Original Article | Breast Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2024.1101
Korean J Radiol 2025;26(6):532-545

Korean Journal of Radiology
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Surveillance Outcomes by Imaging Methods in the First 5 Years After Breast Cancer Surgery

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Objective: To compare the outcomes of imaging methods (mammography alone, ultrasound [US] alone, mammography combined with US, and magnetic resonance imaging [MRI]-based examination) for surveillance during the first 5 years after breast cancer surgery.

Materials and Methods: This retrospective cohort study analyzed the medical records of patients who underwent breast cancer surgery at a single institution between January 2011 and December 2015. Imaging surveillance was performed at 6-month or 1-year intervals during the first 5 years.

Results: A total of 6371 women (median age, 49 years; age range, 20–90 years) underwent 28199 mammograms, 42759 US, and 2619 MRI examinations. Of 172 second breast cancer diagnoses, 19 (11.0%) were interval cancers. Mammography combined with US demonstrated higher cancer detection rate (CDR) compared to mammography alone (odds ratios [OR] = 3.31, 95% confidence interval [CI]: 1.52–8.96, $P = 0.009$) and US alone (OR = 2.80, 95% CI: 1.71–4.65, $P < 0.001$), whereas there was no statistical significance when compared with MRI-based examinations (OR = 0.89, 95% CI: 0.49–1.74, $P > 0.999$). A statistically significant interaction was observed between the mammographic breast density (MBD) and CDR of the imaging methods (P for interaction = 0.003).

Conclusion: The CDR of surveillance mammography combined with US was comparable with that of MRI-based examinations in an intensive surveillance setting. Considering the significant interaction between MBD and the CDR, a tailored approach for surveillance based on breast density is warranted.

Keywords: Personal history of breast cancer; Surveillance; Mammography; Ultrasound; Magnetic resonance imaging

INTRODUCTION

Breast cancer survivors face a risk of local/regional recurrence or new primary cancer in the contralateral breast. Recurrences and second breast cancers (SBC) are associated with an increased incidence of distant metastases and breast cancer mortality [1]. Post-treatment imaging surveillance aims to detect early recurrence of breast cancer, enabling early interventions that improve survival and preserve the quality of life [2]. To achieve this goal, most guidelines [3-5] recommend annual mammography in women with a personal history of breast cancer (PHBC).

However, mammography has lower sensitivity and is associated with higher interval cancer rates (ICR) in women with PHBC than in those without [6]. To increase the early detection of SBC [7-9] and reduce the number of biologically aggressive interval cancers diagnosed

Received: July 5, 2024 **Revised:** March 6, 2025
Accepted: March 7, 2025
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after annual screening with mammography alone [10], conducting mammography at semiannual intervals [11] or supplemental surveillance imaging with magnetic resonance imaging (MRI) [7,8,12] or breast ultrasound (US) has been attempted [7,8,13]. In patients with PHBC, optimal imaging modalities and intervals for effective surveillance have not been established [14,15]. Ideally, the effects of the imaging modality and surveillance interval on surveillance outcomes should be evaluated using constant sets of imaging methods and surveillance intervals in a prospective trial; however, this is not feasible in a retrospective study. Considering that imaging methods and surveillance intervals vary in clinical practice, reviewing large amounts of real-world data using various imaging combinations can provide valuable insights into optimal postoperative surveillance strategies. Previous studies on the surveillance outcomes of imaging modalities have included a limited number of patients with a specific imaging modality or combinations [12,16,17] or have separated the results according to imaging modality from multiple interpretation sessions with various combinations [8,18]. However, concurrent imaging modalities affect imaging interpretation, even if other imaging results are negative. Thus, we considered the combination of imaging modalities performed together as a "unit" and evaluated the real-world performance of imaging combinations. Our study focused on the first 5 years after surgery for the first breast cancer (FBC) because approximately 70% of in-breast recurrences occur within 5 years of treatment [19].

This study aimed to compare the overall and subgroup outcomes of actual imaging methods (mammography alone, US alone, mammography combined with US, and MRI-based examination) for surveillance during the first 5 years after FBC surgery.

MATERIALS AND METHODS

Participants

This retrospective study was approved by the Institutional Review Board of the Samsung Medical Center (IRB No. 2022-07-025), which waived the requirement for informed consent.

We reviewed the surgery database and identified 7447 consecutive women who underwent breast cancer surgery for ductal carcinoma in situ (DCIS) or American Joint Committee on Cancer 8th edition [20] stage I–III invasive cancer between January 2011 and December 2015. The exclusion criteria were as follows: 1) distant metastasis at the FBC diagnosis (n = 42), 2) loss of two or more consecutive follow-up imaging (n = 249), 3) preexisting malignancy in another organ (n = 51), 4) bilateral synchronous breast cancer at diagnosis (n = 278), and 5) breast cancer surgery owing to recurrent breast cancer (n = 456). Finally, we included 6371 women (median age, 49 years; range, 20–90 years) (Fig. 1).

