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Mammographic breast density change following postoperative adjuvant therapy in hormone receptor-positive breast cancer patients

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Abstract

Several studies have been reported that postoperative adjuvant endocrine therapy decreases mammographic breast density and that breast density change may be a prognostic factor for recurrence, however there are few studies on relationship between postoperative adjuvant therapy and breast density in Japan. We investigated changes in the breast density following postoperative adjuvant therapy in hormone receptor (HR)-positive breast cancer and whether breast density change is related to recurrence. We analyzed data from 240 HR-positive breast cancer patients who underwent surgery and received postoperative adjuvant therapy at our institution. The breast density was measured by contralateral breast mammography (MMG) using the Breast Imaging Reporting and Data System (the BI-RADS) classification, and breast density reduction was defined as the reduction of the BI-RADS density score on follow-up MMG compared with the pretreatment value. The breast density was reduced in 22 (9.2%) patients. Of patients with breast density reduction, 19 (86.4%) received a selective estrogen receptor modulator (SERM), and these patients showed significantly higher rates of breast density reduction compared with those receiving an aromatase inhibitor (AI ; $p < 0.001$). The addition of chemotherapy was not associated with the breast density reduction. Fifteen (6.1%) patients had recurrent disease. There was no patient with breast density reduction showed recurrence, however no significant correlation between breast density reduction and recurrence. In this study, the breast density reduction in adjuvant therapy of Japanese HR-positive breast cancer patients did not become a predictor of recurrence.

Key words : breast density, adjuvant therapy, breast cancer, hormone receptor-positive, mammography

Introduction

Around 70% of breast cancers are estrogen-dependent ; their development and growth are closely associated with internal and/or external estrogen levels. The mammary glands are the major target organs of estrogen, and the breast density may be correlated with estrogen levels. Thus, the breast density is a clinically significant factor in breast cancer, on which a large number of studies have been reported. Especially, a number of studies indicated that a high mammo-

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graphic breast density is a marker of an increased risk of developing breast cancer.[1–3]

Also, there are several studies on breast density change as a prognostic factor of breast cancer. It has been reported that postoperative adjuvant endocrine therapy decreases the mammographic breast density, and that breast density change may be a prognostic factor for recurrence, especially in premenopausal breast cancer.[4–7] On the other hand, there have been few studies on the relationship between postoperative adjuvant therapy and the breast density in Japan.

Adjuvant endocrine therapy decreases the risk of recurrence in patients with hormone receptor-positive (HR-positive) breast cancer.[8–10] Five years of adjuvant hormone therapy is a standard of care for HR-positive breast cancer patients. There also exist 10-year data on the efficacy of adjuvant hormone therapy.[11] However, adjuvant endocrine therapy targets microscopic metastases and, thus, its effectiveness cannot be determined during the treatment course. As some patients show recurrence during or early after adjuvant endocrine therapy, it is important to understand the sensitivity or resistance to adjuvant endocrine therapy.

There have been few reports on the association between chemotherapy and the breast density, while chemotherapy for premenopausal breast cancer may be associated with chemotherapy-induced amenorrhea, leading to a reduced breast density indirectly. It has been shown that chemotherapy-induced amenorrhea correlates with the prognosis of breast cancer patients.[12,13] It will be interesting to clarify whether breast density reduction caused by adjuvant chemotherapy can be a surrogate marker of the prognosis of breast cancer patients.

We retrospectively investigated breast density reduction following postoperative adjuvant therapy (endocrine therapy or chemotherapy) in Japanese patients with HR-positive breast cancer at our institution. Moreover, we evaluated the association between breast density reduction and metastases and recurrence of the disease.

Methods

Patients

Among 338 HR-positive breast cancer patients who underwent surgery and received postoperative adjuvant therapy at our institution between January 2010 and December 2011, we included those who received mammography (MMG) before and after the start of adjuvant therapy. Patients were excluded if: 1) they had a history of breast cancer; 2) they underwent surgery for the contralateral breast; 3) they had synchronous bilateral breast cancer; or 4) distant metastasis was observed at diagnosis. We analyzed data on 240 patients included retrospectively. HR positivity was defined as being either estrogen receptor-positive (ER-positive) and / or progesterone receptor-positive (PgR-positive).

