Table 5
Adjusted logistic regression model of clinicopathologic factors and pathologic complete response.

$N = 248$	OR[a]	95% CI	P
Subtype			<0.05
ER (+), HER2 (−)			Reference
ER (+), HER2 (+)	1.04	0.20 to 5.35	0.97
HER2 type	4.46	1.42 to 14.00	<0.05
Triple negative	6.29	2.52 to 15.71	<0.05
BMI (WHO)			0.40
<18.5			Reference
18.5 ≤ BMI < 25	0.34	0.09 to 1.23	0.10
25 ≤ BMI < 30	0.34	0.08 to 1.46	0.15
≥30	0.001	0.00 to 3.75E+11	0.67
BMI (AABC)			0.22
<18.5			Reference
18.5 ≤ BMI < 23	0.40	0.11 to 1.46	0.17
23 ≤ BMI < 27.5	0.26	0.06 to 1.06	0.06
≥27.5	0.21	0.04 to 1.14	0.07
Tumor stage			0.05
1			Reference
2	0.26	0.09 to 0.77	<0.05
3	0.22	0.05 to 0.98	<0.05
4	0.18	0.05 to 0.70	<0.05
Menopausal status			0.83
Pre			Reference
Post	1.00	0.45 to 2.20	0.99

[a] OR: odds ratio.

than in the normal-weight group. No significant difference was noted in OS among the 4 groups (Fig. 1C and D). Using AABC, both DFS and OS were significantly shorter in the high-risk than in the increased but acceptable risk group (Fig. 1E and F). The relationship between BMI and pCR in the non-pCR group was also analyzed. On stratification with the WHO BMI classification, overweight groups showed a significantly poorer DFS compared to the normal-range group. Using ABCC, DFS was significantly shorter in the high-risk than in the increased but acceptable risk group (Fig. 2A and B). On the other hand, no effect of BMI on DFS or OS was observed in the pCR group (when categorized by the WHO BMI classification or AABC)(data not shown).

Secondly, the relationship between the subtype and pCR was analyzed. In the non-pCR group, patients with the HER2 Type had more recurrences than those with the ER (+), HER (−) type and ER (+), HER (+) type. Furthermore, patients with the HER2 type also showed a poorer OS compared to the ER (+), HER (−) type and ER (+), HER (−) type (Fig. 2C and D). When the relationship between BMI and the survival curve was investigated by each subtype, the obese group with ER (+), HER (−) type showed a significantly poorer DFS compared to the normal range in the WHO BMI classification, and high-risk group patients with the HER2 type had a poorer DFS compared to the others in ABCC (Fig. 2E and F).

In multivariate analysis, pCR (HR 0.26; 95% CI, 0.08 to 0.87; $P < 0.05$), HER2 type (HR 2.94; 95% CI, 1.37 to 6.32; $P < 0.05$), and T stage were significantly correlated with DFS (Table 5). BMI was not a significant factor for DFS and OS using either the WHO or ABCC (Table 6).

Discussion

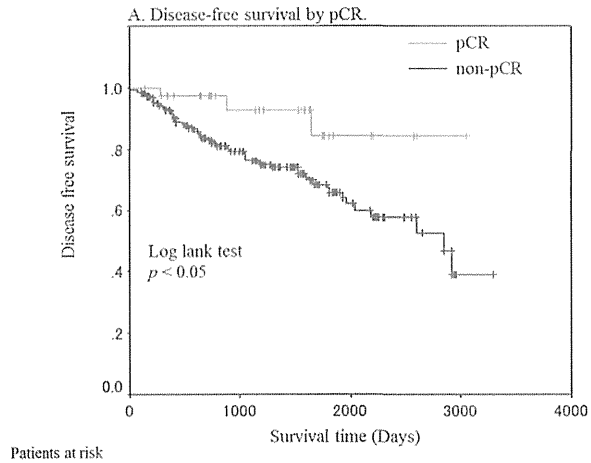
Commonly, obese patients can obtain less benefit from chemotherapy or hormone therapy for breast cancer compared to normal shape individuals. Furthermore, several studies have reported these patients also had worse DFS or OS [4–9]. In addition to BMI, patients with the ER (+), HER (−) Type showed a significantly lower pCR rate compared to other subtypes. Although these factors are important for predicting the chemotherapeutic effect on NAC, their combination effect is still uncertain. To the best of our knowledge, this is the first study to analyze the effect of the combination of obesity and subtype on NAC, including the chemotherapeutic effect and prognosis.

Some reports demonstrated that patients who achieved pCR after NAC had significantly better DFS and OS [19,20] The present study similarly showed that patients with a pCR had better DFS and OS, regardless of BMI or subtype. Patients with pCR are likely to have a more favorable prognosis compared with non-pCR groups. Therefore, it is important to screen patients with non-pCR for risk factors for recurrence, and, in the near future, the selection of individualized adjuvant therapy for such patients may be needed.

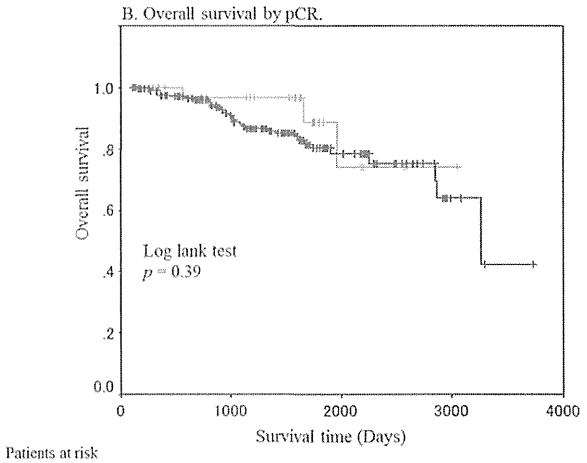
In the present study, patients with the ER (+), HER (−) type and higher BMI had a higher risk of recurrence and this suggested a strong relationship between hormone receptor status and obesity. In the adjuvant setting, several studies reported that the subtype predicts the grade of chemotherapeutic effect, and patients with the ER (+), HER (−) type tend to get only a small benefit [21,22]. For example, with a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) therapy, some reports pointed out patients who were positive for hormone receptor had less benefit compared to patients with the triple-negative type [23,24]. Obese patients tend to have chronic inflammation in their microenvironment and their hormone status changes to a favorable environment for tumor progression. Adipokine and tumor necrosis factor-alpha (TNF-α) are known as inflammatory cytokines and are produced from adipose tissue, while the serum estrogen or aromatase levels chronically increase [12,25]. Considering these results, it is highly probable that patients with the ER (+), HER (−) type and high BMI can obtain more benefits from NAC with a hormonal agent rather than a chemotherapeutic agent, which induces many side effects but has little benefits. Moreover, hormonal neo-adjuvant therapy may be a better option for these patients who have a hormone-enriched environment. Recently, Ki-67 or OncotypeDX® has been used to predict the chemotherapeutic effect on patients with the ER (+), HER (−) Type. In the near future, using a combination of these predictive tools is going to be an effective way to detect subgroups which can get an NAC benefit.

In the neo-adjuvant setting, the chemotherapeutic dose in NAC is still another important problem for obese patients. In addition to the hormonal environment changing, obese patients tend to have changed in hemodynamics, drug clearance, and drug distribution compared to normal weight individuals. In some reports, dosage adjustment for obese patients was recommend because of their increased serum protein level and decreased hepatic metabolism that strongly affect drug effects [26–29]. In hormonal therapy, Sestak et al. suggested that dosage adjustment for obese postmenopausal woman with breast cancer may be an effective option because it is likely that a normal dose of an aromatase inhibitor is not enough to suppress the aromatase level in patients with an enriched aromatase environment [30]. As drug doses for chemotherapy, the ASCO guidelines recommend calculation using the actual weight regardless of BMI for obese patients [15]. We calculated the dose using the actual weight. Concerning the fact that there are no significant differences in RDI or hematological adverse events between BMI categories in the present study, drug dosing should be decided according to the BSA calculated by actual body measurements regardless of BMI.

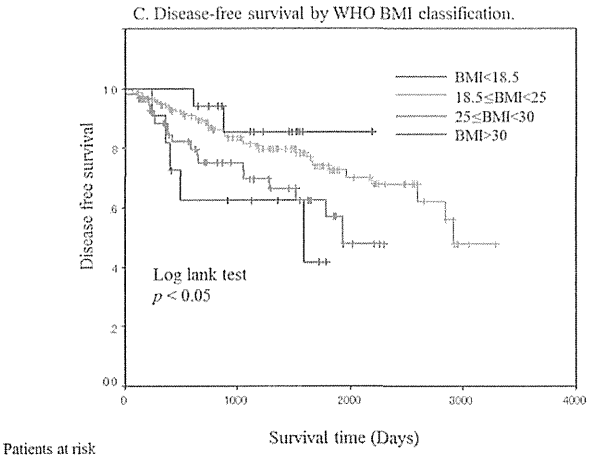
There was no major difference between the findings obtained using AABC and the WHO classification, but DFS was significantly shorter in the ER (+)/HER (−) type in the non-pCR group when the WHO classification was used, whereas DFS was significantly shorter in the HER2 type when AABC was used. Cross-talk between ER and growth factors, such as HER2, mediated by the signal transmission pathway is known [31], but there have been only a few reports on the relationship between obesity and the HER2 type. Although no