Imaging Surveillance

For women with PHBC, semi-annual surveillance imaging examinations are partially covered by the Korea National Health Insurance Service for up to 5 years after cancer surgery, with patients responsible for only 5% of the costs covered by insurance. According to this national guideline, our tertiary referral hospital offers annual two-dimensional mammography (Lorad Selenia, Hologic, Bedford, Mass, or Senographe 2000D, GE Healthcare, Milwaukee, WI, USA) and whole-breast US (Aixplorer, SuperSonic Imagine, Aix-en-

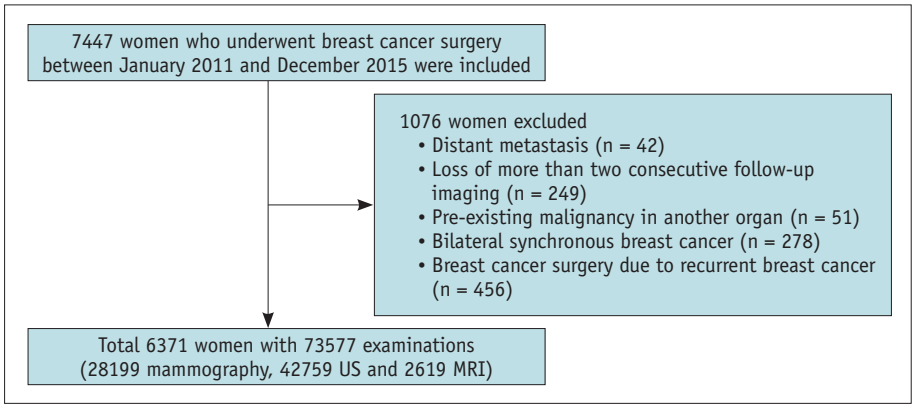

Fig. 1. Flowchart of the study population. A total of 7447 women who underwent breast cancer surgery were included. After excluding 1076 women, the final cohort was 6371 women with 73577 examinations (28199 mammograms, 42759 US, and 2619 MRI). US = ultrasound, MRI = magnetic resonance imaging

 https://doi.org/10.3348/kjr.2024.1101

Provence, France, and iU22, Philips Medical Systems, Bothell, WA, USA) supplemented by in-between imaging surveillance with various imaging methods at 6-month intervals for the first 5 years and annually thereafter for patients with PHBC. MRI (1.5T or 3T Achieva, Philips Medical Systems, Best, the Netherlands) was usually recommended for surveillance of premenopausal women with dense breasts, age ≤50 years, known genetic mutations, or a family history of breast cancer. However, referring surgeons make decisions on surveillance intervals (annual or semiannual) and imaging methods, considering clinicopathological factors, and patient and surgeon preferences for imaging modalities.

In this study, whole-breast US examinations, including both axillae, were performed by radiologists with 3–30 years of experience. One of the 10 radiologists with at least 2 years of experience in breast imaging prospectively interpreted the mammography and MRI examinations according to the breast imaging reporting and data system (BI-RADS) final assessment category [21].

Data Collection

Data on age, menopausal status, *BRCA* mutation status, mammographic breast density (MBD), receipt of preoperative breast MRI, family history of breast cancer in a first-degree relative, clinicopathological characteristics of FBC and SBC, date of FBC surgery, date of in-breast recurrence, and last follow-up or death were collected from medical records. Two breast radiologists (M.K.K. and E.S.K.) retrospectively reviewed the radiological reports of the BI-RADS overall assessment prospectively assessed. Positive hormone receptor (HR) was defined as 1% or more of cells staining positive for estrogen or progesterone receptors in immunohistochemical assays. Human epidermal growth factor receptor type 2 (HER2) status was evaluated according to the American Society of Clinical Oncology and the College of American Pathologists guidelines [22].

Outcome Measures

SBC was defined as cancer in the ipsilateral breast following breast-conserving surgery or contralateral breast cancer [23]. The cancer detection rate (CDR), abnormal interpretation rate (AIR), sensitivity, specificity, positive predictive value (PPV) for recall (PPV_1), PPV for biopsy (PPV_3), and ICR were assessed according to BI-RADS [21]. Interval cancers were defined as breast cancers diagnosed after a negative screening but before the next scheduled screening round [24]. For the analysis of surveillance outcomes, a finding of BI-RADS category 0, 3, 4, or 5 was considered positive, whereas BI-RADS category 1 or 2 was considered negative. We evaluated the outcomes based on the imaging methods, given that the interpretations of same-day examinations may have influenced each other. In the case of mammography combined with US, mammography was always performed first, followed by US, with the US interpretation incorporating the findings from mammography. Additionally, the official interpretation of the mammography was reviewed by a separate radiologist who referenced the US findings. Other imaging combinations, as well as MRI-based examinations, were interpreted with reference to the concurrently performed examinations. To determine the combined assessment, we applied a hierarchical ranking of categories: 5 > 4 > (0) > 3 > 2 > 1 [25].

To measure the outcomes of imaging surveillance, we ended the follow-up period at the next surveillance examination at 6 months or 1 year for all outcome measures [26]. The imaging method conducted in the same round was counted as a single unit only if concurrent imaging was scheduled and not added. The outcomes were compared according to the imaging methods (mammography alone, US alone, mammography combined with US, and MRI-based examinations) overall and in subgroups defined by age, tumor subtype, histological type, MBD, and prior imaging method. Based on a previous study [18], imaging methods that included MRI were classified as MRI-based examinations.

Statistical Analysis

A Lasagna plot was used to show the postoperative surveillance examinations using imaging methods and intervals [27]. Continuous variables were summarized as medians and interquartile ranges (IQRs). The clinicopathological characteristics of the patients and FBCs were compared based on SBC status and surveillance MRI. The chi-square test or Fisher's exact test was used to compare categorical variables.

Surveillance outcomes were calculated according to imaging methods over 5 years using various measures, including CDR, AIR, sensitivity, specificity, PPV_1, PPV_3, and ICR, along with their 95% confidence intervals (CIs). We estimated CIs using the Wilson score method with continuity correction, which is suitable for small sample sizes or extreme proportions [28]. To evaluate surveillance outcomes across imaging methods, we constructed models incorporating covariates, such as surveillance round number, MBD, tumor

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subtype, age, histologic type, and prior and current imaging methods. Generalized estimating equations (GEE) with a correlation structure that minimizes the quasi-information criterion were used for repeated measures within each subject [29]. For small samples, a penalized GEE was applied with a Firth-type penalty term and Firth's penalized logistic regression for sensitivity outcomes [30,31]. Odds ratios (OR) with the corresponding 95% CIs are presented. The overall *P*-value for comparing outcomes among the imaging methods in the multivariable model was obtained using the Wald test or the likelihood ratio test. In addition, we examined the interaction effects by adding interaction terms between the outcome measures of the imaging methods and each covariate one by one to the multivariable model.