Breast density assessment

Pretreatment MMG was taken within 6 months before the start of treatment and follow-up MMG was taken between 6 months and 2 years after the start of adjuvant therapy. The breast density was measured in the unaffected breast using the Breast Imaging Reporting and Data System (BI-RADS) classification and classified into extremely dense, heterogeneously dense, scattered fibro glandular densities, and almost entirely fat. A radiologist and breast surgeon who were board-certified physicians for mammogram-reading classified the type of category using digital mammogram images. All images were digitized for assessment. Breast density reduction was defined as the lowered case of the BI-RADS density classification of the contralateral breast at the follow-up visit from the pretreatment value.

Statistical analysis

All statistical analyses were performed using JMP Ver11 (SAS Institute, Cary, NC, USA). The association between breast density reduction and clinicopathological factors was assessed with the t- test or χ^2 test. Progression-free survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test. $p<0.05$ was considered significant.

Results

Patient background and breast density reduction

The median age of the included patients was 56.7 years (range, 27 to 89 years). A total of 105 (43.7%) patients were premenopausal women and 135 (56.3%) were postmenopausal women. The median follow-up from the initiation of postoperative therapy to follow-up MMG was 12.2 months (range, 7 to 24 months). The mammographic breast density was reduced in 22 (9.2%) patients. In a univariate analysis, we found that

Table 1 Patients' characteristics

Variables	Total		Breast density reduction		No breast density reduction		p-Value
	No.	%	No.	%	No.	%	
Total	240		22	9.2	218	90.8	
Age (years)							
Median (range)	56.7	(27-89)	48.4	(27-71)	57.6	(28-89)	0.001
Menopausal status							
Premenopausal	105	43.7	21	95.5	84	38.5	<0.001
Postmenopausal	135	56.3	1	4.5	134	61.5	
BMI (kg/m^2)							
Median (range)	22.6	(16-40)	22.4	(17-32)	22.7	(16-40)	0.740
Tumor size (mm)							
Median (range)	15.6	(0.1-65)	18.7	(0.1-56)	15.3	(0.1-65)	0.255
Pathological nodal status							
Negative	173	72.1	15	68.2	158	72.5	0.669
Positive	67	27.9	7	31.8	60	27.5	
ER status							
+	234	97.5	20	90.9	214	98.2	0.038
−	6	2.5	2	9.1	4	1.8	
PgR status							
+	187	77.9	20	90.9	167	76.6	0.123
−	53	22.1	2	9.1	51	23.4	
HER2 status							
+	61	25.4	5	22.7	56	25.7	0.761
−	179	74.6	17	77.3	162	74.3	
Interval to follow-up mammography (months)							
median (range)	12.2	(7-24)	11.9	(9-23)	12.2	(7-24)	0.794

ER : estrogen receptor, PgR : progesterone receptor

the age, menopausal status, and ER status were associated with the breast density reduction. Such a reduction was more frequently observed in younger patients. Most of the patients with breast density reduction were premenopausal women (95.5%, 21 out of 22 patients ; Table 1).

Postoperative adjuvant therapy and breast density reduction

Table 2 shows the adjuvant therapy for the included patients. We analyzed the association between the types of postoperative adjuvant therapy used and breast density reduction. There were no differences among endocrine therapy alone, chemotherapy alone, and the combination of chemotherapy and endocrine therapy (Fig. 1a). Then, we evaluated the association between types of endocrine therapy and breast density reduction : 19 (86.4%) patients were found to use a selective estrogen receptor modulator (SERM) among those with breast density change, showing a significant difference compared with those receiving an aromatase inhibitor (AI ; Fig. 1b). Of the patients treated with SERMs, 17 patients were treated in combination with LH-RH analogue. Among them, 4 patients were observed a breast density reduction, but there was no statistically significant difference ($p=0.554$). We assessed the breast density change between endocrine therapy alone and the addition of chemotherapy by each type of endocrine therapy, and found that the addition of chemotherapy was not associated with breast density change (Fig. 1c).