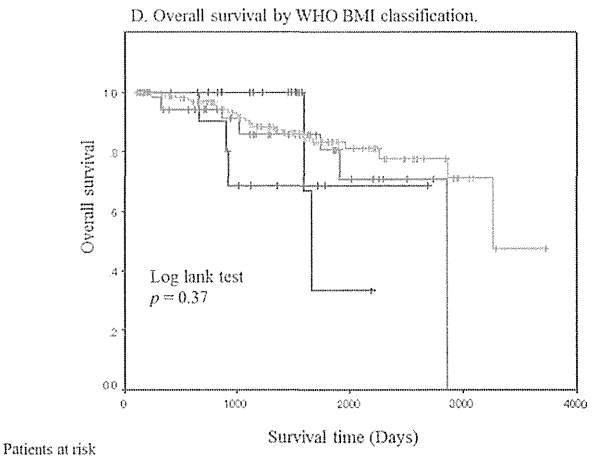
Patients at risk				
pCR	37	20	5	1
non-pCR	211	114	32	1



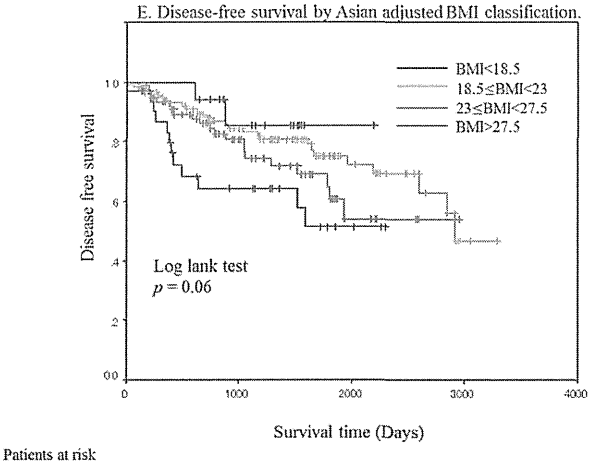
Patients at risk				
pCR	37	21	5	1
non-pCR	211	134	41	5



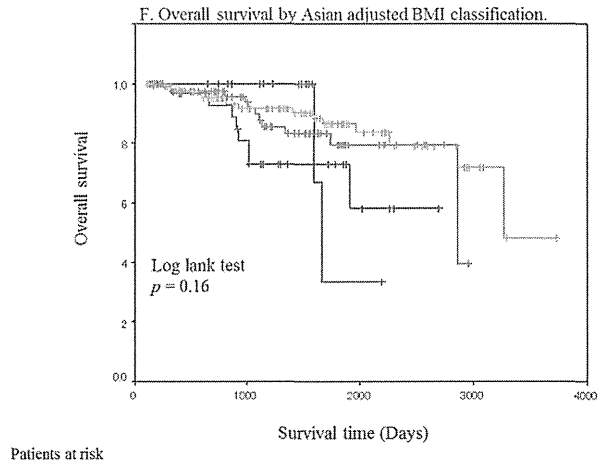
Patients at risk				
BMI<18.5	17	11	2	0
18.5≤BMI<25	163	91	31	2
25≤BMI<30	57	27	4	0
BMI>30	11	5	0	0



Patients at risk				
BMI<18.5	17	13	2	0
18.5≤BMI<25	163	102	36	6
25≤BMI<30	57	34	7	0
BMI>30	11	6	1	0



Patients at risk				
BMI<18.5	17	11	2	0
18.5≤BMI<23	118	68	25	2
27.5≤BMI<30	80	39	6	0
BMI>30	33	15	3	0



Patients at risk				
BMI<18.5	17	13	2	0
18.5≤BMI<23	118	74	29	6
27.5≤BMI<30	80	48	11	0
BMI>30	33	19	3	0

Fig. 1. Disease-free survival and overall survival stratified by pCR or BMI. A: Disease-free survival by pCR. B: Overall survival by pCR. C: Disease-free survival by WHO BMI classification. D: Overall survival by WHO BMI classification. E: Disease-free survival by Asian adjusted BMI classification. F: Overall survival by Asian adjusted BMI classification.

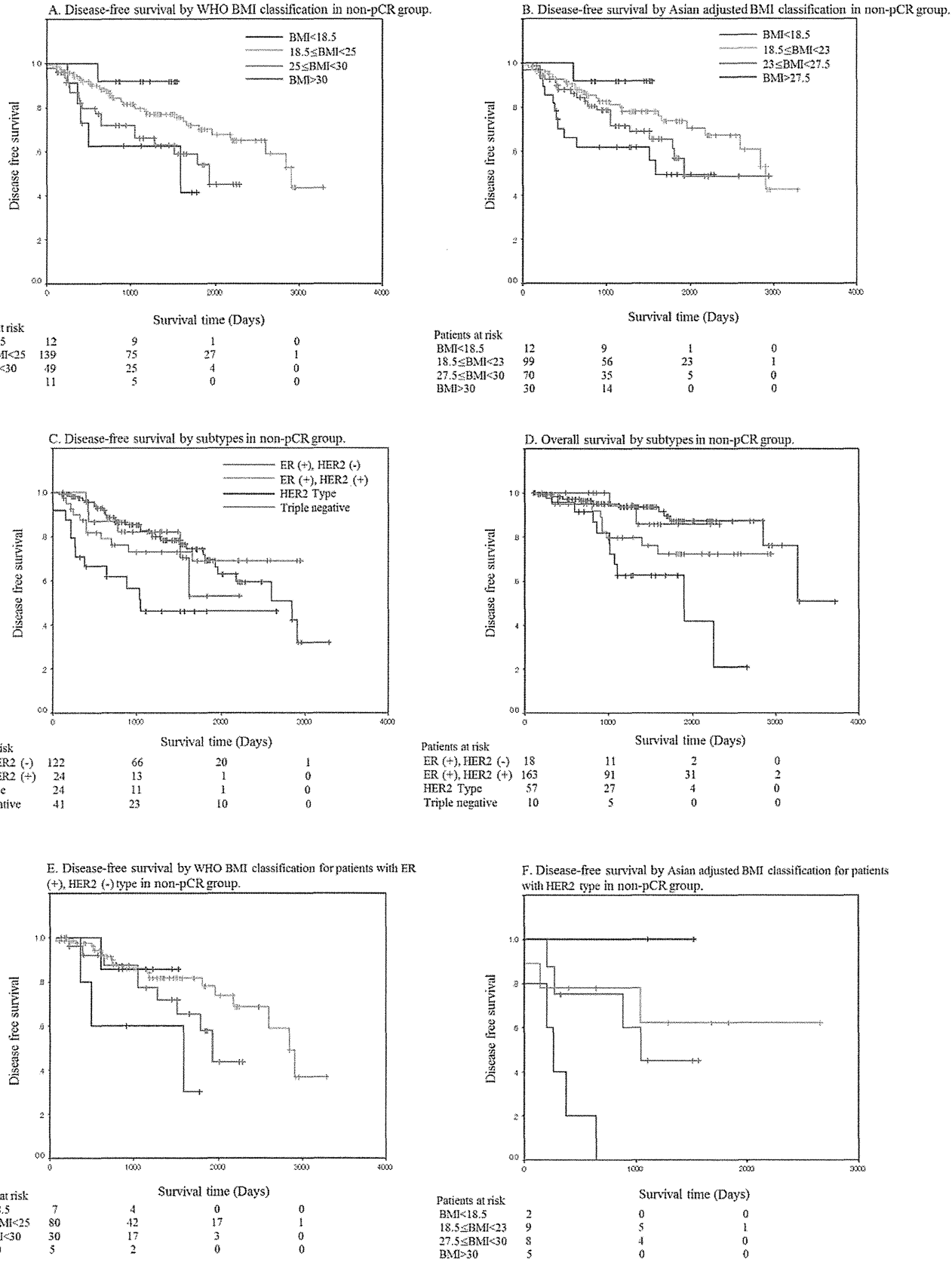


Fig. 2. The relationships between BMI and subtypes in non-pCR group. A: Disease-free survival by WHO BMI classification in non-pCR group. B: Disease-free survival by Asian adjusted BMI classification in non-pCR group. C: Disease-free survival by subtypes in non-pCR group. D: Overall survival by subtypes in non-pCR group. E: Disease-free survival by WHO BMI classification for patients with ER (+), HER2 (−) type in non-pCR group. F: Disease-free survival by Asian adjusted BMI classification for patients with HER2 type in non-pCR group.

Table 6
Result of cox hazards regression model for DFS and OS.

$N = 248$	HR[a]	DFS 95% CI	p	HR	OS 95% CI	p
pCR						
No						
Yes	0.26	0.08 to 0.87	<0.05	0.57	0.14 to 2.26	0.42
Subtype			<0.05			<0.05
ER (+), HER (−)						
ER (+), HER (+)	0.99	0.40 to 2.43	0.98	1.03	0.28 to 3.75	0.96
HER2 type	2.94	1.37 to 6.32	<0.05	4.56	1.89 to 11.01	<0.05
Triple negative	1.03	0.52 to 2.04	0.94	1.67	0.68 to 4.12	0.27
BMI (WHO)			0.06			0.25
<18.5						
18.5 ≤ BMI < 25	0.88	0.26 to 2.98	0.84	0.48	0.10 to 2.28	0.36
25 ≤ BMI < 30	1.58	0.45 to 5.61	0.48	0.56	0.11 to 2.95	0.49
≥30	2.72	0.63 to 11.82	0.18	1.69	0.25 to 11.45	0.59
BMI (AABC)			0.13			0.37
<18.5						
18.5 ≤ BMI < 23	0.82	0.24 to 2.82	0.75	0.41	0.08 to 2.01	0.27
23 ≤ BMI < 27.5	1.31	0.38 to 4.53	0.67	0.61	0.12 to 3.04	0.54
≥27.5	1.94	0.52 to 7.19	0.32	0.88	0.16 to 4.69	0.88
Tumor Stage			<0.05			<0.05
1						
2	0.39	0.16 to 0.96	<0.05	0.15	0.04 to 0.53	<0.05
3	0.47	0.16 to 1.42	0.18	0.40	0.10 to 1.59	0.19
4	1.09	0.44 to 2.71	0.84	1.34	0.44 to 4.09	0.61
Menopausal Status			0.77			0.99
Pre						
Post	0.75	0.43 to 1.29	0.29	0.91	0.46 to 1.80	0.78

[a] HR: hazard ratio.

definite conclusion can be made from these findings alone, the risk of obesity may be different between Western people and Asians. Further investigation of the characteristics of Asians with regard to the relationship of BMI with the subtype and prognosis is expected.

