Clinical impact of follow-up imaging on mortality in Korean breast cancer patients: A national cohort study

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Abstract
Background: As the incidence of breast cancer has increased and the survival rate has improved, supporting the optimal follow-up strategy has become an important issue. This study aimed to evaluate follow-up imaging usage after breast cancer surgery and the implications on mortality in Korea.

Methods: This study included 96,575 breast cancer patients diagnosed during 2002–2010 and registered in the Korea Central Cancer Registry, Statistics Korea, and Korean National Health Insurance Service. We evaluated the frequency of breast imaging (mammography and breast MRI) and systemic imaging for evaluating the presence of distant metastasis (chest CT, bone scan, and PET-CT), and performed analyses to determine if they had an effect on mortality.

Results: The median follow-up period was 72.9 months (range: 12.0–133.3) and 7.5% of the patients died. Among all patients, 54.7%, 16.2%, 45.6%, and 8.5% received 3 or more mammograms, chest CTs, bone scans, and PET-CTs within 3 years after surgery, respectively. Among patients who developed recurrence after 3 or more years, a comparison of overall mortality and breast-cancer specific mortality according to the frequency of imaging by modality (<3 vs. ≥3) showed that only mammography had significantly reduced mortality (hazard ratio [HR]: 0.72, 95% CI: 0.61–0.84, p < 0.0001; HR: 0.72, 95% CI: 0.61–0.84; p < 0.0001).

Conclusions: This study showed that only frequent mammography reduced mortality and frequent imaging follow-up with other modalities did not when compared to less frequent imaging. This finding provides supportive evidence that clinicians need to adhere to the current guidelines for surveillance after breast cancer surgery.

Keywords
breast cancer, follow-up, image, surgery, surveillance, survivors
1 INTRODUCTION

As the incidence of breast cancer has increased and the survival rate has improved, determining the ideal follow-up strategy has become an important issue. Follow-up in breast cancer patients is aimed at the detection of recurrence, metastasis, or new primary cancers; evaluation of treatment-related long-term or late effects, adherence to the recommended therapy and screening; and psychosocial and decision-making support.

Current guidelines recommend regular follow-up with history taking, physical examination, and annual mammography to detect new primary cancers, recurrence, and treatment-related adverse effects. In contrast, they do not recommend regular systemic imaging such as chest computed tomography (CT), bone scan, and positron emission tomography (PET)-CT for the follow-up of asymptomatic breast cancer patients. These recommendations are based on results from prior studies which established that early diagnosis of distant metastasis provides no additional advantage for survival or health-related quality of life (QoL).

Despite these guidelines, the patient fear of recurrence and clinician inclination for early detection of disease recurrence result in frequent usage of systemic imaging. In a previous survey of medical and surgical breast oncologists conducted by the Korean Breast Cancer Society, 50% of respondents indicated that they perform follow-up chest CT more than once a year for the first 5 years and PET-CT more than once a year for the first 3 years.

This study aimed to evaluate the recent clinical usage of follow-up imaging by frequency and modality after curative treatment among Korean breast cancer patients and their implications on mortality. Towards this goal, we analyzed the combined data of the Korea Central Cancer Registry (KCCR), Statistics Korea, and Korean National Health Insurance Service (KNHIS) (Big Data-Based Guideline for Work-up and Interval after Surgery in Breast Cancer Patients: BIG-WISE Study).

2 METHODS

2.1 Study design and population

This BIG-WISE study was approved by the Institutional Review Board of the National Cancer Center, Korea (NCC 2016-0209), and the requirement for informed consent was waived because of the use of de-identified data. The subjects were Korean female breast cancer patients (with International Classification of Diseases, 10th revision [ICD-10] code) diagnosed between 2002 and 2010 and registered in the KCCR, Statistics Korea, and KNHIS.

