRI, magnetic resonance imaging; PTSD, posttraumatic stress disorder.

Plasma IL-6 levels

Blood samples were collected from a peripheral vein into ethylenediaminetetraacetate-2Na tubes and immediately centrifuged at 4°C and 2300*g* 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 radiotherapy 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

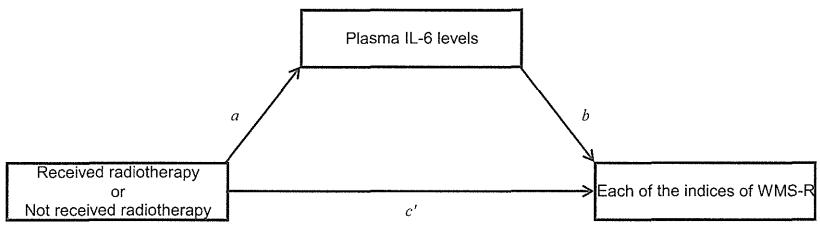

Figure 2. Illustration of a mediation model [38], which hypothesizes that radiotherapy exerts an indirect effect on each of the indices of the Wechsler Memory Scale-Revised (WMS-R) through plasma interleukin (IL)-6 levels. Path *a* represents the effect of radiotherapy on plasma IL-6 levels, the proposed 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.
[1]Two 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.

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.
[1]One missing value was excluded.
[2]Two missing values were excluded.
[3]Three 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.
[1]Regression coefficient between each pair of variables corresponding with each symbol representing each path in Figure 2.
[2]The plasma IL-6 levels and the index of WMS-R of 96 patients (received radiotherapy 49 and not received 47) were available for analysis.
[3]The plasma IL-6 levels and the index of WMS-R of 95 patients (received radiotherapy 48 and not received 47) were available for analysis.
[4]The 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 $P < 0.05$.

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 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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Observational Study of Axilla Treatment for Breast Cancer Patients with 1–3 Positive Micrometastases or Macrometastases in Sentinel Lymph Nodes

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Sentinel node biopsy is a standard procedure in clinically node-negative breast cancer patients. It has eliminated unnecessary axillary lymph node dissection in more than half of the early breast cancers. However, one of the unresolved issues in sentinel node biopsy is how to manage axilla surgery for sentinel node-positive patients and clinically node-negative patients. To evaluate the outcome of no axillary lymph node dissection in sentinel node-positive breast cancer, a prospective cohort study registering early breast cancer patients with positive sentinel nodes has been conducted (UMIN 000011782). Patients with 1–3 positive micrometastases or macrometastases in sentinel lymph nodes are eligible for the study. The primary endpoint is the recurrence rate of regional lymph nodes in patients treated with sentinel node biopsy. Patients treated with sentinel node biopsy followed by axillary lymph node dissection are also registered simultaneously to compare the prognosis. The propensity score matching is used to make the distributions of baseline risk factors comparable.

Key words: sentinel node biopsy – breast cancer – propensity score – lymph node dissection

INTRODUCTION

Until the 21st century, axillary lymph node dissection (ALND) was a standard procedure for operable breast cancer patients. However, it can cause lymphedema, peripheral nerve injury, shoulder dysfunction and other complications that compromise functional activity and quality of life. Sentinel node biopsy (SNB) is the most accurate method for detecting axillary lymph node metastases in early breast cancer. Large clinical trials that compared SNB with ALND were launched in the 1990s. The National Surgical Adjuvant Breast & Bowel Project (NASBP) B32 showed that SNB provided an outcome equivalent to that of SNB + ALND for sentinel node-negative patients (1). In this study, occult metastases that were found in negative sentinel lymph nodes with a detailed histological examination had a very small impact on the prognosis, since adjuvant therapy could have reduced systemic dissemination of cancer cells (2).