The present study had some limitations. Initially, although almost all patients received Taxane-based and/or Anthracycline-based chemotherapy, Trastuzumab, which is a key drug for HER2-positive patients were not administered to all patients in a standardized way. Many major studies have confirmed a strong effect of Trastuzumab on HER2-positive breast cancer in NAC. Secondly, the present study possibly had less statistical power because the obese population was relatively small compared to the reports from Western countries. To obtain more evidence, a prospective study with a standardized chemotherapeutic regimen will be needed in the future.

Conclusion

In conclusion, this study showed that subtypes and BMI were predictive factors both for NAC effect and prognosis after NAC. Furthermore, non-pCR patients with the ER (+), HER (−) type and high BMI were a high risk group for recurrence after NAC. In the clinical setting, appropriate intervention aimed at improving outcomes for obese patients may improve prognosis. Moreover, modifying the follow-up schedule after surgery for these high risk patients will be an effective option.

Ethical approval

Ethical approval was obtained for this study.

Funding sources

None declared.

Conflict of interest statement

None declared.

Acknowledgments

The authors would like to express gratitude to all patients who participated to this study.

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OPEN

The Relationship Between Skeletal-Related Events and Bone Scan Index for the Treatment of Bone Metastasis With Breast Cancer Patients

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Abstract: The aim of the present study was to investigate the relationships between the automated bone scan index (aBSI) and skeletal-related events (SRE) in breast cancer patients with bone metastasis. A computer-aided software (BONENAVI™) that was developed using an Artificial Neural Network (Artificial Neural Network) was used for the present analysis.

Forty-five patients diagnosed with bone metastasis due to breast cancer from April 2005 through March 2013 were retrospectively analyzed. Before and after the time of initial treatment, aBSI, Artificial Neural Network score, and hotspot number were calculated, and the relationships between these scores and SRE were analyzed.

Twenty cases showed decreased (improved) aBSI values after initial treatment (Group A), and 25 cases showed unchanged/increased (worsened) aBSI values (Group B). Chi-square analysis revealed a significant difference in incident numbers of SRE between the two groups—one case in Group A and 12 in Group B ($P < 0.001$). Event-free survival was significantly shorter in Group B (hazard ratio: 8.31, 95% CI: 1.33–12.14, log-rank test; $P < 0.05$). The groups were also divided by the results of 2 radiologists' visual scan interpretations, and no significant differences were shown in the number of SRE ($P = 0.82$, $P = 0.10$). When correlation analyses were performed between aBSI and bone metabolic or tumor markers, alkaline phosphatase was significantly correlated with aBSI at the time of initial treatment ($R = 0.69$, $P < 0.05$).

In conclusion, aBSI is proposed as a useful and objective imaging biomarker in the detection of breast-cancer patients with bone metastasis at high risk of SRE.

(*Medicine* 93(28):e269)

Abbreviations: aBSI = automated bone scan index, ANN = artificial neural network, ER = estrogen receptor, HER2 = human epidermal growth factor 2, PgR = progesterone receptor, SRE = skeletal related events.

Editor: Partha Sinha.
Received: September 5, 2014; revised: October 9, 2014; accepted: October 20, 2014.
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Naohito Yamamoto received research funding from Pfizer, Bayer, Parexel, and Eli Lilly. Those funders had no control over the interpretation, or publication of this work. This study was presented on the 9th European breast cancer conference, 19–21 March 2014 at Glasgow, Scotland.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000269

INTRODUCTION

Recently, newly developed molecular agents targeted against receptor activator of nuclear factor κ-B ligand have shown remarkable outcomes in preventing skeletal-related events (SRE) in breast cancer patients with bone metastasis.[1] On the other hand, few biomarkers evaluating the extent of bone metastasis have been developed.

Bone scan index (BSI) is a new imaging biomarker that was originally reported by Erdi et al at the Memorial Sloan Kettering Cancer Center in 1997. The BSI evaluates the range of bone metastasis—"hot spots" are expressed as a percentage of total bone amount.[2] BSI was originally calculated manually, but recently the automated BSI (aBSI) has been developed by imitating an Artificial Neural Network (Artificial Neural Network), such as in the human brain. Therefore, BSI has become a more convenient tool.[3,4] While bone scintigraphy has been widely used to evaluate bone metastasis for a long time and allows visual interpretation of the metastatic site, quantitative evaluation of bone metastasis on a bone scan requires certain skills. In contrast, aBSI is an objective quantitative measure.

In the American Society of Clinical Oncology Clinical Practice Guideline, routine bone scans in non-symptomatic breast cancer patients are not recommended on the basis of negative reported opinions.[5] On the other hand, the aim of bone metastasis treatment has recently shifted to the reduction of SRE, and reconsideration of the usefulness of the bone scan has been suggested, particularly for patients with a high risk for SRE.[6] The role of the bone scan is set to change in the near future to a means of obtaining an imaging biomarker to help reduce SRE.

The usefulness of the aBSI as an imaging biomarker has been previously investigated in prostate cancer, but only sporadically in bone metastasis treatment in breast cancer.[7,8] The relationship between aBSI and SRE in breast cancer warrants renewed analysis because the manifestation of bone metastasis in breast cancer differs from that in prostate cancer.

The aim of this study was to investigate the usefulness of the aBSI as an imaging biomarker in bone metastasis treatment in breast cancer.

MATERIALS AND METHODS

Patient Selection

Among 97 patients diagnosed with breast cancer by undergoing a core biopsy or surgery from April 2005 through March 2013, 45 matched according to the following criteria were included in the study: bone metastasis detected at the initial outpatient examination on bone scan or computed tomography (27 cases), or during the follow-up period after surgery

(18 cases), and bone scan performed with methylene-diphosphonic acid technetium (MDP) before and after treatment. The MDP bone scan images were required because BONENAVI™ requires 99mTc images for matching with its own database. If applicable, the detection of bone metastasis manifesting within the treatment period was recorded according to the order of its appearance relative to that of other metastatic sites (eg, liver and lung). Ethical approval was obtained for this study from the Ethical Board of the institutional review board.

Bone Scintigraphy Procedure

The bone scan devices used for the present study were dual-head nuclear gamma camera systems (GCA 7200A/UI and eCAM; TOSHIBA, Co. Ltd., Tokyo, Japan). 740 mBq (20 mCi) Technetium-99m methylene diphosphonate (Tc99m-MDP) was given intravenously. The low energy high-resolution collimator was selected, and scanning was performed 2 hours after the administration. During scanning, the patients were supine position and dual-head anterior and posterior whole body images were obtained at 15 cm/min. Collected data were analyzed by a single nuclear physician (HI) using the computed-aided diagnosis software BONENAVI™ (FUJIFILM RI Pharma, Co. Ltd., Tokyo, Japan; EXINIbone, EXINI Diagnostics, Lund, Sweden). In addition to aBSI, the ANN and hot spot numbers were calculated. ANN predicts the possibility of bone metastasis in each individual hot spot by showing continuous numbers ranging from 0 to 1 by imitating a human neural network based on the Japanese database (Figure 1).[4]

Follow-Up After Surgery

The patients were categorized according to pathological findings into three risk groups as advocated by the St. Gallen International Breast Cancer Congress in 2007.[9] The follow-up period was set to 6 years; bone scans were performed in the intermediate group (second year and fifth year) and high-risk group (once a year until the fifth year) but not in the low-risk group. Serum biomarkers were measured twice a year until the fifth year regardless of the risk.

Definition of SRE

The SRE were defined as follows: palsy, pathological fracture, radiation, and surgery. An oncologic orthopedic surgeon judged whether palsy was due to bone metastasis or other reasons, as well as diagnosed pathological fracture. A radiotherapist judged the necessity of radiotherapy. The dosage of radiotherapy was set to 30 gray, divided into 10 treatments, for pain control or palsy. Some patients received radiotherapy for mitigating urgent palsy arising from tumor compression of the spinal cord. Those cases were classified in the palsy group, and the radiation group included the patients that underwent radiotherapy for other reasons.

