RESEARCH ARTICLE

Breast Cancer Recurrence According to Molecular Subtype

Hee Jin Shim[1], Sung Hun Kim[1]*, Bong Joo Kang[1], Byung Gil Choi[1], Hyeon Sook Kim[2], Eun Suk Cha[3], Byung Joo Song[4]

Abstract

Background: To evaluate the location of tumor relapse and imaging modality for detection according to the breast cancer subtype: luminal A, luminal B, HER2 positive luminal B, nonluminal HER2 positive, and triple negative. Materials and Methods: A total of 1244 patients with breast cancer with known estrogen receptor (ER), progesterone receptor (PR), Ki-67 and human epidermal growth factor receptor 2 (HER2), who underwent breast surgery from 2009 to 2012 were analyzed. Patients were classified into the following categories: luminal A (n=458), luminal B (n=241), HER2 positive luminal B (n=227), nonluminal HER2 positive (n=145) and triple negative (n=173). A total of 105 cases of relapse were detected in 102 patients: locoregional recurrence (n=46), recurrence in the contralateral breast (n=28) and distant metastasis (n=31). Comparison of proportions was used to determine the difference between subtypes. Results: Relapse rates by subtypes are as follows: luminal A 23 of 458 (5.02%), luminal B 19 of 241(7.88%), HER2 positive luminal B 15 of 227 (6.61%), nonluminal HER2 postive 19 of 145 (13.10%) and triple negative 29 of 173(16.76%). Luminal A tumors had the lowest rate of recurrence and had significantly lower recurrence rate in comparison with nonluminal HER2 postive (p=0.0017) and triple negative subtypes (p<0.0001). Compared with all other subtypes except nonluminal HER2 positive, triple negative tumors had the highest rate of tumor recurrence (p<0.01). Triple negatives were most likely to develop contralateral recurrence against all subtypes (p<0.05). Detection rate of locoregional and contralateral tumor recurrence were 28.3% on mammography (n=17/60). Conclusions: Luminal A tumors are associated with a low risk of recurrence while triple negative lesions have a high risk. In case of triple negative tumors, the contralateral breast has much more recurrence as compared with all other subtype. In terms of detection rates, breast USG was the best modality for detecting tumor recurrence, compared with other modalities (p<0.05). Subtyping of breast tumors using a molecular gene expression panel can identify patients who have increased risk of recurrence and allow prediction of locations of tumor recurrence for each subtype.

Keywords: Breast neoplasms - recurrence - triple negative breast neoplasms - receptors - estrogen - ultrasonography

Asian Pac J Cancer Prev, **15 (14)**, 5539-5544

Introduction

In recent management of breast cancer, several methods have been utilized, including variable surgical techniques, various regimens of chemotherapy, hormone therapy and radiation therapy for local and systemic therapy. Appropriate treatments for individual patients can improve their prognosis. Additionally, improved prognosis can be achieved with the early detection of tumor recurrence (Houssami et al., 2009). A better understanding of the risk of tumor recurrence would be of benefit to therapeutic decision-making and to conducting appropriate follow-ups.

As is already well known, to acknowledge the risk and pattern of tumor recurrence, the molecular subtype is important to the oncologist and to the surgeon when determining treatment options (Goldhirsch et al., 2011; Lowery et al., 2012). Understanding the relationship between molecular subtypes and tumor recurrence is also important to the radiologist. During routine postoperative follow-up, more attention should be paid to detecting tumor recurrence in patients with more aggressive subtypes of breast cancer, such as the triple negative subtype.

Currently, cancer biology is important in predicting disease progression. Gene expression profiling can facilitate the understanding that breast cancer is not one entity but rather consists of biologically distinct molecular subtypes with significant prognostic and differences (Sørlie et al., 2001; Kadivar et al., 2012). Breast cancer can be divided into multiple subgroups in various manners using the expression of various biomarkers. Goldhirsh et al. (2011) categorized breast cancer into 5 subtypes using the expression or amplification of estrogen receptor (ER),

