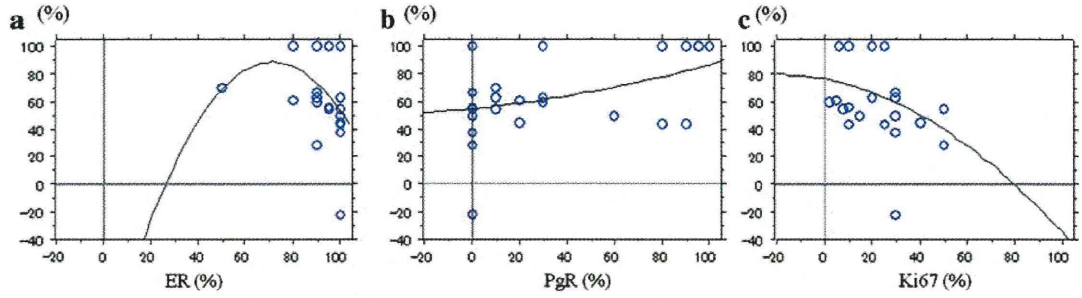

Fig. 4 The correlation between **a** ER, **b** PgR, and **c** Ki67 expression at baseline and clinical response. The *vertical axis* indicates the reduction rate of the tumor size evaluated by caliper

grade 3 (1 patient) wound infection, grade 3 hematoma (1 patient), and grade 2 skin breakdown (1 patient). None of the patients suffered radiation pneumonitis.

Predictive marker

The correlation between ER, PgR, and Ki67 expression at baseline and clinical response is shown in Fig. 4. These markers were not significantly associated with clinical response according to Spearman's correlation coefficient (data not shown).

In Table 2, the correlation between ER, PgR, and Ki67 expression at baseline and clinical and pathological response at 12 weeks and at the time of surgery is presented. Between clinical responders (complete response or partial response) and non-responders (stable disease or progressive disease) at 12 weeks, there was a significant difference in the PgR expression at baseline ($p = 0.0243$ by Fisher's exact test).

We analyzed the correlation between changes in the expression levels of ER, PgR and Ki67 and in clinical and pathological response to treatment. These results are shown in Table 3. Changes in the expression levels of these markers were not significantly associated with clinical or pathological response.

Moreover, we performed the univariate and multivariate analysis of ER, PgR, HER2, and Ki67 with respect to clinical and pathological responses to evaluate predictive factors (Table 4).

Table 2 Correlation between expression levels of ER, PgR, and Ki67 and clinical and pathological response at 12 weeks and at the time of surgery

	ER (%)	PgR (%)	Ki67 (%)
Clinical response			
CR or PR*	95	47***	18
SD or PD*	91	15***	28
CR or PR**	93	33	21
SD or PD**	95	0	40
Pathological response			
Grade 0 or 1a**	93	35	23
Grade 1b, 2 or 3**	93	27	23

ER estrogen receptor, *PgR* progesterone receptor, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

* At 12 weeks, ** at surgery, *** there is significant difference ($p = 0.0243$ by Fisher's exact test)

Table 3 The correlation between changes in the expression levels of ER, PgR and Ki67 and clinical and pathological response at the time of surgery

	ER (%)	PgR (%)	Ki67 (%)
Clinical response			
CR or PR	7	21	4
SD or PD	0	0	35
Pathological response			
Grade 0 or 1a	−2	32	2
Grade 1b, 2 or 3	13	12	9

ER estrogen receptor, *PgR* progesterone receptor, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Discussion

This prospective study of combined neoadjuvant endocrine therapy and RT demonstrated marked efficacy with limited toxicity. To our knowledge, this is the first prospective study of neoadjuvant AI and RT. The overall objective response rate of 92 % in this study is highly encouraging, particularly given the low toxicity of the regimen. As compared with previous studies of neoadjuvant endocrine therapy using AI [1–3] or neoadjuvant hormone (the majority was tamoxifen) and RT [8], the response rate in this study was higher. The combination of anastrozole and RT seems at least to be additive in terms of tumor shrinkage in a neoadjuvant setting. Preclinical data [13] demonstrated the radiosensitization effect of letrozole, one of the third AIs, which is similar to our results. Although

Table 4 Univariate and multivariate analysis with respect to clinical and pathological responses