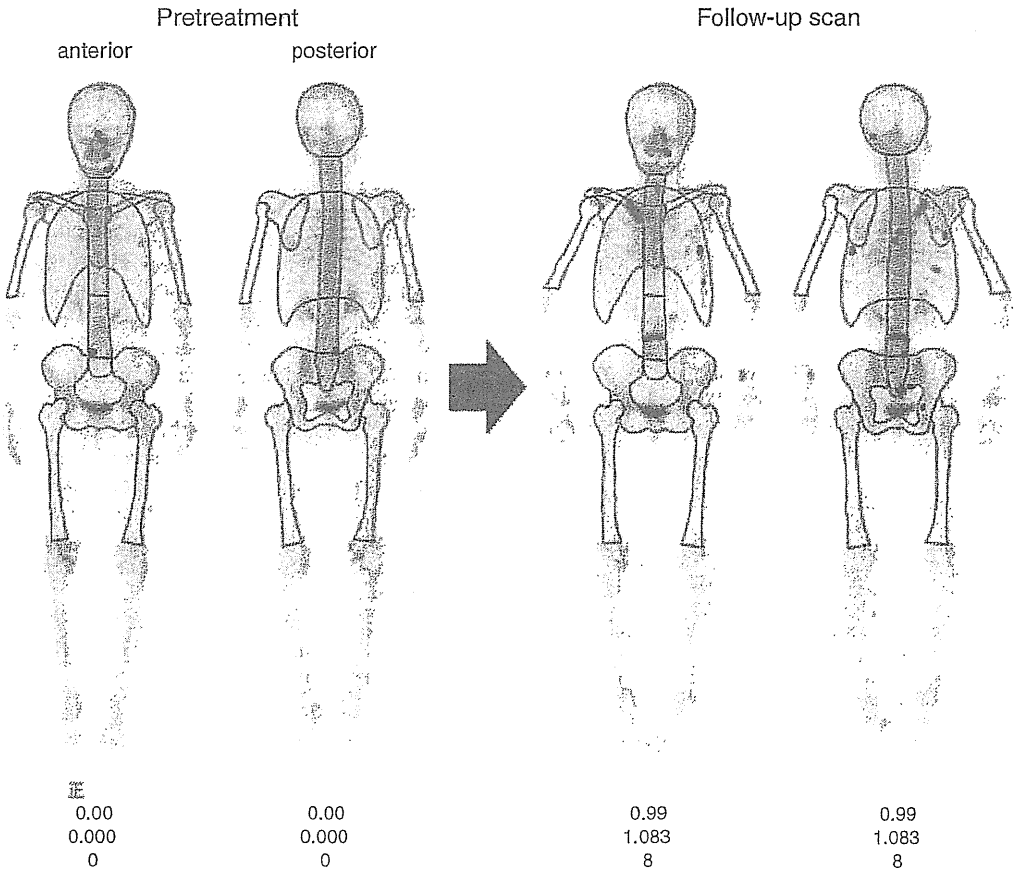

FIGURE 1. aBSI: aBSI reflects the burden of the skeleton. The tumor burden is expressed as a percentage of the total skeletal mass. ANN: Each individual hotspot was classified as metastasis or not. The possibility of metastasis was expressed by the continuous ANN number, ranging from 0 to 1.

Statistical Methods

Patients were divided into two groups according to the initial aBSI change with the bone metastatic treatment: Group A included patients with decreased aBSI values, and Group B included patients with unchanged/increased (worsened) aBSI values. The study patients were also divided into two groups (Group A: improved, Group B: unchanged/worsened) according to visual scan interpretations of two radiologists (HI and TT), and the aBSI results were compared with the radiologists' results. To avoid information bias, the radiologists were blinded to information about SRE and aBSI results, and were required to read the images independently. The reproducibility between the readers was evaluated by Cohen Kappa statistic.

Incident numbers of SRE in each group were analyzed by chi-square test. The associations of a bone metabolic marker (alkaline phosphatase [ALP]), a cell injury marker (lactate dehydrogenase [LDH]), and tumor markers (carcino-embryo antigen [CEA] and carbohydrate antigen 15-3 [CA15-3]) with aBSI were also analyzed. Event-free survival (EFS) was defined as the period from initial diagnosis of bone metastasis to the incidence of SRE. When initial metastasis was diagnosed at distant organs such as the lung or liver, and bone metastasis was found as the second or third site during the treatment period, EFS was defined as the period from the time of bone metastasis to the onset of SRE. Overall survival (OS) was defined as the period from initial diagnosis of bone metastasis to death. Survival curves were compared by drawing the Kaplan–Meier curves, and log-rank tests were performed. All analyses were performed two-sided, and $P < 0.05$ was considered significant. GraphPad Prism5™ (GraphPad Software, Inc., La Jolla, CA, USA) was used as statistical software.

RESULTS

Patient Demographics

Thirty-one patients were diagnosed with bone metastasis as an initial recurrence after surgery. On the other hand, metastasis occurred first at other sites and then in bone in 4 patients: bone was the second site in 3 patients and the third in 1. In subtypes, 42 patients were estrogen positive and 12 were positive for human epidermal growth factor receptor-2 (HER2); only 1 patient was triple negative (TN), and bone was diagnosed as the third metastatic site. When SRE were stratified by subtype, there were 8 ER (+), HER2 (−) type cases, 3 ER (+), HER2 (+) type cases, and 1 case each in the HER2 (+) type and TN type, suggesting increased frequency in the ER (+),

TABLE 1. Patient Demographics

Demographics	No. of Patients N = 45	Demographics	No. of Patients N = 45
Presence of visceral metastases		aBSI (pretreatment, median, range)	0.28 (0.0–9.0)
None	28	ANN (mean ± SD)	0.57 ± 0.35
Liver	3	Hot spot	1.8
Lung	8	Bone-modifying agents	
Other	6	Yes	29
Order of bone metastasis		No	16
First	31	Perior SRE	
Second	3	Yes	5
Third	1	No	40
Age (year, median, range)	48 (28–72)	Type of SRE	
BMI (kg/m^2, median, range)	23.1 (14.0–35.2)	Palsy	5
Menopausal status		Radiation	7
Premenopausal	22	Surgery	1
Postmenopausal	22	Fracture	0
Unknown	1	SRE	
ER		Yes	13
Positive	42	No	32
Negative	3	Survival prognosis	
PgR		Death	20
Positive	31	Survival	25
Negative	14	Event free survival (day, mean)	1289
HER2		Overall survival (day, mean)	1342
Positive	12		
Negative	32		
Unknown	1		
Serum bone metabolizing marker			
LDH (IU/L, mean ± SD)	219.6 ± 76.6		
ALP (IU/L, mean ± SD)	330.6 ± 234.9		
Tumor marker			
CEA (ng/mL, mean ± SD)	43.2 ± 158.9		
CA15-3 (U/mL, mean ± SD)	106.8 ± 219.8		

aBSI = automated bone scan index, ALP = alkaline phosphatase, ANN = artificial neural network, BMI = body mass index, CA15-3 = carbohydrate antigen 15-3, CEA = carcino-embryo antigen, ER = estrogen receptor, HER2 = human epidermal growth factor 2, LDH = lactate dehydrogenase, PgR = progesterone receptor, SRE = skeletal related event.

HER2 (−) type. Thirteen SRE were encountered, 5 palsy, 7 radiation, 1 surgery, 0 fractures. Five patients in the palsy group received radiation therapy for the purpose of prevention or palliative treatment, and those cases were counted as palsy, not radiation. Seven patients received radiation therapy for the purpose of pain control because of bone metastasis. Median aBSI before initiating treatment was 0.28 (range, 0.0–9.0). Bone modifying agents (BMA) were administered in 29 patients, zoledronic acid in 28 and denosumab in 1. Average follow-up period from initial bone scan to the first follow-up was 401 days, 505 days in group A and 324 days in group B (Table 1).

SRE and aBSI Change

The number of cases in Group A was 20 and in Group B was 25. Median rate of change in each group was −54.2% (range, 0% to −95.8%) in Group A and 195.9% (100–6717.6%) in Group B. Univariate analysis showed no significant differences in patient demographics between Groups A and B. Thirteen patients experienced SRE during the follow-up period, but only 1 of these patients was in Group A. Univariate analysis showed significant differences in the incidence of SRE between the two groups (Table 2, chi-square test, $P < 0.05$). The patient in Group A who experienced SRE received emergency radiation therapy because of emerging palsy due to spinal cord compression by spinal bone metastasis.

Visual Scan Interpretation

When the study patients were divided by the visual scan interpretations of two radiologists, Group A (improved)/Group B (unchanged/worsened) patient numbers were 11/34 (Radiologist A) and 12/33 (Radiologist B). High reproducibility between the readers was obtained as shown by Cohen Kappa statistic ($\kappa = 0.731$). Further, reproducibility between the aBSI and radiologist judgment was 0.645 for Radiologist A and 0.673 for Radiologist B; both these values were considered significantly coefficient.

TABLE 2. Result of Univariate Analysis between Decreased and Unchanged/Increased aBSI Group

Demographics	Decreased Group (Group A) No. of Patients (N = 20)	Unchanged/Increased Group (Group B) No. of Patients (N = 25)	*P*
Order of bone metastasis			
First	18	22	0.91
Second	1	2	
Third	1	1	
Age (year, median, range)	49 (28–72)	46 (32–70)	0.92
BMI (kg/m^2, median, range)	24 (19.1–35.2)	22.2 (14.0–34.9)	0.12
Menopausal status			
Premenopausal	11	11	0.36
Postmenopausal	8	14	
Unknown	1	0	
ER			
Positive	19	23	0.69
Negative	1	2	
PgR			
Positive	14	17	0.89
Negative	6	8	
HER2			
Positive	3	9	0.14
Negative	16	16	
Unknown	1	0	
Perior SRE			
Yes	3	2	0.46
No	17	23	
SRE			
Yes	1	12	< 0.001*
No	19	13	
Type of SRE			
Palsy	0	5	
Radiation	1	6	
Surgery	0	1	
Fracture	0	0	
Bone modifying agents			
Yes	9	20	0.02*
No	11	5	

BMI = body mass index, ER = estrogen receptor, HER2 = human epidermal growth factor 2, PgR = progesterone receptor, SRE = skeletal related event.

* Statistically significant with $P < 0.05$.

aBSI and Serum Biomarkers

Correlation analyses between a bone metabolic marker, cell injury marker, and tumor marker and aBSI at the time treatment started yielded the following results: LDH, $R=0.12$, $P=0.45$; ALP, $R=0.69$, $P<0.05$; CEA, $R=0.01$, $P=0.93$; and CA15-3, $R=0.04$, $P=0.79$. From those results, ALP appeared to have considerable correlation with the aBSI (Figure 2A–D).

EFS and Overall Survival

The median follow-up time was 1342 days. Thirteen patients experienced SRE in the follow-up period, and the median EFS was 1289 days. Kaplan–Meier curves were created for Groups A and B to compare EFS, and a log-rank test showed significantly shortened EFS in Group B (hazard ratio: 8.31, 95% CI: 1.33–12.14, $P<0.05$) (Figure 3A). No significant differences in EFS were observed between the two groups categorized by the radiologists' interpretations ($P=0.82$, $P=0.10$) (Figure 3C, D).