*[1]Department of Radiology, [4]Department of Surgery, The Catholic University of Korea, Seoul St. Mary's Hospital, [2]Department of Radiology, The Catholic University of Korea, St. Paul Hospital, [3]Department of Radiology, Mokdong Hospital, Ewha Woman's University, School of Medicine, Seoul, Korea *For correspondence: rad-ksh@catholic.ac.kr*

progesterone receptor (PR), human epidermal growth factor receptor type 2 (HER2) and Ki-67: luminal A (ER- and/or PR-positive/HER2-negative/low Ki-67), luminal B (ER- and/or PR-positive/HER2-negative/high Ki-67), HER2-positive luminal B (ER- and/or PR-positive/HER2 overexpression/any Ki-67), non-luminal HER2-positive (ER and PR absent/HER2 overexpression), and triple negative (ER and PR absent/HER2-negative). Each of these subtypes shows different responses to systemic therapy and different clinical outcomes (Spitale et al., 2009).

Although most studies of molecular subtypes in breast cancer have reported differences in morbidity and survival, only a few studies have found differences in the rate and location of tumor recurrence. The effects of the molecular subtype of breast cancer on locoregional recurrence, contralateral breast recurrence and distant metastasis have not been identified to date. In this study, we planned to assess the influence of breast cancer subtype on the rate of tumor recurrence in patients with newly diagnosed breast cancer. We also approved a plan to establish a relationship between these molecular subtypes and the location of tumor recurrence, classified into 3 parts: locoregional recurrence, contralateral breast recurrence and distant metastasis.

Materials and Methods

Patient population

This retrospective, single-institution study was approved by the institutional review board. This study included 1295 female patients diagnosed with breast cancer who underwent breast surgery at our institution between 2008 and 2012. Patients who did not undergo surgery for advanced breast cancer (n=13) or who underwent breast surgery at an outside hospital (n=8) were excluded. Patients with metastatic disease at presentation were also excluded even if they underwent surgery (n=13). After surgery, patients tumor samples were sent to a laboratory for gene expression profiling, using DNA microarray. The majority of these cases had immunochemistry data available for ER, PR, HER2 and Ki-67. After excluding patients who did not have any DNA microarray results (n=17), 1266 breast cancers in 1244 patients constituted our study population (patients with bilateral breast cancer, n=22). In the patients with synchronous breast cancer, the larger or more invasive mass of the bilateral masses was regarded as the primary cancer.

The diagnosis of tumor recurrence was undertaken with histologically confirmed lesions, which were obtained by ultrasound-guided core needle biopsy or surgical excision. These procedures were performed in patients, revealing abnormal findings on postoperative follow-up mammography, breast USG, breast MRI and PET-CT. In disqualifying patients who had not undergone biopsy or excision for histological confirmation despite a suspicion of recurrence on imaging studies (n=6), 105 recurrent breast cancers in 102 patients were excluded.

The recurrent tumors were divided into three types by relapse location: locoregional recurrence, recurrence in the contralateral breast and distant metastasis. A locoregional recurrence was defined as follows: *i*) ipsilateral chest wall recurrence in women who underwent mastectomy; *ii*) ipsilateral in-breast recurrence in patients achieving breast conservation; and *iii*) ipsilateral regional lymph node (axillary, supraclavicular or infraclavicular, internal mammary) recurrence. The definition of recurrence in the contralateral breast was the same as that for locoregional recurrence, except it occurred in the contralateral breast. Distant metastasis was defined as spread from the breast to distant organs. In the case of synchronous bilateral cancer, the location of recurrence depended upon that of the main tumor. We set the tumor with the higher cancer stage or larger size as the main mass between bilateral masses.

Definition of breast cancer molecular subtype

The molecular subtypes of breast cancer were based on gene expression profiles, using DNA microarray analysis. As previously noted, immunohistochemistry (IHC) for ER, PR, HER2 and Ki-67 was performed by comparing DNA microarray results. Different IHC markers were used as surrogates for the molecular classification of breast cancer. A consensus on the most appropriate classification of breast cancer is currently lacking. In this study, we used a modified definition that creates five subtypes. Goldhirsch et al. (2011) developed a classification based on ER/PR and HER2 expression, coupled with amplification of the Ki-67 labeling index (Goldhirsch et al., 2011). The five subtypes are as follows: luminal A (ER- and/or PR-positive/HER2 negative/low Ki-67), luminal B (ER- and/or PR-positive/HER2-negative/high Ki-67), HER2-positive luminal B (ER- and/or PR-positive/HER2 overexpression/any Ki-67), non-luminal HER2-positive (ER and PR absent/HER2 overexpression) and triple negative (ER and PR absent/HER2-negative). The cutoff value for Ki-67 is 14% (Table 1).