Of the 96,575 breast cancer patients initially identified, we excluded 27,031 patients who were male (n = 480), did not undergo breast cancer surgery (n = 12,390), did not have 3 years of data on imaging in the KNHIS (n = 12,393), had distant metastasis at diagnosis (n = 949), or had less than 12 months of follow-up (n = 816) (Figure 1). Finally, 69,544 breast cancer patients were included in the analysis. Age at diagnosis was classified as <30, 30–39, 40–49, 50–59, 60–69, and ≥70 years. Comorbidities were evaluated using the Charlson Comorbidity Index (CCI) and categorized as 0, 1, and ≥2. Stage at diagnosis, the data on which became available in the KCCR starting in 2005, was classified as local, regional, and missing/unknown following the Surveillance, Epidemiology, and End Results staging system.
2.2 | Data sources

For this BIG-WISE study, we established a merged database from three national cohorts: KCCR, KNHIS, and Statistics Korea. KCCR is a population-based national cancer registry that includes information on more than 98% of patients with newly diagnosed cancer in Korea.14,15 The KNHIS is the single insurer of the Korean public health system, and tracks medical information including cancer treatment status (chemotherapy, radiotherapy, and endocrine therapy) and imaging studies.16 Mortality data were obtained from Statistics Korea.17

2.3 | Imaging modalities

As follow-up imaging modalities after surgery, breast imaging (mammography and breast MRI), systemic scans to assess the presence of distant metastasis (chest X-ray, chest CT, bone scan, and PET-CT) and treatment-related imaging (DEXA) were evaluated. We investigated the date at which each follow-up modality was performed and the number of studies performed for each modality.

To assess the effect of follow-up imaging on clinical outcomes, patients were divided into two groups according to the number of studies performed for each modality. A cutoff value of 3 was set based on annual check for 3 years. Univariate and multivariate analyses were performed comparing overall and breast cancer-related mortality between the divided groups for each imaging modality. An additional analysis was performed in patients with recurrence after 3 or more years to determine whether the frequent follow-up imaging during 3 years after curative treatment can improve clinical outcomes in recurrent patients.

2.4 | Assessment of recurrence and death

Mortality data were obtained from Statistics Korea with the date of the last follow-up as December 31, 2011.17 The cause of death was recorded and classified according to ICD-10 code.12 Because KCCR and KNHIS did not have the exact medical information on the date or site of recurrence, we defined recurrence as the presence of new breast cancer surgery, chemotherapy, or radiotherapy, or a change of hormonal therapy, excluding switching and extended therapy, after completion of curative treatments.

2.5 | Statistical analysis

Baseline characteristics and imaging modality after surgery were expressed as frequencies in percent. Between-group comparisons of patient characteristics at diagnosis and treatment status (adjuvant chemotherapy, adjuvant radiotherapy, adjuvant hormonal therapy) were performed using the chi-squared test or Fisher’s exact test, as appropriate. Cox proportional model was used to evaluate the association between patient survival and the frequency of imaging follow-up for each modality after surgery. Age at diagnosis, treatment status (chemotherapy, radiotherapy, adjuvant hormonal therapy), and CCI without cancer were adjusted for in the multivariable Cox proportional hazard model. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc.), and a p value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Baseline characteristics for 69,544 breast cancer patients are summarized in Table 1. The most common age at diagnosis was 40–49 years (28,383/69,544; 40.8%), followed by 50–59 years (17,358/69,544; 25.0%). In total, 36.8% (25,583/69,544) and 25.3% (17,617/69,544) of the patients had localized disease and regional metastasis, respectively, and 14.4% patients (10,032/69,544) had a CCI score of ≥3. Overall, 76.3% (53,035/69,544) underwent adjuvant chemotherapy; 61.1% (42,504/69,544), adjuvant radiotherapy; and 69.8% (48,511/69,544), adjuvant hormonal therapy.

The median follow-up period was 72.9 months (range: 12.0–133.3), and 11,676 patients (16.8%) experienced recurrence and 5241 (7.5%) died, 83.1% of whom died from breast cancer.