Event occurrence and breast density change

Of all patients included, 15 (6.2%) developed an event. The events included loco-regional, distant disease, and contralateral recurrences in 6, 8, and 1 patient, respectively. No recurrence occurred in patients with breast density reduction. We evaluated the relationship between breast density change and progression-free survival. The median follow-up period was 48.8 months (range, 10 to 63 months). The 5-years

Table 2 Adjuvant therapy

		Total (n=247)		Breast density reduction (n=22)		No breast density reduction (n=218)	
		No.	%	No.	%	No.	%
Neoadjuvant therapy							
No		235	97.9	22	100	213	97.7
Yes	CT	5	2.1	0	0	5	2.3
	ET	0	0	0	0	0	0
Adjuvant therapy							
ET	AI	79	32.9	1	4.5	78	35.8
	SERM	72	30.0	11	50	61	28.0
CT		3	1.3	1	4.5	2	0.9
ET+CT	AI	55	22.9	1	4.5	54	24.8
	SERM	31	12.9	8	36.5	23	10.5
Radiation therapy							
No		62	25.8	7	31.8	55	25.2
Yes		178	74.2	15	68.2	163	74.8

AI aromatase inhibitor, SERM selective estrogen receptor modulator

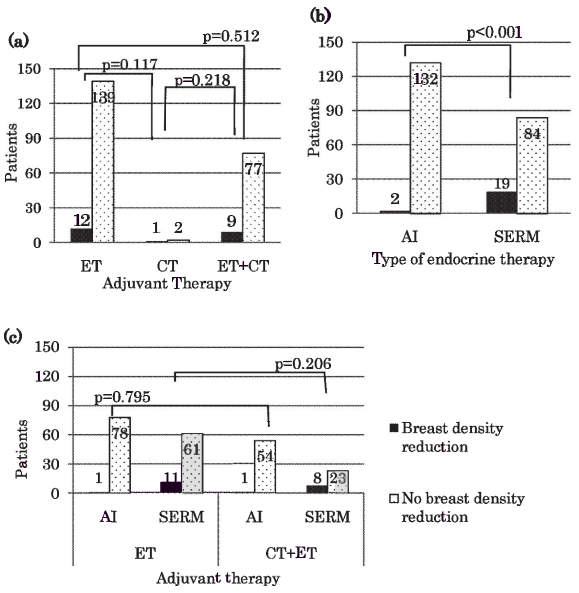

Fig. 1 Association of breast density reduction with postoperative adjuvant therapy
(a) types of postoperative adjuvant therapy, (b) types of endocrine therapy, (c) endocrine therapy alone and the addition of chemotherapy by each type of endocrine therapy. ET: endocrine therapy, CT: chemotherapy, SERM: selective estrogen receptor modulator, AI: aromatase inhibitor.

event-free survival was 100% for patients with breast density reduction and 88.8% for those without breast density reduction, with no significant difference (p=0.2112; Fig. 2).

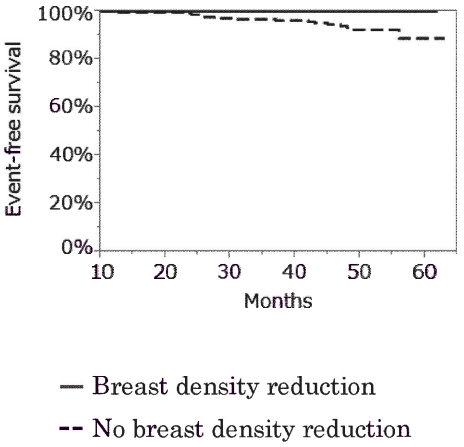

Fig. 2 Event-free survival curves according to breast density reduction
The 5-year event-free survival rate was 100% for patients with breast density reduction and 88.8% for those without breast density reduction, with no significant difference (p=0.2112).