Definition of diagnostic modality of tumor recurrence

The diagnosis of tumor recurrence was undertaken by detecting abnormalities on mammography, ultrasound, breast MRI, PET and other imaging modalities. If an abnormality was detected on mammography, it was classified as a "mammography-detected recurrence". In cases of detection of an abnormality on ultrasound, MRI or PET-CT, the recurrences were categorized as "ultrasound-detected recurrence", "MRI-detected recurrence" or "PET detected recurrence", respectively. If tumor recurrence was diagnosed on other image modalities, it was classified as "remainder-detected recurrence". In patients with distant metastasis, no tumor recurrence was detected on mammography or breast ultrasound because recurrent tumors were located outside of the breast. After excluding the patients (n=31) who had distant metastasis, 74 recurrent cancers in 72 patients were included.

Statistical analysis

Differences in clinicopathologic features among patients assigned to the five breast cancer molecular subtypes were examined using the x^2 test. The clinicopathologic features included age at diagnosis, tumor size, lymph node status, cancer stage, and method

of local treatment. The recurrence rate of each molecular subtype was measured using comparison of proportions. Analysis of recurrence rate was conducted separately for patients with locoregional recurrence, contralateral recurrence and distant metastasis. The statistical analyses were performed using statistical software (MedCalc, version 12, Mariakerke, Belgium). An error in probability of $p<0.05$ was considered significantly significant.

Results

The majority of the patients had luminal A tumors (36.8%, 458 of 1244), followed by luminal B (19.4%, 241 of 1244), HER2-positive luminal B (18.2%, 227 of 1244), triple negative (13.9%, 173 of 1244), and non-luminal HER2-positive (11.7%, 145 of 1244) tumors. The clinicopathologic features, which are listed in Table 2, indicated significant differences in age, tumor size, lymph node status and cancer stage among the subtype cohorts. Regarding the type of local treatment, there were no differences among the subtypes.

Eight percent of the total cohort of patients had a relapse of their breast cancer. Among 105 recurrent tumors in 102 patients, 31 recurrent tumors emerged as distant metastases. Forty-six tumors were locoregional recurrences, and 28 recurrent tumors were located in the contralateral breast (Table 3). The total recurrence rate of triple negative tumors was the highest (16.7%, 29 of 173), followed by those of non-luminal HER2-positive tumors (13.1%, 19 of 145), luminal B tumors (7.9%, 19 of 241), and HER2-positive luminal B tumors (6.6%, 15 of 227). Only 5.0% of patients with luminal A tumors had a recurrence of cancer, showing a significant difference from the total recurrent rates of patients with non-luminal HER2-positive tumors (13.1%, 19 of 145; p=0.0017) and triple negative tumors (16.76%, 29 of 173, p<0.0001) (Table 4). In common with the overall recurrence rate, the proportion of locoregional recurrence in the patients with luminal A tumors was the lowest: 1.7% (8 of 458) of patients (Table 5). There was a statistically significant difference between this rate and the rate of locoregional recurrence in patients with non-luminal HER2-positive tumors (5.1%, 8 of 145; p=0.0304) This difference was also demonstrated between patients with luminal A tumors and those with triple negative tumors (8.1%, 14 of 173; p=0.0003). As previously noted, the total recurrence rate in the subgroup with triple negative tumors was the highest compared with the other subtypes, except for the non-luminal HER2-positive subgroups: there were statistically significant differences from the recurrence rates in the