3.2 | Imaging follow-up

After completion of surgery, 93.1% (64,754/69,544) of survivors underwent mammography; 6.8% (4737/69,544), breast MRI; 94.5% (65,713/69,544), chest radiography; 71.3% (49,588/69,544), chest CT; 84.5% (58,746/69,544), bone scan; 67.1% (46,680/69,544), PET-CT; and 53.8% (37,389/69,544), DEXA. In total, 97.2% (67,587/69,544) underwent CT, bone scan, or PET at least once (Table 2). Within 3 years of breast cancer surgery, ≥1 and ≥3 mammography examinations were performed in 89.6% (62,288/69,544) and 54.7% (27,353/69,544), chest radiography; 71.3% (49,588/69,544), chest CT; 84.5% (58,746/69,544), bone scan; 67.1% (46,680/69,544), PET-CT; and 53.8% (37,389/69,544), DEXA. In total, 97.2% (67,587/69,544) underwent CT, bone scan, or PET at least once (Table 2). Within 3 years of breast cancer surgery, ≥1 and ≥3 mammography examinations were performed in 89.6% (62,288/69,544) and 54.7% (27,353/69,544), chest radiography; 71.3% (49,588/69,544), chest CT; 84.5% (58,746/69,544), bone scan; 67.1% (46,680/69,544), PET-CT; and 53.8% (37,389/69,544), DEXA. In total, 97.2% (67,587/69,544) underwent CT, bone scan, or PET at least once (Table 2). Within 3 years of breast cancer surgery, ≥1 and ≥3 mammography examinations were performed in 89.6% (62,288/69,544) and 54.7% (27,353/69,544), chest radiography; 71.3% (49,588/69,544), chest CT; 84.5% (58,746/69,544), bone scan; 67.1% (46,680/69,544), PET-CT; and 53.8% (37,389/69,544), DEXA. In total, 97.2% (67,587/69,544) underwent CT, bone scan, or PET at least once (Table 2). Within 3 years of breast cancer surgery, ≥1 and ≥3 mammography examinations were performed in 89.6% (62,288/69,544) and 54.7% (27,353/69,544), chest radiography; 71.3% (49,588/69,544), chest CT; 84.5% (58,746/69,544), bone scan; 67.1% (46,680/69,544), PET-CT; and 53.8% (37,389/69,544), DEXA. In total, 97.2% (67,587/69,544) underwent CT, bone scan, or PET at least once (Table 2). Within 3 years of breast cancer surgery, ≥1 and ≥3 mammography examinations were performed in 89.6% (62,288/69,544) and 54.7% (27,353/69,544), chest radiography; 71.3% (49,588/69,544), chest CT; 84.5% (58,746/69,544), bone scan; 67.1% (46,680/69,544), PET-CT; and 53.8% (37,389/69,544), DEXA. In total, 97.2% (67,587/69,544) underwent CT, bone scan, or PET at least once (Table 2). Within 3 years of breast cancer surgery, ≥1 and ≥3 mammography examinations were performed in 89.6% (62,288/69,544) and 54.7% (27,353/69,544), chest radiography; 71.3% (49,588/69,544), chest CT; 84.5% (58,746/69,544), bone scan; 67.1% (46,680/69,544), PET-CT; and 53.8% (37,389/69,544), DEXA. In total, 97.2% (67,587/69,544) underwent CT, bone scan, or PET at least once (Table 2). Within 3 years of breast cancer surgery, ≥1 and ≥3 mammography examinations were performed in 89.6% (62,288/69,544) and 54.7% (27,353/69,544), chest radiography; 71.3% (49,588/69,544), chest CT; 84.5% (58,746/69,544), bone scan; 67.1% (46,680/69,544), PET-CT; and 53.8% (37,389/69,544), DEXA. In total, 97.2% (67,587/69,544) underwent CT, bone scan, or PET at least once (Table 2). Within 3 years of breast cancer surgery, ≥1 and ≥3 mammography examinations were performed in 89.6% (62,288/69,544) and 54.7% (27,353/69,544), chest radiography; 71.3% (49,588/69,544), chest CT; 84.5% (58,746/69,544), bone scan; 67.1% (46,680/69,544), PET-CT; and 53.8% (37,389/69,544), DEXA. In total, 97.2% (67,587/69,544) underwent CT, bone scan, or PET at least once (Table 2).
Young women aged <30 years underwent less mammography (576/1157, 49.8%, \(p < 0.001\)) and more breast MRI (73/1157, 6.3%, \(p < 0.001\), Table 3). Old women aged ≥70 years had less imaging work-up (mammography: 37.6% (1170/3111), breast MRI: 1.3% (39/3111), chest radiography: 48.5% (1509/3111), chest CT: 11.0% (343/3111), bone scan: 27.5% (856/3111), and PET-CT: 5.9% (183/3111), Table 3). Patients with local disease underwent more mammography (14,987/25,583, 58.6%) and breast MRI (1281/25,583, 5.0%). Systemic imaging work-ups were performed in patients with regional disease, those who underwent chemotherapy, and those who underwent radiotherapy (Table 3). Patients who underwent adjuvant hormonal therapy underwent more bone scan (46.9% (22,729/48,511) vs. 42.7% (8990/21,033), \(p < 0.001\)) and less chest CT (15.6% (7589/48,511) vs. 17.5% (3685/21,033), \(p < 0.001\)) and PET-CT (7.9% (3826/48,511) vs. 10.0% (2101/21,033), \(p < 0.001\)).