All statistical analyses were performed using R Statistical Software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria). Two-tailed *P*-values <0.05 were considered statistically significant.

RESULTS

Patient Demographics and Outcomes

FBC was diagnosed as an invasive cancer in 5638 (88.5%) and DCIS in 733 (11.5%) of the 6371 women, and 6302 (98.9%) underwent preoperative breast MRI for FBC. During the study period, 172 SBCs were detected in 172 women (2.7%). Table 1 shows the baseline demographics and FBC characteristics of the patients according to their SBC status, along with the characteristics of SBC. SBCs were significantly associated with age <50 years ($P = 0.008$), *BRCA* mutations ($P = 0.001$), dense breasts ($P = 0.004$), higher FBC tumor grade ($P < 0.001$), and HR-/HER2+ or HR-/HER2- FBC subtypes ($P < 0.001$). The incidence of SBC was significantly higher in the group that did not undergo MRI than in the group that did (Supplementary Table 1).

Characteristics of Second Breast Cancer According to Imaging Methods

The characteristics of the SBCs based on the detection imaging methods are summarized in Table 2. No significant differences were observed in the characteristics of FBC and SBCs based on the detection imaging method used. Although not statistically significant, the invasive tumor size detected using MRI-based examinations was the smallest. In addition, DCIS was most commonly identified using mammography alone, whereas the HR-/HER2+ breast cancer subtype was relatively well detected using both mammography alone and MRI-based examinations. Details of the SBCs detected in each screening round are provided in Supplementary Table 2.

Characteristics of Interval Breast Cancers

Of 172 SBCs, 19 (11.0%) were identified as interval cancers. Table 3 presents the detailed characteristics of interval cancer cases. Seventeen (89.5%) of the 19 patients with interval cancers were symptomatic. One of the remaining two interval cancers was detected by outside US, whereas the other was discovered on a PET-CT scan. All the interval cancers were invasive ductal carcinomas. Eight of 19 (42.1%) interval cancers were developed in HR-/HER2- subtype and 14 of 17 (82.4%) interval cancers were high-grade. The median time between the last examination and detection of interval cancers was 5 (IQR, 4–5) months. The median time between the first surgery and the SBC diagnosis was 37.2 (IQR, 19.9–49.0) months overall, and 31.0 (IQR, 16.5–36.3) months for interval cancers.

Details of Surveillance Imaging

A total of 6371 women underwent 28199 mammograms, 42759 US examinations, and 2619 MRI examinations during the first 5 years after breast cancer surgery. The following imaging methods were used: 4766 mammography alone, 19524 US alone, 22876 mammography combined with US, and 2619 MRI-based examinations. Most MRI-based examinations consisted of MRI-only (1949, 74.4%), whereas the remainder consisted of MRI combined with mammography (311, 11.9%), MRI combined with US (113, 4.3%), and MRI combined with both US and mammography (246, 9.4%).

During the study period, most women underwent multiple surveillance rounds, with a median of eight (IQR, 7–9) surveillance rounds per woman. The number of imaging methods performed at 6 months and 1 year were 39859 (80.1%) and 9926 (19.9%), respectively. The number of imaging methods and surveillance intervals used are summarized in Figure 2.

Surveillance Outcomes According to Imaging Methods and Effect of Clinical and Radiologic Variables

Supplementary Table 3 summarizes the overall surveillance outcomes according to imaging methods. Table 4 summarizes the effects of clinical and radiologic variables on surveillance outcomes in the multivariable analysis. The results of the detailed subgroup analyses are

 https://doi.org/10.3348/kjr.2024.1101

Table 1. Clinicopathological characteristics of the patients according to recurrence outcome

	All patients (n = 6371)	Women with a second breast cancer (n = 172)	Women without a second breast cancer (n = 6199)	*P*
Patient characteristics				
Age at first breast cancer diagnosis				0.008
<50 yrs	3459 (54.3)	111 (64.5)	3348 (54.0)	
≥50 yrs	2912 (45.7)	61 (35.5)	2851 (46.0)	
First-degree family history of breast cancer				0.456
No	5847 (91.8)	161 (93.6)	5686 (91.7)	
Yes	524 (8.2)	11 (6.4)	513 (8.3)	
Menopausal status				0.005
Premenopausal	3723 (58.4)	119 (69.2)	3604 (58.1)	
Postmenopausal	2648 (41.6)	53 (30.8)	2595 (41.9)	
BRCA mutation				0.001
Negative	6251 (98.1)	162 (94.2)	6089 (98.2)	
Positive	120 (1.9)	10 (5.8)	110 (1.8)	
Mammographic breast density				0.004
BI-RADS A or B	1586 (24.9)	26 (15.1)	1560 (25.2)	
BI-RADS C or D	4785 (75.1)	146 (84.9)	4639 (74.8)	
First breast cancer characteristics and treatment				
Stage				0.313
Ductal carcinoma in situ, stage 0	733 (11.5)	21 (12.2)	712 (11.5)	
Invasive cancer, stage I	2818 (44.2)	71 (41.3)	2747 (44.3)	
Invasive cancer, stage II	2031 (31.9)	51 (29.7)	1980 (31.9)	
Invasive cancer, stage III	789 (12.4)	29 (16.9)	760 (12.3)	
Histologic grade (n = 6304)*				<0.001
1	1845 (29.3)	29 (17.1)	1816 (29.6)	
2	2707 (42.9)	65 (38.2)	2642 (43.1)	
3	1752 (27.8)	76 (44.7)	1676 (27.3)	
Histologic type				0.926
Ductal	5789 (90.9)	157 (91.3)	5632 (90.9)	
Lobular	246 (3.9)	7 (4.1)	239 (3.9)	
Other	336 (5.3)	8 (4.7)	328 (5.3)	
Neoadjuvant chemotherapy				<0.001
No	5904 (92.7)	144 (83.7)	5760 (92.9)	
Yes	467 (7.3)	28 (16.3)	439 (7.1)	
Adjuvant chemotherapy				0.855
No	2840 (44.6)	75 (43.6)	2765 (44.6)	
Yes	3531 (55.4)	97 (56.4)	3434 (55.4)	
Adjuvant radiation therapy				0.464
No	1571 (24.7)	47 (27.3)	1524 (24.6)	
Yes	4800 (75.3)	125 (72.7)	4675 (75.4)	
Adjuvant endocrine therapy				<0.001
No	1429 (22.4)	78 (45.3)	1351 (21.8)	
Yes	4942 (77.6)	94 (54.7)	4848 (78.2)	
Type of surgery				0.004
Breast-conserving surgery	4415 (69.3)	137 (79.7)	4278 (69.0)	
Mastectomy	1956 (30.7)	35 (20.3)	1921 (31.0)	
Resection margin				0.430
Negative	6231 (97.8)	167 (97.1)	6064 (97.8)	
Positive	140 (2.2)	5 (2.9)	135 (2.2)	