Table 1. Surrogate Definitions of Intrinsic Subtype of Breast Cancer

Subtype	Clinico-pathologic definition	Notes
Luminal A	ER and/or PR positive	The cut-point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping (Cheang et al., 2009)
	HER2 negative	
	Ki-67 low (<14%)	
Luminal B	ER and/or PR positive	High Ki-67 is a marker of higher proliferation and poor prognosis in multiple gene assay (Wirapati et al., 2008)
	HER2 negative	
	Ki-67 high	
HER2-positive luminal B	ER and/or PR positive	
	HER2 over-expressed	
	Any Ki-67	
Non-luminal HER2 positive	HER2 over-expressed	
	ER and PR absent	
Triple negative	ER and PR absent	In our study, 'triple negative' mingled with 'basal like' because approximately 80% overlap between 'triple negative' and intrinsic 'basal-like' subtype. But actually 'triple negative' also includes some special histological types such as medullary and adenoid cystic carcinoma with low risks of distant recurrence.
	HER2 negative	

Table 2. Distribution of Clinical CharacteristicsAmong the Various Breast Cancer Subtype

		Luminal A (n=458)		Luminal B (n=241)		HER2 + luminal B		Non-luminal HER2+ (n=145)		Triple negative (n=173)		X^2P (n=227)
		No of patient	%	No of patient	%	No of patient	%	No of patient	%	No of patient	%	
Age	≤40	54	12	24	14	28	12	11	7	40	30	0.0001
	>40	404	88	204	86	199	88	134	93	133	70	
Tumor size	<2	298	65	124	52	110	48	62	43	78	45	0.0005
	2-5	134	29	107	44	97	43	55	38	85	49	
	>5	26	6	10	4	20	9	28	19	10	3	
Lymph node	Negative	367	80	182	76	144	63	94	65	128	74	0.0365
	Positive	91	10	59	24	83	37	51	35	45	26	
Tumor stage	*in situ*	85	19	16	7	42	19	27	19	7	4	0.0015
	I	208	45	96	40	75	34	43	30	68	39	
	IIA	97	21	73	30	59	26	31	21	65	38	
	IIB	26	5	38	16	30	13	16	11	15	9	
	IIIA	28	6	10	4	11	5	13	9	14	8	
	IIIB	12	3	6	2	10	5	15	10	4	2	
	IV	2	1	2	1	0	0	0	0	0	0	
Local treatment	BCS	341	75	172	71	161	71	88	61	132	76	0.1462
	Mastectomy	117	25	69	29	66	29	57	39	41	24	

luminal A (5.0%, 23 of 458; p<0.0001), luminal B (7.9%, 19 of 241; p=0.0086) and HER2-positive luminal B (6.6%, 15 of 227; p=0.0023) subgroups. The rate of locoregional recurrence in the patients with triple negative tumors was also the highest, compared with the rates in patients with luminal A (1.7%, 8 of 458; p=0.0003) and HER2-positive luminal B tumors (3.1%, 6 of 227; p=0.0247). Regarding recurrence in the contralateral breast, the triple negative subtype exhibited the greatest risk of recurrence (7.5%, 13 of 173) (Table 6). It showed statistically significant differences from the other subtypes: luminal A (1.5%, 7 of 458; p=0.0004), luminal B (1.7%, 4 of 241; p=0.0067), luminal B HER2-positive (0.4%, 1 of 227; p=0.0497) and non-luminal HER2-positive (2.1%, 3 of 145, p=0.0004). In the distant metastasis group, the non-luminal HER2 positive subtype was the strongest risk of recurrence (5.5%, 8 of 145) (Table 7). However, the rate of distant metastasis of the non-luminal HER2-positive subtype did not exhibit statistically significant differences from the other subtypes, except for the luminal A subtype (1.7%, 8 of 458; p=0.0304).

Table 3. Overall Rate of Locoreginal Recurrence, Contralateral Breast Recurrence and Distant Metastasis

Subtype	Locoregional recurrence (n=46)		Contralateral recurrence (n=28)		Distance metastasis (n=31)	
	No of event	%	No of event	%	No of event	%
Luminal A (n=23)	8	1.75	7	1.53	8	1.75
Luminal B (n=19)	10	4.15	4	1.66	5	2.07
HER2 positive luminal B (n=19)	6	2.64	1	0.44	8	0.35
Non-luminalHER2 positive (n=15)	8	5.52	3	2.07	8	5.52
Triple negative (n=29)	14	8.09	13	7.51	2	1.16