### 3.3 | Survival according to pattern of imaging work-up

Our analysis of the association between imaging follow-up and clinical outcomes showed that the patients who underwent more systemic imaging follow-up had higher rates of recurrence, breast cancer-related mortality, and overall mortality (Table 4). To determine whether frequent imaging follow-up resulted in a lower mortality rate, we separately compared the HRs for breast cancer-related mortality and overall mortality according to the number of imaging studies performed for each modality (<3 vs. ≥3) within 3 years among patients who developed recurrence 3 years after surgery (Table 5). In univariate analyses, patients who underwent mammography ≥3 times showed a lower overall mortality rate (HR: 0.69, 95% CI: 0.59–0.81, \(p < 0.001\)) and breast cancer-related mortality rate (HR: 0.69, 95% CI: 0.58–0.81, \(p < 0.001\)) compared to those who underwent mammography <3 times. After adjusting for age at diagnosis, chemotherapy, radiotherapy, adjuvant hormonal therapy, and comorbidities, only frequent mammography significantly influenced overall mortality (HR: 0.72, 95% CI: 0.61–0.84, \(p < 0.001\)) and breast cancer-related mortality (HR: 0.72, 95% CI: 0.61–0.84, \(p < 0.001\)). After additionally adjusting for the stage at diagnosis, any breast imaging including mammography and systemic imaging did not influence survivals (Table 5).

### 4 | DISCUSSION

This study found that among the imaging modalities used for follow-up surveillance after curative surgery for breast cancer, only frequent mammography is associated with survival, and frequent use of other imaging modalities did not lower the rates of overall and breast cancer-related mortality, particularly in patients who developed recurrence after surgery. Further, the pattern of imaging follow-up differed by age, stage, and type of treatment.
TABLE 2  Follow-up frequency and modality after surgery by time period