	Univariate analyses				Multivariate analyses			
	Odds	95 % CI		*p* value	Odds	95 % CI		*p* value
Clinical response								
ER*	0.975	0.812	1.170	0.7849	24.291	0.000	–	0.9962
PgR*	3.898	$1.393e^{-88}$	$1.091e^{89}$	0.9896	0.647	$1.610e^{-126}$	$2.601e^{125}$	0.9976
Ki67*	0.908	0.804	1.027	0.1233	0.158	$1.112e^{-318}$	–	0.9960
HER2**	57045.248	$2.598e^{-309}$	–	0.9763	43.608	0.000	–	0.9998
ER***	0.957	0.822	1.113	0.5673	3.403	0.000	–	0.9978
PgR***	–	–	–	–	0.871	$1.723e^{-213}$	$4.402e^{212}$	0.9996
Ki67***	1.024	0.869	1.206	0.7768	3.343	0.000	–	0.9980
Pathological response								
ER*	1.000	0.928	1.078	>0.9999	0.851	0.569	1.274	0.4331
PgR*	0.994	0.972	1.016	0.5891	1.012	0.961	1.064	0.6593
Ki67*	1.003	0.947	1.063	0.9163	1.135	0.953	1.352	0.1567
HER2**	2.250	0.200	25.374	0.5118	723.911	0.000	–	0.9984
ER***	0.944	0.871	1.024	0.1648	0.724	0.507	1.034	0.0760
PgR***	0.996	0.961	1.032	0.8157	1.042	0.965	1.126	0.2933
Ki67***	0.981	0.926	1.039	0.5194	0.735	0.526	1.029	0.0726

ER estrogen receptor, *PgR* progesterone receptor, *CI* confidence interval

* At baseline, ** at baseline and 12 weeks, *** at 12 weeks

the clinical response in this study was high, the pathological response was low (grade 1a: 10 of 25 patients), which was consistent with the results for neoadjuvant hormone therapy. The reason for the discrepancy between clinical response and histopathological findings is unknown.

Toxicity during neoadjuvant therapy was acceptable, with no grade 3 toxicities. The results of this study suggest that anastrozole does not exacerbate radiation-induced acute adverse effects. These results are compatible with other reports of concurrent AI and RT in the adjuvant setting [14, 15]. On the other hand, concurrent RT and chemotherapy in a neoadjuvant therapy will increase skin-related toxicity and lead to a delay in surgery [16, 17]. These reports regarding neoadjuvant chemoradiation consisted of twice weekly paclitaxel and concurrent RT. In both studies, grade 3 skin desquamation occurred.

A major concern on the use of neoadjuvant RT is the development of postoperative complications. In this study 2 of the 25 (8 %) patients had grade 3 toxicity. This complication rate seems relatively higher than that of conventional neoadjuvant treatment. One retrospective study of concurrent endocrine therapy and RT [8] reported that none of the patients had either a wound infection or a voluminous hematoma after tumorectomy. In contrast, studies of neoadjuvant chemoradiotherapy reported several postoperative toxicities. Formenti et al. [16] reported their results of a phase II study of neoadjuvant chemoradiation that consisted of paclitaxel at 30 mg/m^2 delivered intravenously for 1 h twice weekly for a total of 8–10 weeks and concurrent RT (45 Gy at 1.8 Gy/fraction). Modified radical mastectomy was performed at least 2 weeks after the completion of chemoradiation or on recovery from skin toxicity. Postmastectomy complications occurred in 6 (14 %) of 44 patients. These complications included four infections with delayed wound healing, one transverse rectus abdominis myocutaneous flap necrosis that required revision, and one mastitis with grade 3 dermal injury. In another report of neoadjuvant chemoradiation by Chakravarthy et al. [17], of the three patients who underwent transverse rectus abdominis myocutaneous flap reconstruction, two required revisions.

To date, there is limited information regarding the optimal timing of surgery after neoadjuvant RT. However, surgery just after RT seems to be too early in terms of maximizing the radiation effect. In a retrospective study of neoadjuvant hormone administration (the majority was tamoxifen) and RT [8], the median time between the end of RT and surgery was 8 weeks.

There are no reports describing how endocrine therapy and concurrent RT affect biological markers such as ER, PgR, HER2, and Ki67 expression in breast cancer tissue. In this study, these markers were not significantly associated with clinical or pathological response. Further research to predict the response for endocrine therapy and concurrent RT is warranted.