Table 4. Difference of Overall Recurrent Rate

Landmarksubtype Type, Recurrent rate	Compared subtype		Difference of recurrent rate	
	Type	Recurrent rate	Difference	p- value
Luminal A, 5.02%				
	Luminal B	7.88%	2.86%	0.1781
	HER2 + luminal B	6.61%	1.59%	0.4988
	Nonluminal HER2 +	13.10%	8.08%	0.0017*
	Triple negative	16.76%	11.74%	<0.0001*
Luminal B, 7.88%				
	Luminal A	5.02%	2.86%	0.1781
	HER2 + luminal B	6.61%	5.22%	0.1361
	Nonluminal HER2 +	13.10%	5.22%	0.1361
	Triple negative	16.76%	8.88%	0.0086
HER2+luminal B, 6.61%				
	Luminal A	5.02%	1.59%	0.4988
	Luminal B	7.88%	5.22%	0.1361
	Nonluminal HER2 +	13.10%	6.50%	0.0529
	Triple negative	16.76%	10.16%	0.0023
Nonluminal HER2 +, 13.10%				
	Luminal A	5.02%	8.08%	0.0017
	Luminal B	7.88%	5.22%	0.1361
	HER2 + luminal B	6.61%	6.50%	0.0529
	Triple negative	16.76%	3.66%	0.4528
Triple negative, 16.76%				
	Luminal A	5.02%	11.74%	<0.0001*
	Luminal B	7.88%	8.88%	0.0086*
	HER2 + luminal B	6.61%	10.16%	0.0023*
	Nonluminal HER2 +	13.10%	3.66%	0.4528

In locoregional and contralateral recurrences, the detection rates of tumor relapse were 28.3% on mammography (n=17/60), 87.3% on ultrasound (n=55/63), 100% on MRI (n=10/10) and 61.1% on PET-CT (n=22/36). The detection rate on ultrasound was the highest, with a statistically significant difference from the rate on mammography (p<0.0001) and PET-CT (p=0.0057). Only one recurrent tumor in a patient who underwent mastectomy was classified as "remainder-detected recurrence". It was located in the deep chest wall and was detected on chest CT.

Table 5. Difference of Locoregional Recurrence Rate

Landmarksubtype Type, Recurrent rate	Compared subtype		Difference of recurrent rate	
	Type	Recurrent rate	Difference	p- value
Luminal A, 1.75%				
	Luminal B	4.15%	2.40%	0.0979
	HER2 + luminal B	2.64%	0.90%	0.6224
	Nonluminal HER2 +	5.52%	3.77%	0.0304*
	Triple negative	8.90%	6.35%	0.0003*
Luminal B, 4.15%				
	Luminal A	1.75%	2.40%	0.0979
	HER2 + luminal B	2.64%	1.51%	0.5178
	Nonluminal HER2 +	5.52%	1.37%	0.711
	Triple negative	8.90%	3.94%	0.1366
HER2+luminal B, 2.64%				
	Luminal A	1.75%	0.90%	0.6224
	Luminal B	4.15%	1.51%	0.5178
	Nonluminal HER2 +	5.52%	2.88%	0.2535
	Triple negative	8.90%	5.45%	0.0247*
Nonluminal HER2+, 5.52%				
	Luminal A	1.75%	3.77%	0.0304*
	Luminal B	4.15%	1.37%	0.711
	HER2 + luminal B	2.64%	2.88%	0.2535
	Triple negative	8.90%	2.58%	0.4967
Triple negative, 8.90%				
	Luminal A	1.75%	6.35%	0.0003*
	Luminal B	4.15%	3.94%	0.1366
	HER2 + luminal B	2.64%	5.45%	0.0247*
	Nonluminal HER2 +	5.52%	2.58%	0.4967

