Imaging surveillance in breast cancer survivor: A correlation between cancer characteristics and detection modality

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Aims and objectives

The breast cancer is one of the most common cancer in women, and it remains the leading cause of female cancer death [1-4]. In Korea, the number of breast cancer survivors who need long-term surveillance has been increasing since not only with high-incidence of breast cancer which is estimated at 22.9 per 100,000 women per year (2nd most common), but also with the 2nd highest 5-year relative survival rate (91%) [5]. Although significant advances have been made in directed systemic therapy, locoregional relapses are unfortunately common in breast cancer and prognosis has been correlated with conventional clinicopathological parameters including cancer size, grade, lymph node involvement, and cancer subtype [6, 7]. Current recommendations for the surveillance of breast cancer recurrence involve routine follow-up history-taking, clinical breast examination, and annual mammography of breast tissues [1, 2]. There have been several studies on the characteristics of recurred breast cancers, and evaluating efficacy of imaging modality [8-10]. However, the investigations of cancer subtype and their correlation with detection method in recurred breast cancer are limited.

Understanding characteristics of initial and recurrent breast cancer in terms of molecular subtype and their detection method may improve surveillance of local recurrence and has the potential to huge inform decision-making regarding local control strategies for breast cancer.

In this study, we aimed to investigate the characteristics of initial and recurrent breast cancers and to analyze the correlation between cancer subtype and detection mode.
Methods and materials

Patient selection

Our institutional review board approved our study and waived informed consent as the study was performed retrospectively using routinely acquired images. Between 2003 and 2009, 6169 patients (mean age 48.4 ± 10.2 years, 22-89 years) with breast carcinoma were treated by either mastectomy or breast conservation therapy at our institution.

A retrospective review of our database revealed 140 cases of breast cancer recurrence in breasts, chest wall or axilla. All cases were pathologically confirmed by either core needle biopsy or surgery. Among 140 lesions, we excluded three patients who underwent re-excision of breast cancer within 6 months of an operation, which were considered to be synchronous cancers. To analyze the surrogate intrinsic subtype of breast cancer, we reviewed each cancer's immunohistochemistry (IHC) result and identified estrogen receptor, progesterone receptor and HER2 status. Fourteen cases were excluded due to lacking IHC data. Finally, we included 123 recurred breast cancers in 115 women (mean age 45.7 ± 10.6 years, 22-76 years) in our study population.

Imaging technique and interpretation

Our routine clinical practice of preoperative image evaluation for patients who were diagnosed to have breast cancer included digital mammography (MG), US, and breast magnetic resonance imaging (MRI). Our surveillance program after treatment of breast cancer, clinical exam with radiologic examination including MG and US were performed at intervals of 12 months. Screening breast MRI was performed when available, but not in all cases. Before breast US examination, MG examinations were obtained using dedicated digital mammography units (Senographe 2000D units [GE Healthcare, Milwaukee, WI] or LORAD Selenia units [Hologic, Inc., Boston, MA]) and were interpreted by the radiologist who performed US. Breast US was done for bilateral whole breasts and axillary regions in radial and anti-radial planes and/or transverse and sagittal planes. All US examinations were performed by one of the five radiologists using high-resolution US equipment with a 14-16 MHz linear array transducer (HDI 5000 scanner [Advanced Technology Laboratories, Bothell, WA] or LOGIQ 700 scanner [GE Medical Systems, Milwaukee, WI]). We routinely scanned both breast and axilla. In patients who had undergone a mastectomy, sonographic evaluations of the chest wall, contralateral breast and both axilla were performed. After image acquisition, each radiologist recorded whether the patients had any symptom in their breast or axilla. They prospectively interpreted MG and US, and separately recorded findings on each imaging modality, and gave a final assessment according to BI-RADS [11]. In the cases of patients with multiple breast lesions, the lesion with the most serious finding was used for final assessment. Bilateral breast MR imaging examinations were performed with a 1.5-T system (Signa; GE Medical Systems, Milwaukee, WI).
After obtaining a bilateral transverse localizer image, fat-suppressed T2-weighted fast spin-echo sagittal images were obtained (repetition time [TR]/echo time [TE], 5500-7150/85.2; image matrix, 256 x 160; field of view, 200 x 200 mm; and section thickness/gap, 1.5 mm/0 mm). A three-dimensional, T1-weighted fast spoiled gradient-echo sequence was also performed with bilateral sagittal imaging for one precontrast and five postcontrast dynamic series after 91, 180, 360, 449, and 598 seconds (TR/TE, 6.5/2.5; flip angle, 10°; image matrix, 256x160; field of view, 200 x 200 mm; and section thickness/gap, 1.5 mm/0 mm). The acquisition time of each postcontrast series was 76 seconds. In all patients, gadobutrol (Gadovist; Bayer Schering Pharma, Berlin, Germany) was injected into the antecubital vein using an automated injector (Spectris Solaris; Medrad Europe, Maastricht, Netherlands) at a dose of 0.1 mmol/kg and at a rate of 2 mL/sec, followed by a 20-mL saline flush.