|                           | Total | ≤6 months | 6–12 months | 12–24 months | 24–36 months | >36 months | ≤36 months |
|---------------------------|-------|-----------|-------------|--------------|--------------|------------|-----------|
|                           | N     | %         | N           | %            | N            | %          | N         |
| **Local work-up**         |       |           |             |              |              |            |           |
| Mammography               |       |           |             |              |              |            |           |
| No                        | 4790  | 6.9       | 53,995      | 77.6         | 30,735       | 44.2       | 14,666    | 22.4 |
| Yes All                   | 64,754| 93.1      | 15,549      | 22.4         | 38,809       | 55.8       | 50,760    | 77.6 |
| 1 or 2                    | 9309  | 13.4      | 15,498      | 22.3         | 38,491       | 55.4       | 49,019    | 71.8 |
| 3 or 4                    | 15,342| 22.0      | 51          | 0.1          | 302          | 0.4        | 2,001     | 2.9  |
| ≥5                        | 40,103| 57.7      | 0           | 0.0          | 16           | 0.0        | 73        | 0.1  |
| Breast MRI\(^a\)          |       |           |             |              |              |            |           |
| No                        | 64,807| 93.2      | 69,082      | 99.3         | 68,978       | 99.2       | 66,945    | 98.1 |
| Yes All                   | 4737  | 6.8       | 462         | 0.7          | 566          | 0.8        | 1257      | 1.8  |
| 1 or 2                    | 3138  | 4.5       | 455         | 0.7          | 546          | 0.8        | 1121      | 1.6  |
| 2                         | 828   | 1.2       | 7           | 0.0          | 19           | 0.0        | 125       | 0.2  |
| ≥3                        | 771   | 1.1       | 0           | 0.0          | 1            | 0.0        | 3         | 0.1  |
| **Systemic work-up**      |       |           |             |              |              |            |           |
| Chest radiography         |       |           |             |              |              |            |           |
| No                        | 3831  | 5.5       | 28,146      | 40.5         | 24,822       | 35.7       | 14,820    | 21.3 |
| Yes All                   | 65,713| 94.5      | 41,398      | 59.5         | 44,722       | 64.3       | 54,724    | 78.7 |
| 1 or 2                    | 6147  | 8.8       | 24,749      | 35.6         | 39,345       | 56.6       | 45,721    | 65.8 |
| 3 or 4                    | 7718  | 11.1      | 6905        | 9.9          | 4055         | 5.8        | 6332      | 9.1  |
| ≥5                        | 51,848| 74.6      | 9744        | 14.0         | 1322         | 1.9        | 2671      | 3.8  |
| Chest CT                  |       |           |             |              |              |            |           |
| No                        | 19,956| 28.7      | 40,746      | 58.6         | 53,316       | 76.7       | 51,977    | 74.7 |
| Yes All                   | 49,588| 71.3      | 28,798      | 41.4         | 16,228       | 23.3       | 17,567    | 25.3 |