Table 6. Differnce of Recurrence Rate in Contralateral Breast

Landmarksubtype Type, Recurrent rate	Compared subtype		Difference of recurrent rate	
	Type	Recurrent rate	Difference	p- value
Luminal A, 1.53%				
	Luminal B	1.66%	0.13%	0.8513
	HER2+luminal B	2.64%	1.09%	0.385
	Nonluminal HER2+	2.07%	0.54%	0.943
	Triple negative	7.51%	5.99%	0.0004*
Luminal B, 1.66%				
	Luminal A	1.53%	0.13%	0.8513
	HER2+luminal B	2.64%	1.22%	0.4059
	Nonluminal HER2+	2.07%	0.41%	0.9192
	Triple negative	7.51%	5.86%	0.0067*
HER2+luminal B, 2.64%				
	Luminal A	1.53%	0.13%	0.8513
	Luminal B	1.66%	1.22%	0.4059
	Nonluminal HER2+	2.07%	1.63%	0.3324
	Triple negative	7.51%	7.07%	0.0004*
Nonluminal HER2+, 2.07%				
	Luminal A	1.53%	0.13%	0.8513
	Luminal B	1.66%	0.41%	0.9192
	HER2+luminal B	2.64%	1.63%	0.3324
	Triple negative	7.51%	5.45%	0.0497*
Triple negative, 7.51%				
	Luminal A	1.53%	5.99%	0.0004*
	Luminal B	1.66%	5.86%	0.0067*
	HER2+luminal B	2.64%	7.07%	0.0004*
	Nonluminal HER2+	2.07%	5.45%	0.0497*

Table 7. Differnce of Rate of Distance Metastasis

Landmarksubtype Type, Recurrent rate	Compared subtype		Difference of recurrent rate	
	Type	Recurrent rate	Difference	p- value
Luminal A, 1.75%				
	Luminal B	7.88%	0.33%	0.9923
	HER2+luminal B	6.61%	1.40%	0.2437
	Nonluminal HER2+	13.10%	3.77%	0.0304*
	Triple negative	16.76%	0.59%	0.8627
Luminal B, 2.08%				
	Luminal A	5.02%	0.33%	0.9923
	HER2+luminal B	6.61%	1.72%	0.2058
	Nonluminal HER2+	13.10%	3.44%	0.1273
	Triple negative	16.76%	0.92%	0.7428
HER2 + luminal B, 3.52%				
	Luminal A	5.02%	1.40%	0.2437
	Luminal B	7.88%	1.72%	0.2058
	Nonluminal HER2+	13.10%	1.99%	0.5079
	Triple negative	16.76%	0.80%	0.7261
Nonluminal HER2+, 5.52%				
	Luminal A	5.02%	3.77%	0.0304*
	Luminal B	7.88%	3.44%	0.1273
	HER2+luminal B	6.61%	1.99%	0.5079
	Triple negative	16.76%	4.36%	0.0578
Triple negative, 1.16%				
	Luminal A	5.02%	0.59%	0.8627
	Luminal B	7.88%	0.92%	0.7428
	HER2+luminal B	6.61%	0.80%	0.7261
	Nonluminal HER2+	13.10%	4.36%	0.0578

Discussion

In this study of patients with breast cancer, we demonstrated that rates of locoregional recurrence depended on molecular subtype, as determined by immunohistochemistry for ER, PR, HER2 and Ki-67. We observed that patients with luminal A tumors had a lower risk of total tumor recurrence compared to patients with either non-luminal HER2-positive or triple negative tumors. The risk was the same as that for locoregional recurrence. We found that patients with triple negative tumors showed higher risks of total tumor recurrence and locoregional recurrence than patients with a tumor of the other subtypes, except for non-luminal HER2-positive. Patients with triple negative tumors also showed the highest risk of contralateral breast recurrence compared to the other subtypes. Regarding distant metastasis, we found no difference in relapse rate among the molecular subtypes, except for between the luminal A and non-luminal HER2 subtype.

To date, a few studies have attempted to find a relationship between breast cancer molecular subtype and the location of cancer recurrence. Voduc et al. (2010) examined a large cohort study of 2985 patients with breast cancer treated with BCS and mastectomy. They used a similar biomarker immunopanel to categorize six molecular subtypes. In patients treated with BCS, they found that HER2-enriched (called non-luminal HER2-positive in the present study) and basal-like (called triple negative in the present study) tumors were associated with an increased risk of locoregional recurrence in multivariate analysis. In patients treated with mastectomy, the authors observed that luminal A tumors had the lowest risk of locoregional recurrence compared to the other subtypes. The results of the present study are in contrast with the results of Haffty et al. (2006), who observed a greater incidence of local recurrence in a cohort of 482 patients treated with BCS. Local recurrence was not different between TNP and non-TNP breast cancers.