Our study is limited by the small sample size with shorter follow-up. Especially the target sample size ($n = 30$) could not be achieved, and therefore our results

are not confirmed data. In addition, we assessed clinical response by caliper and ultrasound. Using computed tomography or magnetic resonance imaging could improve the accuracy of tumor measurement. Moreover, four patients with HER2-positive tumors were included in this study. Anti-HER2 therapy plus chemotherapy is the standard neoadjuvant treatment for breast cancer patients with HER2-positive tumors worldwide, although patients with HER2-positive tumors were included in other published studies [1–3]. Finally, for clinical node-positive patients at presentation, we performed ipsilateral supraclavicular RT. This procedure may be overtreatment, although there is no consensus on supraclavicular RT for patients who received neoadjuvant therapy.

In conclusion, despite relatively high adverse events and low efficacy in terms of histological response, our preliminary data suggest that neoadjuvant anastrozole and RT have potential for a highly clinical response in postmenopausal women with ER-positive tumors. Further investigations to assess long-term outcomes with this approach are needed.

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ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast Cancer Subtype and Distant Recurrence after Ipsilateral Breast Tumor Recurrence

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ABSTRACT

Background. There is little information about the impact of breast cancer subtype on prognosis after ipsilateral breast tumor recurrence (IBTR).

Methods. One hundred eighty-five patients were classified according to breast cancer subtype, as approximated by estrogen receptor, human epidermal growth factor receptor 2 (HER2), and Ki-67, of IBTR, and we evaluated whether breast cancer subtype was associated with distant recurrence after IBTR.

Results. There was a significant difference in distant disease-free survival (DDFS) after IBTR according to breast cancer subtype defined by a cutoff of the Ki-67 index of 20 % ($p = 0.0074$, log-rank test). The 5-year DDFS rates for patients with luminal A, luminal B, triple-negative, and HER2 types were 86.3, 57.1, 56.6, and 65.9 %, respectively. In addition, breast cancer subtype was significantly associated with distant recurrence after IBTR on adjustment for various clinicopathologic factors ($p = 0.0027$, Cox proportional hazards model).

Conclusions. Our study suggests that breast cancer subtype based on immunohistochemical staining predicts the outcomes of patients with IBTR. Further analyses are needed (UMIN-CTR number UMIN000008136).

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Breast-conserving treatment is the standard treatment for early breast cancer, with similar long-term overall survival to mastectomy.[1,2] Recently, the Early Breast Cancer Trialists' Collaborative Group reported that about 25 % of all first recurrences after breast-conserving surgery and radiotherapy were IBTR (Web Figure 2a in Ref.[3]). IBTR after breast-conserving treatment is associated with an increased risk of distant disease and death.[4–7] However, patients who develop IBTR are a heterogeneous population. Indeed, only a subgroup of patients with IBTR develop systemic recurrence. Therefore, it is clinically useful to verify the risk stratification of patients after IBTR.

Recently, microarray analysis identified breast cancer subtypes with distinct gene expression profiles.[8,9] These subtypes have been shown to divide patients into groups with specific responsiveness to treatments and outcomes. These molecular subtypes can be approximated by immunohistochemical (IHC) staining patterns for estrogen receptor (ER), progesterone receptor, HER2, and Ki-67, providing a clinically useful

differentiation of outcomes.[10–12] More recently, several authors reported that breast cancer subtype was useful in estimating the risk of IBTR.[13–15] At present, however, there is little information about the impact of breast cancer subtype on prognosis after IBTR.

The objective of the current study is to identify the role of breast cancer subtype, as approximated by ER, HER2, and Ki-67, of IBTR in predicting distant recurrence in patients with IBTR.

PATIENTS AND METHODS

A total of 185 consecutive patients with histologically confirmed IBTR without distant metastases who underwent definitive surgery for IBTR between 1989 and 2008 were included in this analysis from eight institutions in Japan. This retrospective study was approved by each institutional review board.

Inclusion criteria were as follows: (1) patients who underwent breast-conserving and axillary surgery (sentinel lymph node biopsy only was allowed if these nodes had no metastases); (2) patients in whom IBTR was confirmed histologically; and (3) patients who underwent definitive surgery for IBTR until 2008.