Twenty patients died during the follow-up period, and the median OS was 1342 days. In OS, the Kaplan–Meier curves showed no significant differences between the 2 groups (hazard ratio: 078, 95% CI: 0.34–1.75, $P=0.54$) (Figure 3B). Similar to the EFS analysis, no significant differences in OS were obtained between the two groups defined by the radiologists' interpretations (data not shown).

DISCUSSION

The present study showed a significant relationship between on-treatment changes in aBSI of bone metastasis and SRE, as well as a correlation between ALP and aBSI. These results suggest that aBSI is useful as an imaging biomarker in bone metastasis treatment for breast cancer.

To date, the relationships between SRE, OS, and BSI have been comprehensively reported in prostate cancer.[10] On the other hand, corresponding information in breast cancer treatment remains unknown, because few reports exist. Prostate and breast cancer both tend to metastasize to bone, and show similar metastatic sites, that is, the vertebra, ribs, and pelvis adjacent to the trunk. However, an important difference in these two types of malignancy is the bone metastasis pattern, that is, ossification exceeds osteoclastic activity in prostate cancer (osteoblastic bone metastases), while a mixed pattern (osteoblastic and osteolytic bone metastases) is seen in breast cancer. Therefore, the positive results of the aBSI as an imaging biomarker in spite of the different bone metastatic characteristics were interesting as well as promising.

Firstly, the present study demonstrated a significant relationship between the on-treatment changes of aBSI and SRE. Dennis et al[7] reported similar findings in prostate cancer treatment; the group in which aBSI more than doubled in 3 or 6 months after treatment displayed significantly worse OS, and on-treatment changes in aBSI was considered a response indicator. However, some limitations exist in the present study.

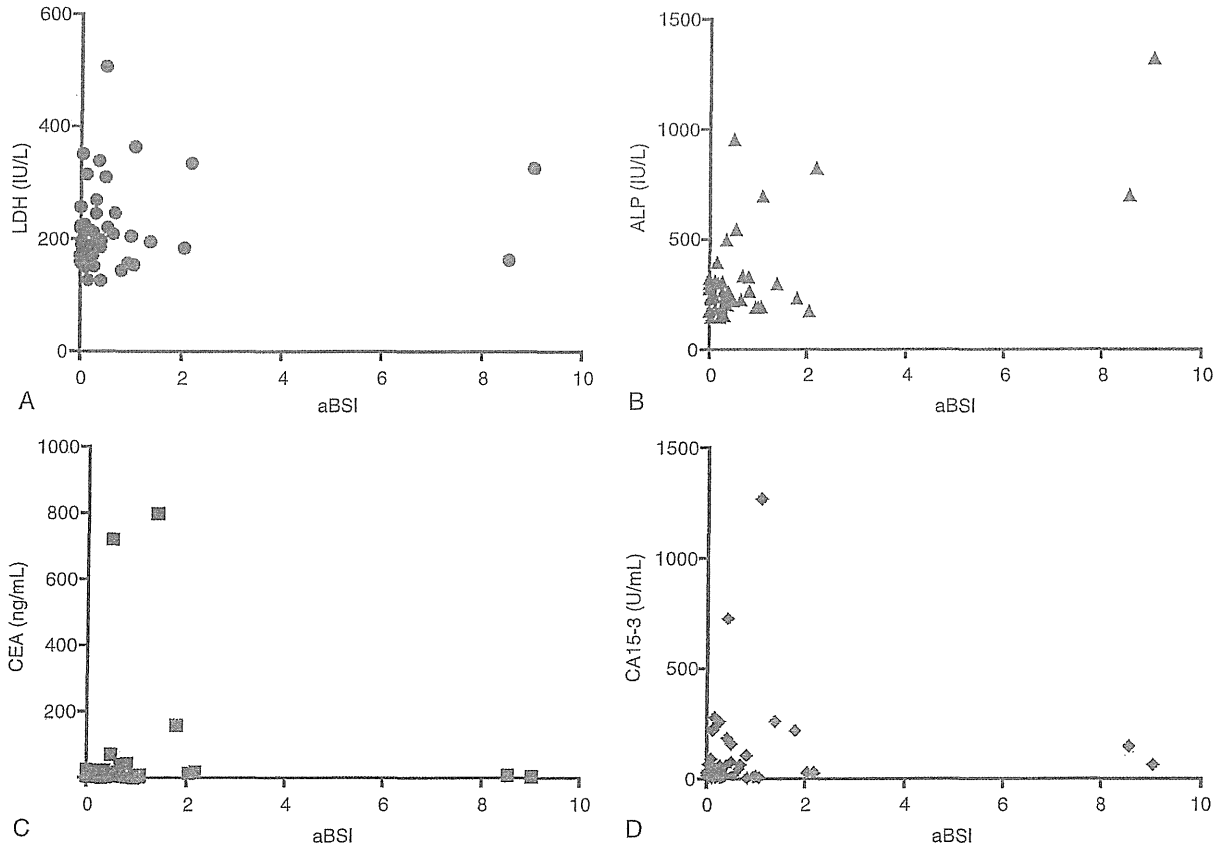

FIGURE 2. (A–D) Correlation analyses between a bone metabolic marker, cell injury marker, and tumor marker and aBSI at the time treatment started. Alkaline phosphatase appeared to have considerable correlation with the aBSI.

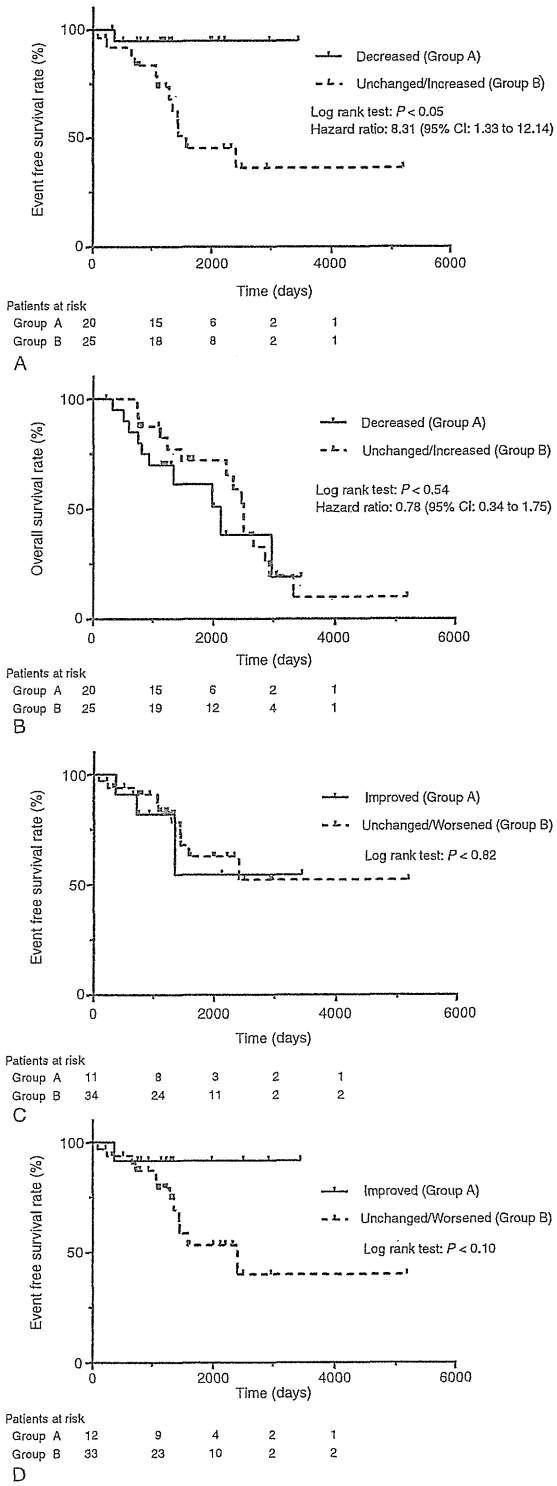

FIGURE 3. (A) Event free survival for SRE in Group A and B divided by aBSI. Survival curve demonstrated that Group B (Unchanged/Increased) significantly shorter event free survival compared to the Group A (Decreased). (B) Overall survival in Groups A and B. No significant differences were found between the two groups. (C, D) Event-free survival for SRE in Group A and B divided by radiologist interpretation. Survival curves demonstrate no significant differences between Group A (Improved) and Group B (Unchanged/Worsened). Figure 3c illustrates the results obtained by Radiologist A and Figure 3d shows those obtained by Radiologist B.

Firstly, an irregular follow-up period might have caused a lead-time bias; secondly, flare effects in the bone scan might have altered study results. Performing bone scans under the influence of flare might have caused a temporary worsening of aBSI, resulting in classification of cases as Group B instead of A. Nine patients underwent a scan from 6 to 9 months after treatment started, which appeared to be the period most influenced by flare. Patients who experienced SRE were 1 of 3 in Group A and 3 of 6 in Group B. Six patients in Group B seemed to have been affected by flare by considering aBSI changing in conjunction with serial bone scan findings. Of those 6 patients, only 1 experienced SRE. Considering these facts, flare seemed to have had relatively little effect on the present study results. However, in the future, prospective study with a standardized follow-up period will be needed to avoid a possible flare effect.

Secondly, the present study demonstrated significant differences in EFS but not OS between the two aBSI groups. The median follow-up period of the present study was 44.7 months, which appeared sufficient because generally the reported median OS for breast cancer patients with bone metastasis is approximately 24 months.[11] However, therapeutic effects of the chemotherapeutic agents or other drugs might have affected the outcome because a long follow-up period spanning years was observed. Therefore, stratifying the subtypes and the treatments is recommended in future analysis of the relationship between aBSI and OS over a long follow-up period.