Original and recurred cancer evaluation

Pre and post-operative MG, US and MRI were retrospectively evaluated by two radiologists with 6-11 years of experience in breast imaging in consensus along with clinical examination and pathologic findings. Reference standard was based on biopsy results. When the patient presented with specific symptom such as palpability or nipple discharge before imaging acquisition, and found the lesion in subsequent imaging modality, it was defined as symptom-detected. In asymptomatic patients, any lesion with abnormal findings on mammography was defined as mammography-detected whether or not it was also visible on US. The lesions that had negative finding on mammogram but were detected on US were defined as US-detected. The lesions that had negative finding on mammogram and US, but were detected on MRI were defined as MRI-detected.

For each BI-RADS category, the cancer rate (the number of cancer cases divided by the total number of cases) was calculated with 95% confidence intervals (CIs). Cancer detection rate per 1000 patients, biopsy rate and positive biopsy rate (how often biopsies done are cancer, PPV3) were calculated according to imaging modalities.

For all biopsied lesions, we recorded the pathology and for malignant cases, we also recorded clinical findings such as age at diagnosis of contralateral breast cancer, previous operation method, TNM staging of previous cancer, interval from first operation to diagnosis of contralateral breast cancer and detection modality of contralateral breast cancer, density at mammography and BI-RADS category and the pathologic findings such as histologic type, tumor size, histological grade, and nodal status.

We also obtained 2-year follow-up results of 1211 patients with reference standard in our study population.

Data Collection and Statistical Analysis
We reviewed medical records including original and recurred cancer histology including cancer size, axillary nodal status, histologic grade, estrogen receptor (ER) expressional status, progesterone receptor expressional status, and Human Epidermal Growth factor receptor 2 (HER2) status. The location of recurred cancer, time interval between original cancer and recurrence, and the mode of detection and the cancer subtype at the original and recurrent cases. We grouped surrogate intrinsic subtypes as follows: Luminal (estrogen receptor (ER) positive and / or progesterone receptor (PR) positive, HER2 negative), HER2+ (HER2 over-expressed or amplified, ER and PR absent) and basal like (ER and PR absent, HER2 negative) based on St. Gallen international expert consensus [12]. Location of recurred cancer was classified as in-breast recurrence (ipsilateral/contralateral), chest wall recurrence and axillary lymph node recurrence. For statistical analysis, Chi-square tests and one way ANOVA were performed to evaluate whether clinicopathologic features (histology of recurred cancer, cancer subtype) and detection method, size, time interval to recurrence were associated with malignancy. A p-value less than 0.05 indicated statistical significance. All statistical analyses were performed with the use of SPSS version 21.0 software (SPSS, Chicago, IL).
Results

Patient ages at initial diagnosis ranged from 22-76 years (mean age 45.7 years), and recurrence cancer identified at mean age of 48.4 years (ranged from 29-79 years). Breast-conserving surgery was performed in 91 cases and mastectomy in 32 for primary cancer treatment.

The original pathology of these lesions included 109 invasive cancers and 14 DCIS. The average size of initial mass was 2.7cm (SD 1.8, 0.1 to 11cm). Regarding recurrence site, among the 123 recurred breast cancers, in-breast recurrence were 86. Twenty-one patients were presented with axillary LN recurrence and 16 cases were recurred in chest wall. The histopathology of in-breast and chest wall recurred mass were invasive carcinomas in 90 cases and ductal carcinomas in situ in 12 cases. The original cancer intrinsic subtypes were not exactly the same with the recur cancer intrinsic subtypes. The IHD based surrogate intrinsic subtypes of the original and recurred breast cancers are summarized at Table 1.

Regarding original 123 cases, 38 cases were presented as palpable mass, 31 cases were detected in MG and 32 cases were detected in US. The MRI detected 23 cases which were negative on MG and US. The intrinsic subtype of original cancers were luminal type in 57, HER2 positive in 26 and basal like type in 40. The age of initial diagnosis in each subtype was as follows: luminal type was 43.8 ± 8.9 years (range from 25 to 72 years), HER2 positive type was 48.6 ± 10.6 years (range from 22 to 63 years) and basal like type was 46.5 ± 12.3 years (range from 28 to 76 years). The recurrence free period of each subtypes was as follows: Luminal type was 38.9 ± 21.4 months, HER2 positive type 30.6 ± 20.4 months and for basal type, 34.8 ± 19.4 months. The mean lesion size of each subtypes were 2.7 ± 1.7cm for luminal type, 2.6 ± 2.5cm for HER2 type and 2.7 ± 1.4cm for basal type. The age, size and recurrence free survival was not significantly different between three original subtypes (p=0.078~0.559).