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Table 1. Clinicopathological characteristics of the patients according to recurrence outcome (continued)

	All patients (n = 6371)	Women with a second breast cancer (n = 172)	Women without a second breast cancer (n = 6199)	*P*
Preoperative MRI				>0.999
No	69 (1.1)	1 (0.6)	68 (1.1)	
Yes	6302 (98.9)	171 (99.4)	6131 (98.9)	
Surveillance MRI				0.025
No	5151 (80.9)	151 (87.8)	5000 (80.7)	
Yes	1220 (19.1)	21 (12.2)	1199 (19.3)	
Tumor subtype (n = 6302)[†]				<0.001
HR+/HER2-	4147 (65.8)	80 (46.8)	4067 (66.3)	
HR+/HER2+	795 (12.6)	21 (12.3)	774 (12.6)	
HR-/HER2+	644 (10.2)	34 (19.9)	610 (9.9)	
HR-/HER2-	716 (11.4)	36 (21.1)	680 (11.1)	
Second breast cancer characteristics (n = 172)				
Invasive tumor size, mm		9.0 [5.0, 15.0]		
Stage				
Ductal carcinoma in situ		43 (25.0)		
Invasive cancer		129 (75.0)		
Histologic type				
Ductal		158 (91.9)		
Lobular		6 (3.5)		
Other		8 (4.7)		
Histologic grade (n = 157)[‡]				
1		26 (16.6)		
2		62 (39.5)		
3		69 (43.9)		
Tumor subtype (n = 163)[§]				
HR+/HER2-		72 (44.2)		
HR+/HER2+		16 (9.8)		
HR-/HER2+		35 (21.5)		
HR-/HER2-		40 (24.5)		

Unless otherwise specified, the data are presented as the number of patients with percentages in parentheses or median with interquartile range in brackets.
*Data were missing for 67 cancers, [†]Data were missing for 69 cancers, [‡]Data were missing for 15 cancers, [§]Data were missing for 9 cancers.
BI-RADS = breast imaging reporting and data system, MRI = magnetic resonance imaging, HR = hormone receptor, HER2 = human epidermal growth factor receptor type 2

presented in Supplementary Tables 4 and 5. Mammography combined with US demonstrated higher CDR compared to mammography alone (OR = 3.31, 95% CI: 1.52–8.96, *P* = 0.009) and US alone (OR = 2.80, 95% CI: 1.71–4.65, *P* < 0.001), whereas there was no statistical significance when compared with MRI-based examination (OR = 0.89, 95% CI: 0.49–1.74, *P* > 0.999) (Table 4). A significant decrease in the AIR and a significant increase in specificity were observed as the rounds progressed, whereas no significant changes were noted in the CDR. Based on the interaction *P*-value, the relative performance rankings among the imaging methods remained consistent across the surveillance rounds. A statistically significant interaction between the MBD and CDR in the imaging methods was observed (*P* for interaction = 0.003) (Table 4). In Supplementary Table 6, US alone in fatty breasts (OR = 0.07, 95% CI: 0.01–0.40, *P* = 0.002) and mammography alone in dense breasts (OR = 0.09, 95% CI: 0.01–0.49, *P* = 0.005) were significantly associated with decreased odds of CDR than mammography alone in fatty breasts. In contrast, US alone (OR = 60.16, 95% CI: 6.49–1114.77, *P* < 0.001), MRI-based examinations (OR = 20.23, 95% CI: 2.07–385.45, *P* = 0.008), and mammography combined with US (OR = 14.72, 95% CI: 2.50–154.36, *P* = 0.003) in dense breasts have increased odds of CDR than

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Table 2. Characteristics of second breast cancers based on detection imaging methods