| 1 or 2                    | 25,228| 36.3      | 28,132      | 40.5         | 15,605       | 22.4       | 16,597    | 22.4 |
| 3 or 4                    | 8,199 | 11.8      | 652         | 0.9          | 606          | 0.9        | 1,528     | 2.3  |
| ≥5                        | 16,161| 23.2      | 14          | 0.0          | 17           | 0.0        | 442       | 0.6  |
| Bone scan                 |       |           |             |              |              |            |           |
| No                        | 10,798| 15.5      | 53,335      | 76.7         | 36,224       | 52.1       | 23,116    | 33.2 |
| Yes All                   | 58,746| 84.5      | 16,209      | 23.3         | 33,320       | 47.9       | 46,428    | 66.8 |
| 1 or 2                    | 11,375| 16.4      | 16,174      | 23.2         | 33,246       | 47.8       | 44,618    | 64.2 |
| 3 or 4                    | 14,116| 20.3      | 35          | 0.1          | 74           | 0.1        | 1,770     | 2.5  |
| ≥5                        | 33,255| 47.8      | 0           | 0.0          | 0            | 0.0        | 89        | 0.1  |
|                          | Total | ≤6 months | 6–12 months | 12–24 months | 24–36 months | >36 months | ≤36 months |
|--------------------------|-------|-----------|-------------|--------------|--------------|------------|-----------|
|                          | N     | %         | N           | %            | N            | %          | N         |
| PET-CT<sup>b</sup>       | No    | 22,864    | 32.9        | 65,598       | 94.3         | 60,426     | 86.9      |
|                          | Yes   | All       | 46,680      | 67.1         | 3946         | 5.7        | 9118      |
|                          |       | 1 or 2    | 28,578      | 41.1         | 3809         | 5.5        | 9027      |
|                          |       | 3 or 4    | 13,076      | 18.8         | 129          | 0.2        | 87        |
|                          |       | ≥5        | 5026        | 7.2          | 8            | 0.0        | 38        |
|                          | DEXA  | No        | 21,155      | 46.2         | 65,725       | 94.5       | 61,705    |
|                          |       | All       | 37,389      | 53.8         | 3819         | 5.5        | 7839      |
|                          |       | 1         | 10,759      | 15.5         | 3747         | 5.4        | 7718      |
|                          |       | 2         | 8749        | 12.6         | 71           | 0.1        | 121       |
|                          |       | ≥3        | 17,861      | 25.7         | 1            | 0.0        | 0         |
|                          | PET-CT, CT, or bone scan | No | 1957 | 2.8 | 31,300 | 45.0 | 26,727 | 38.4 | 15,163 | 21.8 | 14,504 | 21.2 | 11,072 | 16.9 | 6765 | 9.7 |
|                          |       | All       | 67,587      | 97.2         | 38,244       | 55.0       | 42,817    |
|                          |       | 1 or 2    | 6802        | 9.8          | 33,243       | 47.8       | 36,183    |
|                          |       | 3 or 4    | 7473        | 10.7         | 4288         | 6.2        | 5672      |
|                          |       | ≥5        | 53,312      | 76.7         | 713          | 1.0        | 962       |