Discussion

It has been reported that adjuvant therapy with tamoxifen, which is one of the SERMs, was associated with breast density reduction, leading to a decreased risk of breast cancer recurrence in premenopausal women with breast cancer.[5] A previous study reported that adjuvant therapy with tamoxifen reduced the breast density by 20% or greater and decreased the risk of dying from breast cancer by 50% in around half of postmenopausal breast cancer patients.[6] On the other

hand, there are fewer studies on the association between adjuvant therapy with AIs and breast density change in postmenopausal breast cancer patients. Vachon et al. analyzed the correlation between the use of AIs and breast density, and reported no correlation.[14] There have been almost no studies on breast density change following postoperative adjuvant therapy for breast cancer in Japanese women, who are likely to have dense breasts.

In the present study, breast density reduction was only observed in 9.2% of patients. In the previous studies, there were differences in the number of patients, patient selection methods and evaluation modalities to assess the breast density ; in studies in which both pre- and postmenopausal women were included for evaluation, a 5% or greater breast density reduction was observed in 20 to 50% of patients.[6,14] In our patients, fewer women experienced breast density reduction compared with the previous studies. Possible reasons include innate racial differences in the breast density between women of Japanese and Western countries, and differences in measurement modalities. Objective methods for evaluating the breast density using a variety of software products have been reported in a number of studies on the risk of developing breast cancer.[15,16] In this study, we used the BI-RADS classification to evaluate the breast density because of its convenience. Two board-certified physicians for mammogram-reading judged the breast density, while the category could be changed based on subjective judgment. The BI-RADS classification system has 4 categories, and in the case of a slight change, the category remains unchanged. Thus, there is a possibility that fewer patients showed breast density reduction than would be expected.

Breast density reduction was associated with the use of SERMs, not with the use of AIs. This result is consistent with previous studies. Tamoxifen is considered to inhibit breast cancer metastasis by blocking estrogen-mediated signaling via ER. The drug's antiestrogen effects may have an impact on breast density reduction.[17] On the other hand, AIs, which are the standard of care for the adjuvant treatment of postmenopausal women with ER-positive breast cancer, contribute to the prevention of breast cancer recurrence. The mechanism of action includes the marked suppression of estrogen levels in the tumor tissue by inhibiting aromatase, which is responsible for converting adrenogenic androgens to estrogens in the human body. As estrogen levels during the postmenopausal period are much lower than those during premenopause, they may have less of an impact on the normal mammary gland, which might be one of the reasons. In our patients, factors associated with breast density reduction included the age, menopausal status, and ER. Further studies are needed to identify which patient factors or postoperative adjuvant therapy may have influenced breast density reduction using a control group because 86.7% of patients using SERMs were premenopausal women.

In this study, the addition of chemotherapy was not associated with breast density reduction. Some studies have indicated an association between chemotherapy and breast density change because chemotherapy suppresses the ovarian function in premenopausal women with breast cancer.[5] However, the results on the association between the addition of chemotherapy and breast density change are inconsistent,[6] necessitating further studies.

In patients with breast density reduction, there was no recurrence. There was no significant difference between patients with and without breast density reduction. As the numbers of patients with and without breast density reduction were limited, it will be necessary to evaluate the breast density employing an objective and convenient approach in order to increase the sample size.

Conclusions

A total of 9.2% of patients showed breast density reduction following postoperative adjuvant therapy for HR-positive breast cancer. Most breast density reduction cases were observed in premenopausal women, and the breast density was decreased significantly in those receiving SERMs. The addition of chemotherapy was not associated with breast density reduction. Patients with breast density reduction had no recurrent disease. The association between breast density change and breast cancer recurrence will be a subject of future investigation.

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Society (July 2015).

Conflict of interest

The authors declare that they have no conflicts of interest.

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