	Total (n = 153)	MG alone (n = 5)	US alone (n = 33)	MRI-based (n = 12)[‖]	MG + US (n = 103)	*P*
Patient characteristics						
Age at diagnosis, yrs*	46.0 [40.0, 52.0]	51.0 [48.0, 55.0]	49.0 [43.0, 53.0]	42.0 [39.3, 49.5]	46.0 [39.0, 51.0]	0.138
First-degree family history of breast cancer						0.568
No	144 (94.1)	5 (100)	30 (90.9)	11 (91.7)	98 (95.1)	
Yes	9 (5.9)	0 (0.0)	3 (9.1)	1 (8.3)	5 (4.9)	
Menopausal status						0.139
Premenopausal	105 (68.6)	2 (40.0)	21 (63.6)	11 (91.7)	71 (68.9)	
Postmenopausal	48 (31.4)	3 (60.0)	12 (36.4)	1 (8.3)	32 (31.1)	
BRCA mutation						0.037
Negative	146 (95.4)	5 (100)	32 (97.0)	9 (75.0)	100 (97.1)	
Positive	7 (4.6)	0 (0)	1 (3.0)	3 (25.0)	3 (2.9)	
Mammographic density						0.001
BI-RADS A or B	22 (14.4)	4 (80.0)	1 (3.0)	1 (8.3)	16 (15.5)	
BI-RADS C or D	131 (85.6)	1 (20.0)	32 (97.0)	11 (91.7)	87 (84.5)	
First breast cancer characteristics						
Stage						0.587
Ductal carcinoma in situ, stage 0	20 (13.1)	0 (0)	4 (12.1)	1 (8.3)	15 (14.6)	
Invasive cancer, stage I	62 (40.5)	3 (60.0)	12 (36.4)	4 (33.3)	43 (41.7)	
Invasive cancer, stage II	46 (30.1)	1 (20.0)	11 (33.3)	2 (16.7)	32 (31.1)	
Invasive cancer, stage III	25 (16.3)	1 (20.0)	6 (18.2)	5 (41.7)	13 (12.6)	
Histologic type						0.998
Ductal	138 (90.2)	5 (100)	30 (90.9)	12 (100)	91 (88.4)	
Lobular	7 (4.6)	0 (0)	1 (3.0)	0 (0)	6 (5.8)	
Other	8 (5.2)	0 (0)	2 (6.1)	0 (0)	6 (5.8)	
Histologic grade (n = 151)[†]						0.295
1	26 (17.2)	1 (20.0)	9 (27.3)	3 (27.3)	13 (12.7)	
2	59 (39.1)	2 (40.0)	10 (30.3)	3 (27.3)	44 (43.1)	
3	66 (43.7)	2 (40.0)	14 (42.4)	5 (45.5)	45 (44.1)	
Molecular subtype (n = 152)[‡]						0.527
HR+/HER2-	73 (48.0)	2 (40.0)	18 (56.2)	5 (41.7)	48 (46.6)	
HR+/HER2+	20 (13.2)	2 (40.0)	2 (6.2)	3 (25.0)	13 (12.6)	
HR-/HER2+	31 (20.4)	1 (20.0)	6 (18.8)	2 (16.7)	22 (21.4)	
HR-/HER2-	28 (18.4)	0 (0)	6 (18.8)	2 (16.7)	20 (19.4)	
Second breast cancer characteristics						
Invasive tumor size, mm*	8.0 [4.0, 13.0]	16.0 [13.5, 18.5]	9.0 [6.5, 13.0]	4.0 [2.5, 7.5]	8.0 [4.0, 14.0]	0.184
Stage						0.077
Ductal carcinoma in situ	43 (28.1)	3 (60.0)	5 (15.2)	5 (41.7)	30 (29.1)	
Invasive cancer	110 (71.9)	2 (40.0)	28 (84.8)	7 (58.3)	73 (70.9)	
Histologic type						0.396
Ductal	139 (90.8)	5 (100)	28 (84.8)	12 (100)	94 (91.3)	
Lobular	6 (3.9)	0 (0)	3 (9.1)	0 (0)	3 (2.9)	
Other	8 (5.2)	0 (0)	2 (6.1)	0 (0)	6 (5.8)	
Histologic grade						0.984
1	16 (11.4)	0 (0)	3 (10.3)	2 (16.7)	11 (11.7)	
2	66 (47.1)	3 (60.0)	15 (51.7)	5 (41.7)	43 (45.7)	
3	58 (41.4)	2 (40.0)	11 (37.9)	5 (41.7)	40 (42.6)	

https://doi.org/10.3348/kjr.2024.1101

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Table 2. Characteristics of second breast cancers based on detection imaging methods (continued)

	Total (n = 153)	MG alone (n = 5)	US alone (n = 33)	MRI-based (n = 12)[‖]	MG + US (n = 103)	*P*
Nodal status						0.285
Negative	147 (96.1)	4 (80.0)	32 (97.0)	12 (100)	99 (96.1)	
Positive	6 (3.9)	1 (20.0)	1 (3.0)	0 (0)	4 (3.9)	
Molecular subtype (n = 145)[§]						0.157
HR+/HER2-	67 (46.2)	1 (20.0)	16 (50.0)	4 (33.3)	46 (47.9)	
HR+/HER2+	14 (9.7)	1 (20.0)	4 (12.5)	0 (0)	9 (9.4)	
HR-/HER2+	32 (22.1)	2 (40.0)	2 (6.2)	6 (50.0)	22 (22.9)	
HR-/HER2-	32 (20.9)	1 (20.0)	10 (31.2)	2 (16.7)	19 (19.8)	

Unless otherwise specified, the data are presented as the number of patients with percentages in parentheses.
*Data in brackets are interquartile ranges, [†]Data were missing for 2 cancers, [‡]Data were missing for 3 cancers, [§]Data were missing for 8 cancers, [‖]Secondary breast cancers detected through MRI-based examinations were distributed as follows: MRI-only (8 cases), MRI with mammography (2 cases), and MRI with mammography and US (2 cases).
MG = mammography, US = ultrasound, MRI = magnetic resonance imaging, BI-RADS = breast imaging reporting and data system, HR = hormone receptor, HER2 = human epidermal growth factor receptor type 2

mammography alone in fatty breasts. Although there was no significant interaction between the CDR of the previous and current imaging methods (*P* for interaction = 0.89), significant interactions in AIR and specificity were observed between the previous and current imaging methods (*Ps* < 0.001) (Table 4). The CDR of the imaging methods performed 6 months after the MRI-based examination was significantly lower than that after the mammography alone (OR = 0.23, 95% CI: 0.06–0.71, *P* = 0.01) (Table 4) and generally exhibited a decreasing trend across all methods compared with other conditions (1.7, 95% CI: 0.7–4.3, range: 0.0-2.6) (Supplementary Table 4).