<sup>a</sup>Evaluated since 2005.

<sup>b</sup>Since 2006.
| Age at diagnosis (years) | Follow-up imaging | | Stage at diagnosis | | | | | | | | | | Adjuvant chemotherapy | | Adjuvant radiotherapy | | Adjuvant hormonal therapy |
|-------------------------|------------------|------------------|------------------|------------------|------------------|
| | Total | N | % | N | % | N | % | N | % | p-value | N | % | N | % | N | % | p-value |
| Follow-up imaging | 69,544 | 1157 | 100 | 10,905 | 100 | 28,383 | 100 | 17,358 | 100 | 8630 | 100 | 25,583 | 100 | 17,617 | 100 | 26,344 | 100 |
| Mammography | <3 | 31,518 | 581 | 50.2 | 4930 | 45.2 | 12,187 | 42.9 | 7705 | 44.4 | 4174 | 48.4 | 1941 | 62.4 | <0.0001 | 10,596 | 41.4 | 8089 | 45.9 | 12,833 | 48.7 | <0.0001 |
| | ≥3 | 38,026 | 576 | 49.8 | 5975 | 54.8 | 16,196 | 57.1 | 9653 | 55.6 | 4456 | 51.6 | 1170 | 37.6 | | 14,987 | 58.6 | 9528 | 54.1 | 13,511 | 51.3 | |
| Breast MRI | No | 67,267 | 1084 | 93.7 | 10,483 | 96.1 | 27,394 | 96.5 | 16,809 | 96.8 | 8425 | 97.6 | 3072 | 98.7 | <0.0001 | 24,302 | 95.0 | 16,899 | 95.9 | 26,066 | 98.9 | <0.0001 |
| | Yes | 2277 | 273 | 6.3 | 422 | 3.9 | 989 | 3.5 | 549 | 3.2 | 205 | 2.4 | 39 | 1.3 | | 1281 | 5.0 | 718 | 4.1 | 278 | 1.1 | |
| Chest radiography | <3 | 23,332 | 367 | 31.7 | 3365 | 30.9 | 9090 | 32.0 | 5698 | 32.8 | 3210 | 37.2 | 1602 | 51.5 | <0.0001 | 9683 | 37.8 | 5490 | 31.2 | 8159 | 31.0 | <0.0001 |
| | ≥3 | 46,212 | 790 | 68.3 | 7540 | 69.1 | 19,293 | 68.0 | 11,660 | 67.2 | 5420 | 62.8 | 1509 | 48.5 | | 15,900 | 62.2 | 12,127 | 68.8 | 18,185 | 69.0 | |
| Chest CT | <3 | 58,270 | 963 | 83.2 | 8964 | 82.2 | 23,856 | 84.1 | 14,488 | 83.5 | 7231 | 83.8 | 2768 | 89.0 | <0.0001 | 21,499 | 84.0 | 13,107 | 74.4 | 23,664 | 89.8 | <0.0001 |
| | ≥3 | 11,274 | 194 | 16.8 | 1941 | 17.8 | 4527 | 15.9 | 2870 | 16.5 | 1399 | 16.2 | 343 | 11.0 | | 4084 | 16.0 | 4510 | 25.6 | 2680 | 10.2 | |
| Bone scan | <3 | 37,825 | 636 | 55.0 | 5755 | 52.8 | 15,002 | 52.9 | 9317 | 53.7 | 4860 | 56.3 | 2255 | 72.5 | <0.0001 | 14,961 | 58.5 | 9248 | 52.5 | 13,616 | 51.7 | <0.0001 |
| | ≥3 | 31,719 | 521 | 45.0 | 5150 | 47.2 | 13,381 | 47.1 | 8041 | 46.3 | 3770 | 43.7 | 856 | 27.5 | | 10,622 | 41.5 | 8369 | 47.5 | 12,728 | 48.3 | |
| PET-CT | <3 | 63,617 | 1040 | 89.9 | 9918 | 90.9 | 26,067 | 91.8 | 15,756 | 90.8 | 7908 | 91.6 | 2928 | 94.1 | <0.0001 | 23,027 | 90.0 | 14,961 | 84.9 | 25,629 | 97.3 | <0.0001 |
| | ≥3 | 5927 | 117 | 10.1 | 987 | 9.1 | 2316 | 8.2 | 1602 | 9.2 | 722 | 8.4 | 256 | 8.5 | | 2556 | 10.0 | 2656 | 15.1 | 715 | 2.7 | |
| DEXA | Yes | 45,052 | 935 | 80.8 | 8314 | 76.2 | 18,970 | 66.8 | 9874 | 56.9 | 4947 | 57.3 | 2012 | 64.7 | <0.0001 | 14,271 | 55.8 | 9478 | 53.8 | 21,303 | 80.9 | <0.0001 |
| | No | 24,492 | 222 | 19.2 | 2591 | 23.8 | 9413 | 33.2 | 7484 | 43.1 | 3683 | 42.7 | 1099 | 35.3 | | 11,312 | 44.2 | 8139 | 46.2 | 5041 | 19.1 | |
| CT or PET-CT or Bone scan | <3 | 20,847 | 391 | 33.8 | 3243 | 29.7 | 8201 | 28.9 | 4934 | 28.4 | 2584 | 29.9 | 1494 | 48.0 | <0.0001 | 8075 | 31.6 | 3555 | 20.2 | 9217 | 35.0 | <0.0001 |
| | ≥3 | 48,697 | 766 | 66.2 | 7662 | 70.3 | 20,182 | 71.1 | 12,424 | 71.6 | 6046 | 70.1 | 1617 | 52.0 | | 17,508 | 68.4 | 14,062 | 79.8 | 17,127 | 65.0 | |