Exclusion criteria were as follows: (1) synchronous (defined as occurring within 3 months) metastases (at diagnosis of IBTR, bone scan, chest X-ray, liver ultrasonography, or computed tomography scan was performed, and all patients had no evidence of distant metastasis); (2) bilateral breast cancer patients; (3) noninvasive tumor in IBTR specimen; (4) prior malignancy other than breast cancer; (5) patients with tumors located in the skin or muscle only without associated parenchymal disease and (6) patients who received neoadjuvant therapy at the initial treatment.

Questionnaire forms were sent to physicians who participated in this study in December 2011 to collect clinicopathologic patient data. The patient and recurrent disease factors analyzed were age at initial diagnosis and at IBTR, time interval from initial surgery to IBTR, IBTR histological subtype (invasive ductal carcinoma, invasive lobular carcinoma, and other), IBTR lymphovascular invasion status, IBTR estrogen receptor (ER) status, IBTR HER2 status, IBTR grade, and tumor location of IBTR relative to the primary lesion (same quadrant, different quadrant, and unknown). Treatment after IBTR was also examined, including extent of surgery (repeat lumpectomy and mastectomy), surgical margin status (negative and positive), radiotherapy after surgery, and systemic therapy (hormonal therapy, chemotherapy, and trastuzumab).

ER status was determined by immunohistochemistry, and tumors with 10 % or more positively stained tumor cells were classified as positive for ER. HER2 status was considered positive if immunohistochemistry was 3+ or fluorescence in situ hybridization (her-2/*neu* to chromosome 17 ratio) was >2.0. Both ER and HER2 statuses were evaluated by each institution. Proliferation activity was assessed by immunostaining with the Ki-67 antibody (Dako). The Ki-67 index was centrally evaluated by one pathologist (N.A.), from whom all patient data were masked. The proportion of proliferating cells was determined by counting at least 500 tumor cells.

Intrinsic breast cancer subtypes were modified by the criteria recently recommended by the St. Gallen panelists: triple-negative (ER and HER2 negative), HER2 (HER2 positive and ER negative), luminal A (ER positive, Ki-67 low, and HER2 negative), and luminal B (ER positive and Ki-67 high or HER2 positive or both).[16] In this study, three patterns of the cutoff value of the Ki-67 index were defined: (1) 14 % (as recommended by the St. Gallen panelists), (2) 20 % (the median value of prior studies by Nishimura et al.), and (3) 10 %.[17]

Distant disease-free survival (DDFS) was defined as the period from the date of surgery for IBTR to the date of appearance of distant metastases, and was calculated by the Kaplan–Meier method. The log-rank test was used to evaluate differences in DDFS among various patient subgroups. Multivariate analyses for DDFS were performed using the Cox proportional hazards model.

All statistical tests and p values were two-sided, and p values <0.05 were considered significant. All statistical analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC, USA).

RESULTS

A total of 185 patients were registered in this analysis. Patient characteristics are presented in Table 1. The median ages at initial surgery and IBTR were 45 (range 26–84) and 50 (range 29–88) years, respectively. The median time interval from initial surgery to IBTR was 3.8 years (range 0.1–17.1 years). The median follow-up period from surgery for IBTR was 4.5 years (range 0.1–13.2 years). The 5-year DDFS rate was 69.0 %. Among the 101 patients who received breast-conserving surgery for the IBTR, radiotherapy (RT) was omitted at the first diagnosis in 52 patients. Of 37 patients with IBTR who received RT after IBTR surgery, all 37 patients did not receive RT at the initial breast cancer diagnosis.

Various clinical and pathologic factors associated with DDFS are presented in Table 2. The time interval from initial surgery to IBTR, tumor location, lymphovascular invasion of the IBTR, adjuvant chemotherapy, and breast cancer subtype were significantly associated with DDFS by the log-rank test ($p = 0.0074$, defined by a cutoff of the

TABLE 1 Patient characteristics ($n = 185$)