The recurrence detection method and original tumor subtypes are summarized in Figure 1. In 57 original breast cancers with luminal type, 47 luminal cancers recurred after mean interval of 38 months. Among them, 38.2% (18/47) were detected by ultrasonography (most common mode of detection) and 27.6% (13/47) were detected by mammography. In the remaining ten patient, there were eight HER2 positive, and two basal like type. In 26 HER2 positive type, nine cases were recurred as luminal type, 15 HER2 positive type and two basal like type. Within the 15 cases with HER2 positive recur cases, six cases were recurred as palpable mass and five cases were detected on mammography. In 40 basal like type cancers, six luminal type cancers were occurred, 3 HER2 positive types were recurred and 31 basal like type cancers were occurred. With the 31 basal like type cases, 15 cases were presented as papable mass and eight cases were detected on ultrasonography. The original subtype of mass and detection mode of recurred cancer was not statistically significant (p=0.117). However, the mode of detection was
significantly correlated with recurred cancer subtype (p=0.034). The recurrence detected mode and the recurred intrinsic subtypes are summarized in Figure 2. The most common detection method was US in luminal type recurred cancers [32.2% (20/62)]. In HER2 positive subtype, most common detection mode was mammography [38.5% (10/26)]. Whereas basal like type recurred cancers were almost presented as symptomatic mass [48.6% (17/35)].

With 86 cases of in-breast recurred cancers, both initial (p=0.019) and recurred (p=0.004) subtypes were correlated with detection method. Most common detection mode of basal type original cancer was symptom (11/27). Among the 45 recurred luminal cancers detected by ultrasonography in 17 cases and mammography in 15 cases. The most common detection method of recurred HER2 positive type cancers was mammography (9/20). In the 21 recurred basal like type cancers, most common presentation was symptom (12/21).
Table 1: The IHC based surrogate intrinsic subtype of the primary and recurrent breast cancer

<table>
<thead>
<tr>
<th>Primary cancer</th>
<th>Recurred cancer</th>
<th>Luminal (n=62)</th>
<th>HER2 (n=26)</th>
<th>TN (n=35)</th>
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<td>Luminal (n=57)</td>
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<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>HER2 (n=26)</td>
<td>9</td>
<td>15</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TN (n=40)</td>
<td>6</td>
<td>3</td>
<td>31</td>
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</table>

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**Fig. 1:** The mode of detection and the original intrinsic subtypes

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Fig. 2: The mode of detection and the recurred intrinsic subtypes

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Conclusion

The surveillance of breast cancer patient after primary treatment is vary among countries and institutions. In their recommendations for post-treatment surveillance of women treated for primary breast cancer, ASCO(American Society of Clinical Oncology), NCCN(National Comprehensive Cancer Network), ESMO(European Society of Medical Oncology) and NICE(National Institute for Health and Care Excellence) recommends mammography only [13-15]. The other imaging modalities including MRI and US are not routinely recommended. There is no known recent prospective study about each imaging modality yield of recurred breast cancer. In a systemic review of postoperative surveillance of breast cancer patients, ultrasonography showed higher sensitivity (94 -100%) in contralateral breast cancer and higher sensitivity (43-91%) with comparable specificity (31-95.1%) in ipsilateral breast cancer compared with those value of mammography. The MRI showed comparable sensitivity (75-100%) and specificity(666.6-93%) with acceptable accuracy (95%) [15]. In American College of Radiology Imaging Network(ACRIN) 6666 participants, 54% (1426/2659) of women had a personal history of breast cancer. They underwent 4010 screenings and 4.1% (59/1426) were diagnosed with cancer. Regardless of the mammography detected breast cancers, both supplemental ultrasound alone (35/4010) and MRI alone (3/275) detected additional cancers. The MRI was less likely to recall or biopsy unnecessarily in women with personal history of breast cancer than those without [8]. These studies suggest the potential role of supplemental screening imaging test in the breast cancer survivors. There was no established surveillance recommendation of breast cancer regarding the intrinsic subtype.

In our institution, patients routinely have annual breast mammography, ultrasonography and breast MRI after the primary treatment of early breast cancer. As a result, quiet many of recurred cancers detected via ultrasonography and MRI. The surrogate subtype of recurred breast cancers were not exactly the same with the original breast cancer. Most common location of the recurrence was in-breast (n=86) followed by axillary LN (n=21) and chest wall (n=16). The detection method of in-breast recurred cancer was statistically significant correlated between initial (p=0.019) and recurred (p=0.004) breast cancer. Both initial and recurred basal like subtype was presented with symptoms at the moment of recurrence. Regardless of recur site, the breast cancer subtype and the detection mode was correlated in recurred cancer only (p=0.034). Most of the luminal subtype (n=62) was detected by MG (n=16) and US (n=20). The HER2 subtype was detected via MG (n=10) and symptom (n=9). The basal like cancers were most frequently detected by symptom (n=17) (Table 3). This result is consistent with the previous reports. The basal like cancers were more detected with physician or patient clinically than other subtypes and less detected with radiographically [16].
Our results suggest that the basal-like subtype cancers less likely have benefit of imaging screening. In the luminal subtype, US detect more additional cancers than MG. While the HER2 subtype was least detected by US than other imaging modality.

There are several limitation of our study. First, it is retrospectively reviewed. Second, we selected IHC available patients, which may have selection bias.

In conclusion, the breast cancer subtypes were correlated with the mode of detection in screening program of breast cancer survivors. The mammography and ultrasonography surveillance in primary pathology with luminal type and HER2 type may be more beneficial than that with basal like cancers.
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