DISCUSSION

Our study evaluated the outcomes of imaging methods for early postoperative surveillance of breast cancer recurrence in real-world clinical practice, both overall and in subgroups defined by age, tumor subtype, histological type, MBD, and prior imaging methods. The CDR of mammography combined with US and MRI-based examinations were higher than those of mammography alone or US alone, whereas AIR and specificity were significantly poorer than those of mammography alone or US alone. In addition, a significant relationship was found between MBD and the CDR of the imaging methods.

In a recent study by Ha et al. [16] in a cohort with semiannual surveillance, the CDR of the US and MRI groups did not differ significantly; however, the specificity of the MRI group was significantly lower than that of the US group. Considering that more than half of the US or MRI examinations in their study were interpreted with concurrent mammography, their results are consistent with our results. In contrast, in a prospective study conducted by Kuhl et al. [18], the performance of mammography combined with US was significantly lower than that of MRI. In our study, the comparable performance of mammography combined with US and MRI-based examinations may be attributed to the fact that Korean women tend to have relatively small dense breasts, making US examinations technically easier and potentially more accurate than in Western women. The CDRs in this study were relatively low compared to those of previous studies, reported as 10.8–17 per 1000 examinations in women with PHBC [12,32,33], this could be because almost all patients (98.9%) underwent preoperative MRI and intensive postoperative surveillance at 6-month intervals. Small tumors that could have presented as SBC if preoperative MRI had not been performed would have been resected during the first surgery. Additionally, the lower incidence of breast cancer in Asian women than that in other populations may have contributed to the relatively low CDR.

Most guidelines for postoperative surveillance recommend annual mammography in women with PHBC [3-5]. However, with emerging evidence suggesting that supplemental MRI is beneficial for women with dense breasts or PHBC, it is recommended that women diagnosed with breast cancer before the age of 50 years or those with PHBC and dense breasts should undergo annual supplemental breast MRI [34,35]. Our results suggest that women with dense breasts, aged <50 years, HR+/HER2- subtype, or ductal carcinoma could be recommended for surveillance by mammography with US or MRI-based examinations for

 https://doi.org/10.3348/kjr.2024.1101

Table 3. Clinicopathologic characteristics of interval breast cancers

Patient	First breast cancer characteristics						First surgery interval† (mo)	Interval breast cancer characteristics							
Age (y)*	Histology	Hormonal status (ER/PR/HER2)	Stage	Grade	Tumor size (cm)	Surgery type		Last examination interval‡ (mo)	Modality of last examinations	Symptom	Breast site	Histology	Grade	Invasive tumor size (cm)	Nodal status	Hormonal status (ER/PR/HER2)
37	IDC	+/+/+	I	High	1.5	BCS	39	3	MG + US	Yes	Ipsi	IDC	NA	3.0‡	–	–/–/+
33	IDC	–/–/–	III	High	7.0§	BCS	18	5	MG + US	No	Ipsi	IDC	High	2.2	–	–/–/–
52	IDC	–/–/+	I	Low	0.3	BCS	37	5	US	Yes	Ipsi	IDC	High	3.5‖	NA	–/–/+
51	IDC	–/–/–	II	High	2.1	BCS	28	5	MG + US	Yes	Ipsi	IDC	High	2.5	–	–/–/–
50	IDC	+/+/–	II	Intermediate	1.5	BCS	55	4	MG + US	Yes	Contra	IDC	High	1.4	–	+/+/+
32	IDC	+/+/–	III	Intermediate	8.5§	BCS	45	5	MG + US	Yes	Ipsi	IDC	Intermediate	2.5	–	+/+/–
52	IDC	–/–/+	I	Intermediate	0.15	BCS	51	5	US	Yes	Ipsi	IDC	High	1.9	–	–/–/+
58	IDC	–/–/+	III	Intermediate	4.3§	BCS	22	10	MG + US	Yes	Ipsi	IDC	NA	0.8‖	NA	NA
56	IDC	+/+/–	III	Intermediate	8.0§	BCS	34	3	MG	Yes	Ipsi	IDC	Intermediate	3.3	NA	+/–/–
64	IDC	+/+/–	II	High	1.6	BCS	33	4	US	Yes	Ipsi	IDC	Intermediate	1.0	–	+/–/–
29	IDC	+/+/–	II	Intermediate	2.2	BCS	30	2	US	No	Ipsi	IDC	High	0.8	–	+/+/–
42	IDC	–/–/–	I	High	1.4	BCS	40	7	US	Yes	Contra	IDC	High	1.9	–	+/+/–
33	IDC	–/–/–	II	Intermediate	1.9	BCS	16	5	US	Yes	Ipsi	IDC	High	2.5	–	–/–/–
61	IDC	–/–/–	I	High	1.7	BCS	24	3	US	Yes	Ipsi	IDC	High	5.6	–	–/–/–
44	IDC	–/–/–	I	High	0.8	BCS	33	4	MG + US	Yes	Contra	IDC	High	2.2	–	–/–/–
38	IDC	–/–/–	I	High	1.0	BCS	32	8	MRI + MG	Yes	Contra	IDC	High	0.7	–	–/–/–
27	IDC	–/–/–	I	NA	1.8	BCS	26	5	MG	Yes	Contra	IDC	High	1.4	–	–/–/–
41	DCIS	+/+/–	0	NA	1.7	TM	12	5	US	Yes	Contra	IDC	High	0.6	–	+/–/+
48	IDC	+/+/–	I	Low	0.4	TM	32	6	MG	Yes	Contra	IDC	High	2.5	–	–/–/–