Characteristic	No. of patients	(%)
Age at initial diagnosis (years)		
<40	48	25.9
≥40	137	74.1
Age at IBTR (years)		
<40	26	14.1
≥40	159	85.9
Time interval from initial surgery to IBTR (years)		
≤5	111	60.0
>5	74	40.0
Tumor location		
Same quadrant	106	57.3
Different quadrant	63	34.1
Unknown	16	8.6
Margin of initial surgery		
Negative	153	82.7
Positive	18	9.7
Unknown	14	7.6
Radiotherapy after initial surgery		
Yes	89	48.1
No	92	49.7
Unknown	4	2.2
Hormone therapy after initial surgery		
No	70	37.8
Yes	106	57.3
Unknown	9	4.9
Chemotherapy after initial surgery		
No	110	59.5
Yes	67	36.2
Unknown	8	4.3
Trastuzumab after initial surgery[a]		
No	11	91.7
Yes	1	8.3
Tumor size of IBTR (mm)		
≤20	137	74.1
>20	40	21.6
Unknown	8	4.3
Lymph nodal status of IBTR		
Negative	173	93.5
Positive	12	6.5
Lymphovascular invasion of IBTR		
No	84	45.4
Yes	78	42.2
Unknown	23	12.4
Histologic grade of IBTR		
1	40	21.6
2	45	24.3
3	66	35.7
Unknown	34	18.4
ER of IBTR		
Negative	78	42.2
Positive	107	57.8
HER2 of IBTR		
Negative	142	76.8
Positive	43	23.2
Breast cancer subtype (Ki-67 cutoff: 20 %)		
Luminal A	66	35.7
Luminal B	41	22.2
Triple negative	49	26.5
HER2	29	15.7
Surgery for IBTR		
Breast-conserving surgery	101	54.6
Mastectomy	84	45.4
Radiotherapy after IBTR surgery		
Yes	37	20.0
No	148	80.0
Hormone therapy after IBTR		
No	70	37.8
Yes	112	60.5
Unknown	3	1.6
Chemotherapy after IBTR		
No	131	70.8
Yes	50	27.0
Unknown	4	2.2
Trastuzumab after IBTR[a]		
No	33	76.7
Yes	10	23.3

[a] Including only patients with HER2-positive tumors

IBTR ipsilateral breast tumor recurrence, *ER* estrogen receptor

Ki-67 index of 20 %). The 5-year DDFS rates for patients with luminal A, luminal B, triple-negative, and HER2 types, defined by a cutoff of the Ki-67 index of 20 %, were 86.3, 57.1, 56.6, and 65.9 %, respectively (Fig. 1). When the cutoff of the Ki-67 index was 10 or 14 %, breast cancer subtype was also significantly associated with DDFS by the log-rank test ($p = 0.0336$ and 0.0201, respectively).

Multivariate analyses using the time interval from the initial surgery to IBTR, tumor location, lymphovascular invasion of the IBTR, adjuvant chemotherapy, and breast cancer subtype demonstrated that the breast cancer subtype using a 20 % Ki-67 index as a cutoff was an independent predictive factor of DDFS ($p = 0.0027$, Table 3).

Because HER2 and Ki-67 staining of initial tumors was not routinely recorded, we were unable to assess the impact of breast cancer subtype of initial tumors on prognosis. Of 185 patients, 168 patients had information about the ER

TABLE 2 Five-year distant disease-free survival rates according to various clinicopathologic factors

Characteristic	5-year DDFS (%)	*p* value
Age at initial diagnosis (years)		
<40	68.6	0.2211
≥40	69.1	
Age at IBTR (years)		
<40	69.4	0.3904
≥40	69.0	
Time interval from initial surgery to IBTR (years)		
≤5	61.1	0.0003
>5	80.3	
Tumor location		
Same quadrant	61.3	0.0411
Different quadrant	79.9	
Margin of initial surgery		
Negative	67.6	0.2668
Positive	71.4	
Radiotherapy after initial surgery		
Yes	66.3	0.0981
No	72.3	
Hormone therapy after initial surgery		
No	68.9	0.8803
Yes	66.8	
Chemotherapy after initial surgery		
No	72.4	0.1274
Yes	60.1	
Trastuzumab after initial surgery[a]		
No	63.8	0.0515
Yes	0	
Tumor size of IBTR (mm)		
≤20	71.1	0.0724
>20	56.1	
Lymph nodal status of IBTR		
Negative	70.2	0.3862
Positive	50.0	
Lymphovascular invasion of IBTR		
No	80.0	0.0035
Yes	59.8	
Breast cancer subtype (Ki-67 cutoff: 20 %)		
Luminal A	86.3	0.0074
Luminal B	59.1	
Triple negative	56.6	
HER2	65.9	
Surgery for IBTR		
Breast-conserving surgery	72.7	0.2728
Mastectomy	64.6	
Radiotherapy after IBTR surgery		
Yes	69.8	0.2134
No	68.8	
Hormone therapy after IBTR		
No	66.1	0.3586
Yes	71.1	
Chemotherapy after IBTR		
No	74.8	0.0132
Yes	54.5	
Trastuzumab after IBTR[a]		
No	68.6	0.6999
Yes	77.1	