Thirdly, the present study showed that the radiologists could not predict SRE by using visual scan interpretation, even though the visual scan interpretation results showed a significantly high correlation with the aBSI. The radiologists added 9 or 8 cases into the unchanged/worsened group, compared with the aBSI evaluation. This suggests that radiologists tend to have relatively high sensitivity to the bone scan. This result may stem from an unconscious anxiety about misreading the scan. However, the balance of sensitivity and specificity needs to be adjusted according to the situation, for example, screening test or evaluation after specific treatment. In evaluation after treatment, high sensitivity may lead to false-positive results and physicians may consider more imaging analyses or invasive procedures. Such clinical decisions may considerably burden stage IV patients both physically and economically. Whether the aBSI is superior to radiologist interpretation cannot be concluded from the present study design. Therefore, the aBSI is preferably used as an assistant tool for diagnosing at present. For example, in a facility that has few experienced radiologists, assistant use of the aBSI may enable preservation of the appropriate balance between sensitivity and specificity.

To date, there have been few reliable biomarkers for the evaluation of local therapeutic effect in bone metastatic treatment for breast cancer. Therefore, in clinical settings, tumor markers or bone metabolic markers have been frequently selected because these markers reflect the bone remodeling process. The present study demonstrated a significant correlation between ALP and aBSI. Furthermore, the usefulness of several bone metabolic markers for evaluating the therapeutic effects at bone metastatic sites has been reported, for example, bone specific alkaline phosphatase and procollagen I carboxyterminal propeptide as a bone formation marker, and tartrate-resistant acid phosphatase (TRAPC5b), deoxypyridinoline, and type I collagen cross-linked N-telopeptide (NTX) as a bone resorption marker.[12,13] However, as often seen in clinical cases, when distant organ and bone metastasis coexist, it may be difficult to separately evaluate a bone metastatic site by serum

biomarkers, because the on-treatment changes of each organ to the treatment possibly mimic the changes in the markers. Particularly in such situations, using aBSI as an imaging biomarker will permit objective evaluation of the therapeutic outcome.

aBSI is a promising imaging biomarker, although certain weaknesses, such as the difficulty of eliminating the flare effect, need to be noted. In the near future, combining aBSI with serum biomarkers and utilizing the advantages of each will lead to improved accuracy of therapeutic evaluation.

CONCLUSIONS

In conclusion, the present study demonstrated the usefulness of aBSI as an imaging biomarker for SRE in bone metastasis treatment of breast cancer. In addition, the combination of the bone metabolic marker with aBSI has the potential to become a powerful evaluation tool. Further investigative analysis is expected to reveal the usefulness of aBSI as an imaging biomarker, similar to its use in prostate cancer.

In the near future, aBSI as an imaging biomarker might be a useful determining factor when deciding between BMA and aggressive orthopedic intervention, thereby leading to decreased SRE.

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Breast Cancer (2014) 21:643–650
DOI 10.1007/s12282-013-0466-2

Clinicopathological features of young patients (<35 years of age) with breast cancer in a Japanese Breast Cancer Society supported study

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Received: 19 November 2012 / Accepted: 28 March 2013 / Published online: 16 April 2013

Abstract
Background To clarify the clinicopathological features of breast cancer in young females, surveillance data of the Registration Committee of the Japanese Breast Cancer Society were analyzed.
Methods The clinicopathological characteristics were compared between young (<35) patients and non-young (≥35) patients among 109,617 records registered between 2004 and 2009.
Results The numbers of young and non-young patients were 2,982 (2.7 %) and 106,295 (97.0 %), respectively. The young patients had more cases of a familial history of breast cancer, more subjective symptoms, fewer bilateral tumors, lower BMIs, larger tumors, more positive lymph nodes, fewer instances of an ER-positive status, more instances of an HER2-positive status, more triple-negative tumors and more advanced TNM stages. The young patients more frequently received neoadjuvant chemotherapy and breast-conserving therapy (BCT) compared with the non-young patients. Eighty percent of all patients received adjuvant therapy. The young patients were more frequently treated with chemotherapy, molecular targeted therapy and radiation therapy than the non-young patients.
Conclusions In this study, young patients with breast cancer were diagnosed at more advanced stages and had more endocrine-unresponsive tumors than non-young patients. Further prognostic analyses should be conducted in this cohort.

Keywords Breast cancer in young females · Surveillance data

Special Feature organized by Dr. Chikako Shimizu.

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Introduction

The incidence of breast cancer in Japanese females is increasing rapidly. Approximately 61,000 females are diagnosed with breast cancer annually in Japan [1]. Breast cancer rarely occurs in very young females; however, management problems in young patients must be considered, not only health and social aspects, but also familial and reproductive problems. Breast cancer arising in younger females is reported to be more aggressive and associated with unfavorable prognoses [2–8]. Due to the limited number of patients and the lack of clinical trials using young females with breast cancer, both clinicians and patients face a lack of information regarding decision making to select treatment, including the type of surgery

and the choice of adjuvant therapy. Because subsequent life plans may be changed by what kind of treatment is chosen, information on the clinical characteristics of breast cancer in young females and trends in medical treatment is needed in clinical practice. The aim of this study was to clarify the clinicopathological features of breast cancer in young Japanese females and recent trends in treatment choices. With the support of the Registration Committee of the Japanese Breast Cancer Society (JBCS), we analyzed 109,617 cases registered between 2004 and 2009.

Materials and methods

Basic patient data

Comprehensive data on breast cancer patients diagnosed in Japan between 2004 and 2009 were registered with the Registration Committee of the JBCS. The final registry data were reported in 2010, although the patient outcome data have not yet been published. Registrations were made by 490 institutions and included 109,617 female cases. The data collected included age at diagnosis, family history, menstrual status, body mass index and clinicopathological features of the tumor, including tumor size, the presence of lymph node metastases and the receptor status (ER, PgR and HER2), the type of surgery, the use of radiation therapy and the regimens of adjuvant therapy. Since the data belong to the JBCS, permission to use the data was obtained from the JBCS.

Statistical processing

Fischer's exact test was used to compare various prevalence rates among the groups. The unpaired t test was employed to make intergroup comparisons in the numbers of cases and mean values. The significance level was set at less than 0.01 when multiple comparisons were required between two groups. All statistical processing was completed using the SAS software program (version 9.1.3; SAS Institute, Inc., Cary, NC).

Results

Patient backgrounds and clinicopathological characteristics

The age distribution of the patients is shown in Fig. 1. Young breast cancer patients, defined as those less than 35 years of age at diagnosis, were analyzed. The numbers of young and non-young patients were 2,982 (2.7 %) and 106,295 (97.0 %), respectively. Three hundred forty (0.3 %) patients were of unknown age. The median patient age was 58 years. The clinicopathological factors were compared between the young patients and the non-young patients (Table 1). Almost all of the young patients were premenopausal, and 64.1 % of the non-young patients were postmenopausal. The body mass indices of the young patients were lower than those of the non-young patients. According to the definition of the Japan society for the study of obesity, a BMI >25 was regarded as overweight; therefore, 10.4 % of the young patients and 22.8 % of the non-young patients were regarded as being overweight. On the other hand, 11.4 % of the young patients and 5.2 % of the non-young patients were regarded as being thin (BMI ≤18). A family history of breast cancer was found in 12.4 % of the young patients, which was higher than the 9.4 % observed in the

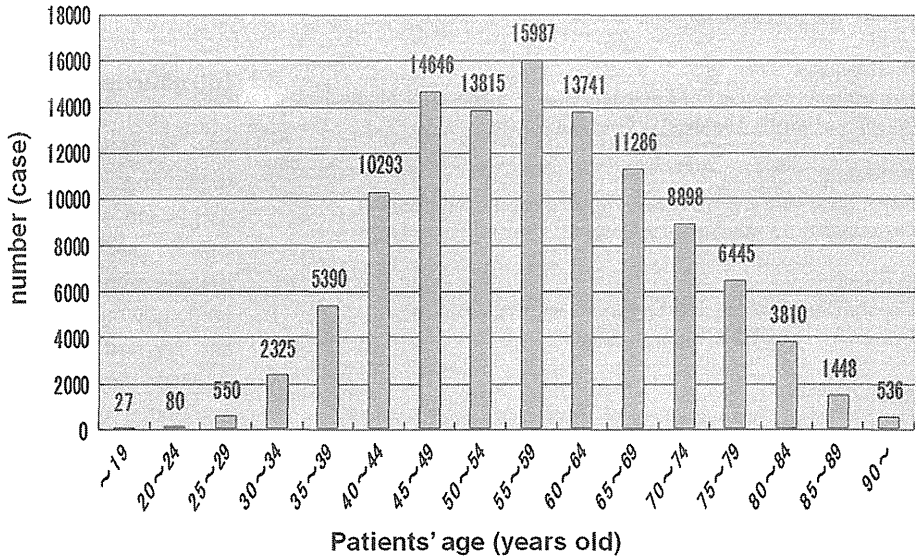

Fig. 1 Distribution of age at diagnosis among patients registered between 2004 and 2008 with the Japanese Breast Cancer Society