*Age at original breast cancer diagnosis, †Interval between original breast cancer surgery and detection of second in-breast cancer, ‡Interval between screening examination and detection of second in-breast cancer, §Pretreatment imaging-based size, as the patient underwent neoadjuvant chemotherapy and achieved pathologic complete response, ‖Imaging-based size, as three patients did not undergo final surgery.

ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor type 2, IDC = invasive ductal carcinoma, BCS = breast-conserving surgery, MG = mammography, US = ultrasound, Ipsi = ipsilateral, NA = not available, MRI = magnetic resonance imaging, TM = total mastectomy

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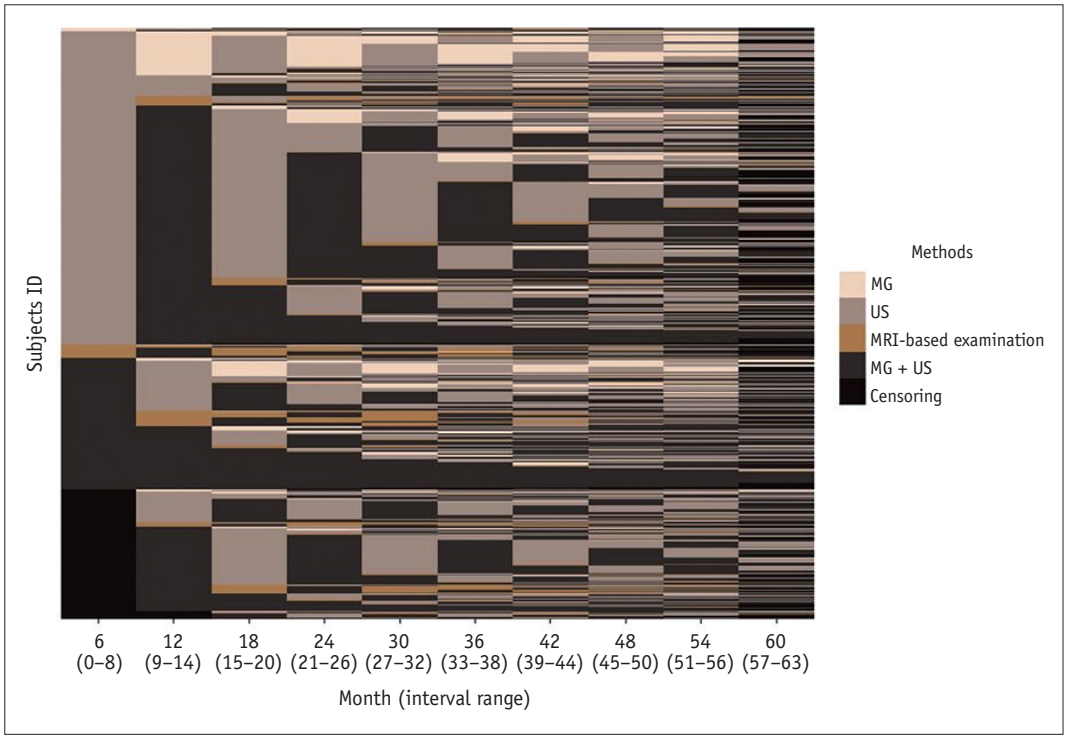

Fig. 2. Lasagna plot summarizing the number, imaging methods, and length of follow-up. The colors indicate imaging methods. The columns (x-axis) represent the 5-year follow-up period for each 6-month interval. The rows (y-axis) represent the women included in the analysis. The areas of black color indicate that the woman's follow-up time was censored owing to the absence of surveillance imaging. MG = mammography, US = ultrasound, MRI = magnetic resonance imaging

early SBC detection, considering the patients' clinical and economic situations. Furthermore, we confirmed that only MBD has a significant interaction with CDR among imaging methods. This underscores the importance of considering the MBD when selecting surveillance imaging modalities. For example, mammography alone may be sufficient for the surveillance of women with fatty breasts. However, in women with dense breasts, mammography alone may have limited effectiveness, necessitating the addition of US or MRI for a more accurate detection of recurrence.

There were no significant differences in the clinicopathological features of FBC and SBC between the imaging methods. Previous studies demonstrated that in US, HER2-negative cancers present more often as masses compared with HER2-positive cancers, which are more frequently non-mass lesions [36]. In contrast, HER2-positive cancers are frequently associated with pleomorphic microcalcifications and multifocality in mammography [37-39]. However, it is important to consider that the lack of statistical significance in our findings may be influenced by the extensive use of imaging surveillance in practice, which could potentially mask different detection patterns across imaging methods.

Our study showed that subsequent surveillance after MRI at 6-month intervals showed significantly decreased CDRs, which is consistent with the findings of prior research [16]. This decrease may result from the high sensitivity of MRI, resulting in fewer positive assessments during follow-up examinations. These findings suggest that if MRI is used, the surveillance interval could be extended, as most breast cancers are detected more than 24 months after negative MRI screening, which is consistent with previous research [23].

Our study has several strengths. First, we conducted an extensive statistical analysis of the overall and subgroup surveillance outcomes. Second, unlike previous studies, we used all imaging combinations performed simultaneously.