For patients with tumor recurrence in the contralateral breast, Bessonova et al. (2011) analyzed the risk associated with hormonal receptor and HER2 status in 1613 patients diagnosed with contralateral breast cancer after treatment of their first breast cancer. The authors found that hormone receptor–negative tumors were regarded as having a higher risk for contralateral second breast cancer. HER2 status did not seem to be a marker of risk for second breast cancer. Similarly, Malone et al. (2010) observed that patients with triple negative primary cancer seemed to have breast cancer of the same type in the contralateral breast. Patients with BRCA1 mutations had an increased risk of developing triple-negative breast cancers, as it was estimated that 20% of women with triple negative breast cancer were BRCA1 mutation carriers (Tun et al., 2011), and they also have a four-fold higher risk of developing contralateral breast cancer, compared to non-BRCA1 mutation carriers. These results were similar to the results of our study.

Haffty et al. (2006) examined a contemporary cohort of 482 patients treated with BCS. In contrast to the results of the present study, the study found that the triple negative subtype was an independent predictor of distant metastasis with statistical significance. García Fernández et al. (2012) observed in a large cohort study that luminal tumors had a significantly smaller chance of distant metastasis than nonluminal HER2-positive and triple negative tumors.

Routine breast ultrasound for the diagnosis of breast cancer recurrence and for screening is not recommended because of high false-positive rates, resulting in unnecessary biopsies and an increase in medical expenses (Gordon and Goldenberg, 1995). However, in this study, breast USG was the best modality for detecting tumor recurrence, compared with other modalities. This finding can be understood in line with the result that the higher breast density of Korean women results in decreased sensitivity of mammography and more useful findings with breast ultrasound. In recent years, the effectiveness of breast ultrasound was reported for the purpose of the diagnosis of breast cancer recurrence. Kim et al. (2010) observed that breast ultrasound was a useful method for the diagnosis of cancer recurrence in patients without clinical symptoms.

The significance of this study is that there have been only a handful of studies examining the associations between breast cancer molecular subtypes and the recurrence rates of subdivided locations: locoregional recurrence, contralateral breast cancer and distant metastasis. In this study, luminal A tumors were associated with low risks of overall recurrence, locoregional recurrence and contralateral recurrence. This result is concordant with repeated observations that luminal A tumors exhibit the best prognosis (van 't Veer et al., 2002; Voduc et al., 2010; Najafi et al., 2013). Triple negative tumors were associated with high risks of overall recurrence, locoregional recurrence and contralateral recurrence. Particularly for contralateral breast recurrence, the higher recurrence rate for triple negative tumors was

statistically significant compared with the rates for other types of recurrence. This result is in agreement with recent observations that triple negative tumors are aggressive. (Malone et al., 2010; Tun et al., 2011). Another notable finding of this study, despite these recent studies with analogous conclusions, is that this study is one of only a few studies to find that triple negative tumors can strongly predict contralateral breast recurrence. In their latest study, Malone et al. (Malone et al., 2010) found that the HR-negative group was associated with a high risk of contralateral breast cancer. However, HER2 status did not seem to be a predictor for a second breast cancer. In the present study, the non-luminal HER2-positive group did not tend to show a marker for contralateral breast cancer, in contrast to the aforementioned study. In terms of distant metastasis, the results of the present study were not in agreement with those of the earlier study, which reported that the non-luminal HER2-positive and triple negative subtypes were associated with a high risk of recurrence, rather than the luminal subtypes (García Fernández et al., 2012). There were no statically significant differences between the non-luminal HER2-positive subtype and the other subtypes, except for the luminal A subtype, despite our having observed that the non-luminal HER2-positive subtype was associated with a higher rate of distant metastasis than the other subtypes. In contrast to earlier studies, we demonstrated that triple negative tumors had the lowest rate of distant metastasis, although there was no statically significant difference.