Table 1 Comparison of the clinicopathological factors between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
Menopausal status					
Pre-menopausal	2,898	97.2	35,037	33	<0.0001
Post-menopausal	48	1.6	68,107	64.1	
Unknown	36	1.2	3,151	3.0	
Body mass index (BMI)					
≦18	339	11.4	5,524	5.2	<0.0001
18< BMI ≦22	1,690	56.7	40,374	38.0	
22< BMI ≦25	514	17.2	30,842	29.0	
25<	310	10.4	24,209	22.8	
Unknown	129	4.3	5,346	5.0	
Family history of breast cancer					
No	2,399	80.4	88,195	83.0	<0.0001
Yes	370	12.4	9,967	9.4	
Unknown	213	7.1	8133	7.7	
Method of detection					
Self-detection	2,482	83.2	71,517	67.3	<0.0001
Screening (with symptoms)	107	3.6	5,233	4.9	
Screening (no symptoms)	251	8.4	22,028	20.7	
Other	99	3.3	6,352	6.0	
Unknown	43	1.4	1,165	1.1	
Bilateral breast cancer					
No	2,904	97.4	98,610	92.8	<0.0001
Synchronous	53	1.8	4,339	4.1	
Metachronous	25	0.8	3,346	3.2	
Size of tumor					
~2.0 cm	1,206	43.4	52,635	53.0	<0.0001
2.1 ~ 5.0 cm	1,231	44.3	39,976	40.2	
~5.1 cm	341	12.3	6,771	6.8	
N					
N0	2,154	72.2	83,992	79	<0.0001
N1	638	21.4	17,409	16.4	
N2	99	3.3	2,703	2.5	
N3	46	1.5	1,181	1.1	
Unknown	45	1.5	1,010	1.0	
M					
M0	2,837	95.1	102,701	96.6	<0.0001
M1	87	2.9	2,328	2.2	
Unknown	58	2	1,266	1.2	
Stage					
0	298	10	9,380	8.8	<0.0001
I	832	27.9	38,723	36.4	
II	1,172	43.9	38,185	39.8	
III	278	10.4	7,369	7.7	
IV	87	3.3	2,328	2.4	
Unknown	315	10.6	10,310	9.7	

BMI body mass index

non-young patients. Synchronous bilateral tumors and metachronous bilateral tumors were found in 1.8 % and 0.8 % of young patients, which were both lower than the rates of 4.1 % and 3.2 % observed in the non-young patients. More than 80 % of the young patients reported subjective symptoms by self detection, which was higher than the 67.3 % of non-young patients who reported similar symptoms. Asymptomatic tumors were detected on screening in only 8.4 % of the young patients, which was much lower than the rate of 20.7 % observed in the non-young patients. The young patients were more likely to be diagnosed with large tumors and advanced-stage tumors than the non-young patients. The mean tumor size was 2.9 cm in the young patients, which was larger than the 2.5 cm observed in the non-young patients ($p < 0.0001$). More than 12 % of the young patients had large tumors (>5 cm), which was higher than the rate of 6.8 % observed in the non-young patients. The distribution of histological subtypes is shown in Fig. 2. The histological tumor subtypes were classified in accordance with the classification of breast carcinoma issued by the Japanese Breast Cancer Society, which is a modified World Health Organization histological classification [9, 10]. The subtypes did not differ significantly between the young and non-young patients. Scirrhous carcinoma was the most frequent histological type in both the young and non-young patients. The frequency of solid-tubular carcinoma in the young patients tended to be higher than that observed in the non-young patients. Invasive lobular carcinoma rarely occurred in the young patients.

Biological markers

The ER, PgR and HER2 expressions were compared between the young and non-young patients (Table 2). The status of ER and PgR was determined according to the immunohistochemical (IHC) technique using monoclonal antibodies. A cutoff level of between 2 and 3 was adopted on the Allred Score [11] or 10 % as a staining proportion [12]. Tumors that were immunohistochemically scored as 3+ or 2+ with a FISH-positive status were regarded as HER2-positive in the majority of individual participating institutions. Of the young patients, 70.8 % had ER-positive tumors, which was lower than the rate of 75.0 % observed in the non-young patients ($p < 0.0001$). The HER2-positive rate in the young patients was 16.3 %, which was higher than the 14.1 % observed in the non-young patients ($p = 0.0032$). The rate of so-called 'triple-negative' [(TN), ER-, PgR- and HER2-negative] tumors was 18.3 % in the young patients, which was higher than the 13.7 % observed in the non-young patients ($p < 0.0001$).

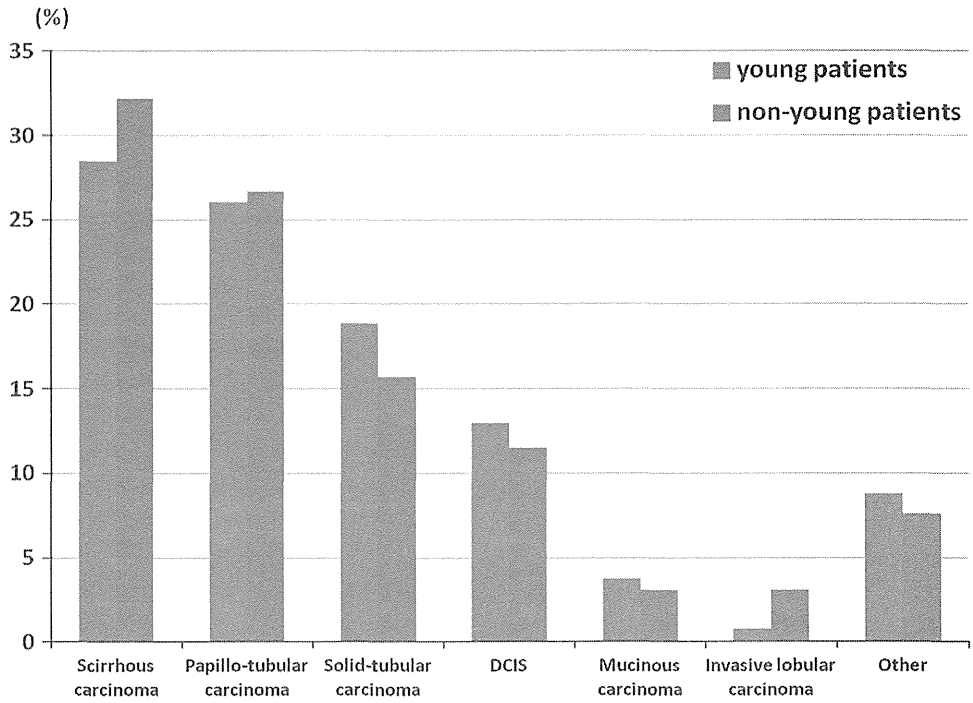

Fig. 2 Distribution of the histological subtypes of breast cancer. *DCIS* ductal carcinoma in situ

Table 2 Comparison of the hormone receptor and HER2 status between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
ER					
Positive	2,110	70.8	79,699	75.0	<0.0001
Negative	792	26.6	23,910	22.5	
Unknown	80	2.7	2,686	2.5	
PgR					
Positive	1,892	63.5	64,728	60.9	0.0082
Negative	999	33.5	38,539	36.3	
Unknown	91	3.1	3,028	2.9	
HER2					
Positive	486	16.3	15,010	14.1	0.0032
Negative	2,183	73.2	80,104	75.4	
Unknown	313	10.5	11,181	10.5	
Triple negative					
Yes	487	18.3	12,998	13.7	<0.0001
No	2,173	81.7	81,605	86.3	

ER estrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

Table 3 Comparison of the type of surgery between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
Surgery for breast					
No	5	0.2	130	0.1	<0.0001
Breast conservation	1,844	62.7	59,822	57.0	
Mastectomy	1,030	35.1	43,982	41.9	
Other	58	2.0	1,023	1.0	
Unknown	2	0.1	49	0.1	
Axillary dissection					
No	168	5.7	7,338	7.0	<0.0001
SNB alone	1,105	37.6	40,495	38.6	
Sampling alone	63	2.1	2,912	2.8	
More than level I	1,575	53.6	53,627	51.1	
Other	14	0.5	488	0.5	
Unknown	14	0.5	146	0.1	

SNB sentinel node biopsy

Surgical treatment

The types of surgery were compared between the young and non-young patients. Both the young and non-young patients were more likely to undergo breast-conserving therapy (BCT) than mastectomy, as shown in Table 3. The rate of BCT in the young patients was higher than that observed in the non-young patients (62.7 % vs. 57.0 %), although the rate of mastectomy in the young patients was lower than that observed in the non-young patients (35.1 % vs. 41.9 %, $p < 0.0001$, respectively). Axillary lymph node dissection was performed in 53.6 % of the young patients, which was higher than the rate of 51.1 % observed in the non-young patients ($p < 0.0001$).

Adjuvant therapy

The details of the neoadjuvant and adjuvant therapy were compared between the young and non-young patients, as shown in Tables 4, 5 and 6. The rate of neoadjuvant therapy was 24.7 % in the young patients, which was significantly higher than the 11.3 % observed in the non-young patients ($p < 0.0001$). Among the patients who received neoadjuvant therapy, 97.1 % and 89.8 % of the young and non-young patients received chemotherapy, 15.7 % and 16.9 % received hormone therapy and 11.9 % and 11.0 % received trastuzumab, respectively. Anthracyclines and taxans were primarily prescribed as neoadjuvant chemotherapy in both the young and non-young patients. LHRHa was prescribed as neoadjuvant hormone therapy in 12.4 % of the young patients, and AI was prescribed in 10.6 % of the non-young patients.

Table 6 shows a comparison of the adjuvant therapies. The young patients were more likely to be treated with chemotherapy, targeted therapy and radiation therapy, but not hormone therapy, compared to the non-young patients. Among the patients who received adjuvant therapy, 55.5 % and 41.5 % of the young and non-young patients received chemotherapy, 76.2 % and 81.2 % received hormone therapy and 9.6 % and 5.8 % received trastuzumab, respectively. In contrast to that observed for neoadjuvant therapy, adjuvant therapy primarily included hormone therapy rather than chemotherapy in both the young and non-young patients. Tamoxifen and LHRHa were most prescribed as adjuvant therapy in the young patients, while AI and tamoxifen were prescribed in the non-young patients.