[a] Including only patients with HER2-positive tumors

IBTR ipsilateral breast tumor recurrence

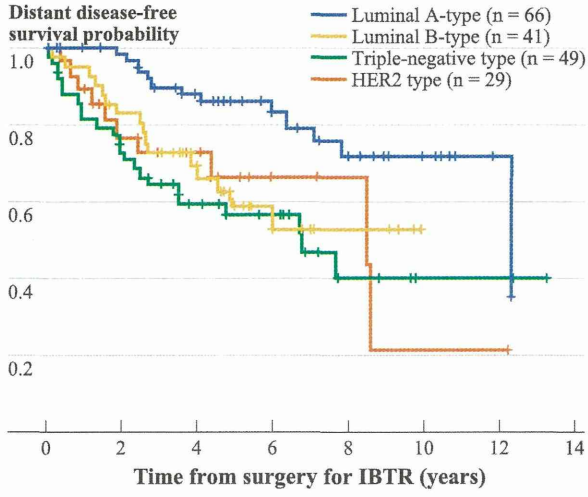

FIG. 1 Distant disease-free survival rates after ipsilateral breast tumor recurrence according to breast cancer subtype

TABLE 3 Multivariate analyses of predictors of distant recurrence after ipsilateral breast tumor recurrence

Characteristic	Hazard ratio	95 % CI	*p* value
Time interval from initial surgery to IBTR (>5 versus ≤5 years)	3.274	1.681–6.379	0.0005
Tumor location (different versus same quadrant)	2.515	1.298–4.874	0.0063
Lymphovascular invasion (no versus yes)	2.247	1.248–4.032	0.0069
Breast cancer subtype (luminal A versus other)	2.865	1.439–5.714	0.0027
Chemotherapy after IBTR (no versus yes)	1.248	0.690–2.257	0.4641

IBTR ipsilateral breast tumor recurrence, *CI* confidence interval

status of both initial and IBTR tumors. We performed statistical analyses to assess the impact of discordance in ER between initial and IBTR tumors on DDFS. The 5-year DDFS rates for patients with discordant ER status were significantly higher (82.1 %; $n = 38$) than those with concordant ER status (62.4 %; $n = 130$; $p = 0.0289$ by log-rank test). Among patients with concordant ER status, the 5-year DDFS rates for patients with ER-positive tumors ($n = 78$) and ER-negative tumors ($n = 52$) were 69.1 and 52.4 %, respectively. Among patients with discordant ER status, the 5-year DDFS rates for patients with ER-positive IBTR tumors ($n = 18$) and ER-negative IBTR tumors ($n = 20$) were 87.8 and 76.5 %, respectively.

DISCUSSION

Although breast cancer subtype based on gene expression or immunohistochemical evaluation can predict the risk of distant recurrences as well as IBTR, there is little information about the impact of breast cancer subtype on prognosis after IBTR.[8–15] To our knowledge, the current study is one of the largest to examine the role of breast cancer subtype in distant metastases of patients after IBTR.

Most studies regarding the risk of distant recurrences after IBTR focused on clinical and pathological factors. Among these studies, the time interval from initial surgery to IBTR, type of recurrence (new primary versus true recurrence), and lymphovascular invasion of IBTR were strong predictors of distant metastases after IBTR, which is consistent with our results.[4,18–21] Furthermore, in our study, breast cancer subtype of IBTR was a predictive factor for distant metastases after IBTR, independent of tumor location, time interval from initial surgery to IBTR, and lymphovascular invasion of the IBTR. In this study, we classified the recurrence type using the tumor location. The tumor location is the most commonly used parameter in new primary versus true recurrence differentiation. However, one of the problems regarding the type of recurrence is the current lack of a standard for classification of new primary versus true recurrence. To exclude confounding findings, we further performed statistical analyses excluding 63 patients with IBTR tumors in a different quadrant from the initial tumor. Multivariate analyses using the time interval from the initial surgery to IBTR, lymphovascular invasion of the IBTR, adjuvant chemotherapy, and breast cancer subtype demonstrated that breast cancer subtype using a 20 % Ki-67 index as a cutoff was an independent predictive factor of DDFS (hazard ratio, 2.500; 95 % confidence interval, 1.168–5.348; $p = 0.0182$).