There are several limitations of our data that preclude drawing definitive conclusions. First, the data sets included in this analysis were all from observational or retrospective series. The second limitation is the differing local treatment (BCS or mastectomy) among the patients with each subtype and the influence that this difference had on recurrence. In addition, 'recurrence in the contralateral breast' and 'second primary contralateral breast cancer' were confounded in this study. If the histological type and molecular subtype of the contralateral breast cancer were the same as those of the primary cancer, we considered the contralateral cancer to be tumor recurrence in the contralateral breast. The possibility of a second primary cancer was ruled out in this study. Another potential limitation was that the period of postoperative follow-up was too short, at only 4 years. Late recurrence was not considered.

In conclusion, we have demonstrated that immunochemical markers can identify patients with increased risks of locoregional recurrence, contralateral breast recurrence and distant metastasis. In this study, the luminal A subgroup was correlated with a low recurrence rate of overall recurrence and locoregional recurrence. The triple negative subtype was an independent risk factor for overall tumor recurrence, locoregional recurrence and contralateral recurrence. In distant metastasis, the patients with non-luminal HER2-positive subtype had a high recurrence rate, but there was statistical significance only between nonluminal HER2-positive subtypes and the luminal A subtype.

As noted above, it is important that not only oncologists and surgeons but also radiologists understand the risks and patterns of tumor recurrence according to molecular biology. In terms of radiology, additional prospective studies on this topic are warranted for clinical application.

References

Bessonova L, Taylor TH, Mehta RS, et al (2011). Risk of a second breast cancer associated with hormone-receptor and HER2/neu status of the first breast cancer. *Cancer Epidemiol Biomarkers Prev*, **20**, 389-96.

García Fernández A, Giménez N, Fraile M, et al (2012). Survival and clinicopathological characteristics of breast cancer patient according to different tumour subtypes as determined by hormone receptor and Her2 immunohistochemistry. a single institution survey spanning 1998 to 2010. *Breast*, **21**, 366-73.

Goldhirsch A, Wood WC, Coates AS, et al (2011). Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen international expert consensus on the primary therapy of early breast cancer 2011. *Ann Oncol*, **22**, 1736-47.

Gordon PB, Goldenberg SL (1995). Malignant breast masses detected only by ultrasound. A retrospective review. *Cancer*, **76**, 626-30.

Haffty BG, Yang Q, Reiss M, et al (2006). Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. *J Clin Oncol*, **24**, 5652-7.

Houssami N, Ciatto S, Martinelli F, et al (2009). Early detection of second breast cancers improves prognosis in breast cancer survivors. *Ann Oncol*, **20**, 1505-10.

Kadivar M, Mafi N, Joulaee A, et al (2012). Breast cancer molecular subtypes and associations with clinicopathological characteristics in Iranian women, 2002- 2011. *Asian Pac J Cancer Prev*, **13**, 1881-6.

Kim HJ, Kwak JY, Choi JW, et al (2010). Impact of US surveillance on detection of clinically occult locoregional recurrence after mastectomy for breast cancer. *Ann Surg Oncol*, **17**, 2670-6.

Lowery AJ, Kell MR, Glynn RW, et al (2012). Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. *Breast Cancer Res Treat*, **133**, 831-41.

Malone KE, Begg CB, Haile RW, et al (2010). Population-based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 or BRCA2. *J Clin Oncol*, **28**, 2404-10.

Najafi B, Anvari S, Roshan ZA (2013). Disease free survival among molecular subtypes of early stage breast cancer between 2001 and 2010 in Iran. *Asian Pac J Cancer Prev*, **14**, 5811-6.

Sørlie T, Perou CM, Tibshirani R, et al (2001). Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA*, **98**, 10869-74.

Spitale A, Mazzola P, Soldini D, et al (2009). Breast cancer classification according to immunohistochemical markers: clinicopathologic features and short-term survival analysis in a population-based study from the South of Switzerland. *Ann Oncol*, **20**, 628-35.

Tun NM, Villani GM, Ong K (2011). Risk of having BRCA mutations in women with triple-negative breast cancer: a systematic review and meta-analysis. *J Clin Oncol*, **29**, 160.

van 't Veer LJ, Dai H, van de Vijver MJ, et al (2002). Gene expression profiling predicts clinical outcome of breast cancer. *Nature*, **415**, 530-6.

Voduc KD, Cheang MC, Tyldesley S, et al (2010). Breast cancer subtypes and the risk of local and regional relapse. *J Clin Oncol*, **28**, 1684-91.