This study has several limitations. First, this was a retrospective study conducted at a single institution. Second, the performance of the imaging methods might have been overestimated in our semiannual intensive surveillance, given the shorter surveillance interval compared to the time it takes to present overt malignant imaging findings. Third, we used the MRI-based examination category based on a previous study that indicated no significant differences among imaging combinations that included MRI [18]. Consequently, it is difficult to determine

 https://doi.org/10.3348/kjr.2024.1101

Table 4. Summarized results for effects of clinical and radiologic variables on performance outcomes in multivariable analysis

Covariate/comparison	CDR			AIR			Specificity		
	OR (95% CI)	*P**	*P* for interaction†	OR (95% CI)	*P**	*P* for interaction†	OR (95% CI)	*P**	*P* for interaction†
No. of surveillance round	1.08 (0.95, 1.24)	0.243	0.580	0.73 (0.71, 0.76)	<0.001	0.312	1.41 (1.36, 1.46)	<0.001	0.282
Imaging methods‡ (reference: left examination)									
MG vs. US	1.18 (0.48, 3.48)	>0.999		0.79 (0.65, 0.97)	0.143		1.03 (0.82, 1.29)	>0.999	
MG vs. MRI	3.72 (1.37, 11.47)	0.058		2.14 (1.71, 2.68)	<0.001		0.39 (0.30, 0.50)	<0.001	
MG vs. MG + US	3.31 (1.52, 8.96)	0.009		2.22 (1.87, 2.65)	<0.001		0.39 (0.32, 0.48)	<0.001	
US vs. MRI	3.15 (1.54, 6.10)	0.014		2.71 (2.29, 3.19)	<0.001		0.38 (0.32, 0.45)	<0.001	
US vs. MG + US	2.80 (1.71, 4.65)	<0.001		2.81 (2.50, 3.16)	<0.001		0.38 (0.33, 0.43)	<0.001	
MRI vs. MG + US	0.89 (0.49, 1.74)	>0.999		1.04 (0.89, 1.22)	>0.999		1.00 (0.85, 1.18)	>0.999	
Mammographic breast density (reference: BI-RADS A or B)			0.003			0.136			0.765
BI-RADS C or D	1.47 (0.92, 2.42)	0.108		1.53 (1.37, 1.71)	<0.001		0.64 (0.57, 0.72)	<0.001	
Tumor subtype (reference: HR+/HER2-)			0.557			0.369			0.499
HR+/HER2+	1.32 (0.75, 2.20)	0.317		1.03 (0.91, 1.16)	0.656		0.99 (0.87, 1.13)	0.880	
HR-/HER2+	2.85 (1.77, 4.47)	<0.001		1.34 (1.18, 1.52)	<0.001		0.79 (0.69, 0.91)	0.001	
HR-/HER2-	2.15 (1.30, 3.43)	0.003		1.02 (0.89, 1.17)	0.746		1.05 (0.91, 1.22)	0.472	
Age (reference: <50 yrs) ≥50 yrs	0.69 (0.47, 1.00)	0.048	0.565	0.89 (0.81, 0.97)	0.010	0.258	1.10 (1.00, 1.20)	0.057	0.304
Histologic type (reference: ductal) Lobular	1.70 (0.73, 3.39)	0.196	0.940	0.82 (0.65, 1.03)	0.085	0.975	1.27 (1.01, 1.63)	0.044	0.939
Prior imaging methods (reference: MG alone)			0.890			<0.001			<0.001
US alone	0.60 (0.31, 1.24)	0.162		0.62 (0.52, 0.75)	<0.001		1.67 (1.37, 2.03)	<0.001	
MRI-based examination	0.23 (0.06, 0.71)	0.010		0.78 (0.62, 0.99)	0.040		1.21 (0.95, 1.54)	0.123	
MG+US	0.66 (0.36, 1.30)	0.217		0.98 (0.83, 1.17)	0.859		0.97 (0.81, 1.16)	0.759	

**P*-values obtained for the multivariable model including surveillance round number, imaging methods, mammographic breast density, tumor subtype, age, histologic type, and prior imaging methods, †*P*-values for interaction between imaging methods and each covariate in the multivariable model, ‡*P*-values obtained using Bonferroni correction in pairwise comparisons between imaging methods.
CDR = cancer detection rate, AIR = abnormal interpretation rate, OR = odds ratio, CI = confidence interval, MG = mammography, US = ultrasound, MRI = magnetic resonance imaging, BI-RADS = breast imaging reporting and data system, HR = hormone receptor, HER2 = human epidermal growth factor receptor type 2

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the exact performance of MRI. Fourth, the performance of mammography, US, and MRI can influence each other, preventing independent evaluation. To reflect real-world data, we analyzed actual imaging combinations, rather than isolating each modality. Finally, given the study's limitations regarding long-term survival data, cost-effectiveness analysis, and patient tolerability assessment, it may be challenging to directly apply our findings to clinical practice.

In conclusion, the outcomes of surveillance mammography combined with US are comparable to those of MRI-based examinations in an intensive surveillance setting. Considering the significant interaction between MBD and the CDR, a tailored approach for surveillance based on breast density is warranted.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2024.1101.

Availability of Data and Material

Data generated or analyzed during the study are available from the corresponding author by request.

Conflicts of Interest

Ji Soo Choi, a Section Editor of the *Korean Journal of Radiology*, was not involved in the editorial evaluation or decision to publish this article. The remaining authors have declared no conflicts of interest.

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Funding Statement

This work was supported by the National Research Foundation of Korea Grant funded by the Korean Government (NRF-2022M3J6A1084843 and RS-2024-00337752).

Acknowledgments

We would like to thank Seon-A Jeong, MS, for her assistance with the statistical analysis.

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