There are a few reports regarding the prognostic significance of ER and HER2 after IBTR. These studies reported that patients with ER negativity, HER2 overexpression, or triple negativity in their IBTR tumors were associated with poor prognosis.[18,22,23] These results are consistent with ours. However, our analyses using breast cancer subtype defined by ER, HER2, and Ki-67 could predict patient outcomes more accurately than these studies.

As a method using molecular markers other than IHC, several authors reported that classifications by DNA clonality or the DNA breakpoint were useful for prognosis after IBTR.[24,25] However, DNA clonality or the DNA breakpoint seems impractical because of the time and expense required. In contrast, the expressions of ER, HER2, and Ki-67 are routinely assessed clinically to guide adjuvant therapy decisions.

Recently, a retrospective analysis from the European Institute of Oncology demonstrated that breast cancer subtype was associated with prognosis after locoregional recurrence following breast-conserving treatment.[26] However, in this report, the statistical analyses of local recurrence (i.e., IBTR) and regional recurrence were not separated. Because IBTR and regional recurrence have different natural histories and prognoses, it is not possible to make definitive conclusions regarding the impact of breast cancer subtype on prognosis after IBTR from this report.

In this study, patients with discordant ER status had significantly higher 5-year DDFS rates than those with concordant ER status. Interestingly, change to aggressive phenotype (i.e., patients with ER-positive primary tumors who had ER-negative IBTR tumors) was not associated with worse prognosis in this study. Further studies including HER2, Ki-67, and breast cancer subtype are warranted.

One of the limitations of our study is the inaccurate classification of breast cancer subtypes because of the lack of gene profiles. However, the low rate of distant recurrence among patients with luminal A-type IBTR tumors in this study is comparable to the low risk for both local and distant recurrence in luminal A-type primary tumors in other reports.

The second limitation is the relatively short follow-up period (median 4.5 years). It could not be ruled out that our finding that patients with luminal A-type IBTR tumors had better DDFS than those with other subtypes merely reflects the different timing of recurrence.[27,28] It is now well known that triple-negative and HER2-positive disease is most likely to recur within the first 3 years, whereas ER-positive disease may recur many years later.

The third limitation is the high frequency of missing data, especially for HER2 and Ki-67 of initial tumors. This limitation is consistent with a prior study regarding the impact of breast cancer subtype on prognosis after locoregional failure reported by Montagna et al..[26] They reported that, among 279 patients, 148 patients (53.0 %) with a missing value for breast cancer subtype were

observed at primary breast cancer or at locoregional recurrence.

Fourth, because central pathology review of ER and HER2 was not performed, it is possible that ER and HER2 status were misclassified in some patients. However, one of our strengths was central staining and review of Ki-67 index.

Small sample sizes were another limitation. However, despite the small numbers, to our knowledge, the current study represents one of the largest series in the literature to date.

In this study, 37 patients did not receive RT at the first diagnosis and then underwent repeat lumpectomy with RT at the time of their recurrence. These patients did not undergo what would be the standard of care. These patients were older than other patients in this study (data not shown), which is consistent with previous reports.[29,30]

Finally, the frequency of repeat lumpectomy for IBTR seemed to be high in this study (54.6 %) compared with that in other countries, for example, the Surveillance, Epidemiology, and End Results registry data during 1988 and 2004 (24 %).[31] However, the frequency in our study is similar to that reported by Gentilini et al. from Italy (51.3 %).[32]

At present, there is a lack of an ideal cutoff of the Ki-67 index.[33] Many cutoffs have been used, although staining levels of 10–20 % have been the most common.[34] In this study, we used three cutoffs (10, 14, and 20 %) for the Ki-67 index, which were used in previous studies of different patient cohorts.[16,17]

In conclusion, our study suggested that breast cancer subtype by IHC predicts outcomes of patients with IBTR. However, further research and validation studies are needed.

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