Table 4 Comparison of the adjuvant therapy between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
Neoadjuvant therapy					
No	2,211	75.2	92,992	88.6	<0.0001
Yes	725	24.7	11,912	11.3	
Unknown	3	0.1	102	0.1	
Adjuvant therapy					
No	569	19.4	19,306	18.4	0.006
Yes	2,326	79.1	84,678	80.6	
Unknown	44	1.5	1,022	1.0	

Table 5 Comparison of the neoadjuvant therapy between young and non-young patients with breast cancer

	Young patients (n = 725)		Non-young patients (n = 11,912)		p value
	N	(%)	N	(%)	
Chemotherapy	704	97.1	10,698	89.8	<0.0001
Anthracyclines	636	87.7	9,002	75.6	
Taxanes	595	82.1	8,732	73.3	
Oral FU	33	4.6	714	6.0	
CMF	1	0.1	31	0.3	
Other	4	0.6	68	0.5	
Hormone therapy	114	15.7	2,014	16.9	<0.0001
Tamoxifen	33	4.6	533	4.5	
GnRH agonist	90	12.4	256	2.1	
AI	2	0.3	1,262	10.6	
MPA	15	2.1	257	2.2	
Trastuzumab					
No	639	88.1	10,607	89.0	0.4488
Yes	86	11.9	1,305	11.0	

Oral FU oral furuorouracil (doxifluridine/tegafur-gimeracil-oteracil potassium/tegafur-uracil/capecitabine), *CMF* cyclophosphamide + methotorexate + 5-FU, *Other* irinotecan hydrochloride, gemcitabine hydrochloride, vinorelbine tartrate, *GnRH agonist* gonadotropin-releasing hormone agonist (goserelin acetate/leuprorelin acetate), *AI* aromatase inihibitors (anastrozole/exemestane/letrozole), *MPA* acetic acid medroxyprogesterone

Table 6 Comparison of the adjuvant therapy between young and non-young patients with breast cancer

	Young patients (n = 2,326)		Non-young patients (n = 84,678)		p value
	N	(%)	N	(%)	
Chemotherapy	1,290	55.5	35,163	41.5	<0.0001
Anthracyclines	1,013	43.6	24,893	29.4	
Taxanes	636	27.3	14,350	16.9	
Oral FU	162	7.0	5,262	6.2	
CMF	42	1.8	2,407	2.8	
Other	9	0.4	155	0.2	
Hormone therapy	1,772	76.2	68,712	81.2	<0.0001
Tamoxifen	1,576	67.8	28,696	33.9	
GnRH agonist	1,291	55.5	11,169	13.2	
AI	37	1.6	40,507	47.8	
MPA	7	0.3	168	0.2	
Trastuzumab					
No	2,102	90.4	79,793	94.2	<0.0001
Yes	224	9.6	4,885	5.8	
Radiation therapy					
No	872	37.5	41,257	48.7	<0.0001
Yes	1,441	62.0	43,112	50.9	
Unknown	13	0.6	309	0.4	

Oral FU oral furuorouracil (doxifluridine/tegafur-gimeracil-oteracil potassium/tegafur-uracil/capecitabine), *CMF* cyclophosphamide + methotorexate + 5-FU, *Other* irinotecan hydrochloride, gemcitabine hydrochloride, vinorelbine tartrate, *GnRH agonist* gonadotropin-releasing hormone agonist (goserelin acetate/leuprorelin acetate), *AI* aromatase inihibitors (anastrozole/exemestane/letrozole), *MPA* acetic acid medroxyprogesterone

Radiation therapy was performed in 62.0 % of the young patients, which was significantly higher than the rate of 50.9 % observed in the non-young patients ($p < 0.0001$). Radiotherapy was indicated for patients who underwent breast-conserving surgery, those with larger tumors and those with four or more positive lymph nodes at the time of surgery.

Discussion

We analyzed data obtained from a large number of breast cancer cases registered with the JBCS in order to characterize and advance our understanding of the features of young breast cancer patients. The median age of breast cancer patients was 58 years old and the percentage of young patients under 35 years of age was 2.7 % in this study. It has been established that a racial difference exists in the incidence rates and age distribution of breast cancer [13]. The age-adjusted breast cancer incidence rate for Japanese women was reported to be 73.4 per 100,000 women per year in 2007, which is still lower than the rate reported in Western countries [1]. In the US, the age-adjusted breast cancer incidence rate was 124.3 per 100,000 women per year in 2009, the median age at the diagnosis of breast cancer was 61 years of age, and the percentage of young patients under 35 years of age was 1.8 % [14]. In the 1990s, the Japanese age-adjusted breast cancer incidence rate was only 37.0–43.6 per 100,000 women per year, with the peak age at the diagnosis of breast cancer reported to range from 45–50 years of age and the percentage of young patients under 35 years of age ranged from 5–7 % [1, 15]. A rapid increase in the incidence rate was seen among middle and old age groups, especially among individuals from 45 to 64 years old; the percentage of young patients compared to all patients has shown a decreasing trend over the past 20 years [13, 15]. Early menarche, late child-bearing and a decreasing birthrate are the current trends among Japanese women, which are factors that appear to influence the present increasing rates of breast cancer in addition to changes in both foods and lifestyles from traditional Japanese customs to Western styles. As the Japanese have recently become more Westernized, the epidemiology of breast cancer might change from the previously observed patterns to Western patterns [16].

Features of the young Japanese patients' backgrounds compared to those of the non-young patients included lower BMIs, more frequent family histories of breast cancer and fewer bilateral tumors. The rate of being overweight was 10.4 % among the young patients and 22.8 % among the non-young patients. According to surveillance data of the Ministry of Health, Labor and Welfare, the rate of overweight Japanese females (BMI >25) was 20.2 % in 2007 [17]. The rates of females who are overweight between the ages of 20–29 and 30–39 are 5.9 and 11.1 %, respectively. This rate increases with age and is highest at 29.5 % among females 60–69 years of age. The weight distribution of Japanese breast cancer patients corresponds to the weight distribution of common Japanese females. In this study, young patients more frequently had a family history of breast cancer, which highlights the possibility of hereditary breast cancer accompanied by the BRCA1/2 mutation and other genetic mutations. A younger age at diagnosis is one of the features of hereditary breast cancer, as well as TN subtype and bilateral tumors [18]. In this study, since the patients were still young and had been little influenced by age, there were few metachronous bilateral tumors in the young patients. It has also been reported that a young age at diagnosis of a first cancer is a risk factor for contralateral breast cancer [19]. In our study, the biological characteristics of breast cancer in the young patients included endocrine-unresponsive tumors such as ER-negative, HER2-positive and TN tumors. Young patients tend to have larger tumors and lymph node metastasis due to delays in detection and/or rapid growth. Young patients hardly notice small-sized tumors due to fact that they have dense breasts. From a viewpoint of morphologic classification, the frequency of solid tubular carcinoma in young patients is higher, and this type has a tendency to exhibit a rapid and expansive growth pattern and prevail in patients with TN breast cancer [20]. These results are similar to those of previous studies from Western and Asian countries [2–8, 13, 21]. Breast cancer in young women is likely mainly caused by either genetic mutations or hereditary factors rather than long-term hormonal, environmental or lifestyle effects, and the biological subtypes of breast cancer in young women tend to be similar and no substantial racial differences are observed.

In terms of trends in treatment choices among young patients, the rate of BCT was higher in the young patients than in the non-young patients, in spite of the young patients exhibiting larger tumor sizes. This is due to the high rate of administration of neoadjuvant chemotherapy in young patients. In Japan, the rate of BCT was over 50 % in 2009. However, the cosmetic results of BCT were not satisfactory for all patients, and knowledge of breast reconstruction became widespread; therefore, the rate of BCT has reached a ceiling [22]. Total mastectomy and immediate reconstruction may replace BCT, especially in young patients who feel severe breast loss or who worry about intramammary recurrence. In the US, females ≤40 years of age are significantly more likely to undergo mastectomy followed by breast reconstruction than BCT compared with older females [23]. As mentioned for adjuvant therapy, both anthracyclines and taxans were used

in most of the young patients in this study. Trastuzumab was also used as adjuvant therapy. Both the pathological complete remission (pCR) rate and the survival rate of patients with breast cancer have dramatically improved because of progress in targeted therapy combined with chemotherapy during the last several years [24, 25]. A prognostic analysis of this cohort is now underway.

Preserving the ovarian function and maintaining fertility are also important issues for young patients who desire childbirth. GnRH agonists given with chemotherapy for early breast cancer have been reported to be associated with a low risk of long-term chemotherapy-induced amenorrhea and a high chance of pregnancy [26]. According to one report, of the 42 patients who attempted pregnancy, 71 % ($n = 30$) managed to achieve pregnancy, including 8 females ≥35 years of age. Although the use of GnRH agonists during chemotherapy is not yet considered to be the standard for protecting ovarian function, 12.4 % of the young patients were treated with a GnRH agonist together with neoadjuvant chemotherapy in the present study. It is important for young patients to make treatment choices based on both breast cancer subtype and personal preference with consideration for life planning, survivorship and long-term side effects. Our study has several limitations; neither the reasons for selecting the type of treatment, the timing and duration of hormone therapy, the subsequent ovarian function nor the disease prognosis was clearly elucidated in these cases. We could confirm that young patients with breast cancer are more likely to have advanced or endocrine-unresponsive tumors than non-young patients; therefore, young patients tended to be treated more aggressively with systemic therapy. Further prognostic analyses and cohort studies of long-term side effects are needed.

Acknowledgments We wish to thank Mr. Naohito Fukui, the NPO Japan Clinical Research Support Unit staff and the Japanese Breast Cancer Society for their collaboration on this study and their ongoing development, maintenance and improvement of this registry. This work was supported by a research fund from the Japanese Breast Cancer Society.

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

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