**TABLE 3** Comparison of follow-up imaging frequency and modality within 3 years after treatment based on clinical characteristics.
Recent guidelines, such as those from the American Society of Clinical Oncology, National Comprehensive Cancer Network (NCCN), and European Society for Medical Oncology (ESMO) do not recommend other laboratory tests (e.g., tumor markers) or imaging tests (e.g., bone scans, chest or abdominal CT, PET-CT) in asymptomatic patients because there is no evidence to support their survival benefit. However, these tests are being performed in clinical practice because of patient and clinician fear of recurrence or metastasis and the belief that early detection using more intensive imaging work-ups reduces cancer-related death. This is supported by the results of the current study, in which 97.2% of the patients underwent a systemic imaging work-up that included a bone scan, CT, or PET-CT. In a survey of clinicians on follow-up after primary treatment of breast cancer conducted by the Korean Breast Cancer Society, most respondents indicated that they conducted more intensive follow-up imaging work-ups than recommended in the current guidelines, similar to the findings of the current study. With respect to the patterns of imaging work-ups, we found that they differed by age, stage, and type of treatment. In young women aged <30, more breast MRIs and fewer mammograms were performed. This could be because of the tendency for dense breast tissue and genetic susceptibility (BRCA1/2 mutation) in these patients. Meanwhile, in patients treated with adjuvant hormonal therapy (i.e., those with hormone receptor-positive breast cancer), fewer bone scans and more chest CTs were performed. This result could be interpreted to mean that clinicians tend to recommend different systemic imaging modalities according to the tumor characteristics, as hormone receptor-positive tumors develop more bone metastases than visceral metastases. We also found that systemic imaging work-ups were more frequently performed in patients with advanced cancer and in patients who received chemotherapy. However, this did not improve overall survival or breast cancer-related survival. Previous randomized controlled trials have found that less-intensive follow-up strategies did not negatively affect patient outcomes or early detection of recurrence. In addition, the intensity of imaging work-up did not affect QoL.

### Table 3

|                      | Adjuvant chemotherapy |                      |                      | Adjuvant radiotherapy |                      |                      | Adjuvant hormonal therapy |                      |
|----------------------|-----------------------|----------------------|----------------------|-----------------------|----------------------|--------------------------|--------------------------|------------------------|
|                      | No                    | Yes                  | p-value              | No                    | Yes                  | p-value                  | No                      | Yes                    | p-value                |
|                      | N                     | %                    | N                    | %                     | p-value              | N                       | %                       | p-value                | N                     | %                     | p-value                |
| Chest CT*            | <3                    | 15,096 91.4          | 43,174 81.4          | <0.0001               | 24,127 89.2          | 34,143 80.3             | <0.0001                 | 17,348 82.5            | 40,922 84.4            | <0.0001               |
|                      | ≥3                    | 1413 8.6             | 9861 18.6            |                       | 2913 10.8            | 8361 19.7              |                         | 3685 17.5             | 7589 15.6              |                       |
| Bone scan*           | <3                    | 11,167 67.6          | 26,658 50.3          | <0.0001               | 15,805 58.5          | 22,020 51.8             | <0.0001                 | 12,043 57.3            | 25,782 53.1            | <0.0001               |
|                      | ≥3                    | 5342 32.4            | 26,377 49.7          |                       | 11,235 41.5          | 20,484 48.2             |                         | 8990 42.7             | 22,729 46.9            |                       |
| PET-CT               | <3                    | 15,816 95.8          | 47,801 90.1          | <0.0001               | 25,307 93.6          | 38,310 90.1             | <0.0001                 | 18,932 90.0            | 44,685 92.1            | <0.0001               |
|                      | ≥3                    | 693 4.2              | 5234 9.9             |                       | 1733 6.4             | 4194 9.9                |                         | 2101 10.0             | 3826 7.9              |                       |
| DEXA                 | No                    | 9821 59.5            | 35,231 66.4          | <0.0001               | 18,822 69.6          | 26,230 61.7             | <0.0001                 | 15,482 73.6            | 29,570 61.0            | <0.0001               |
|                      | Yes                   | 6688 40.5            | 17,804 33.6          |                       | 8218 30.4            | 16,274 38.3             |                         | 5551 26.4             | 18,941 39.0            |                       |
| CT or PET-CT or Bone scan* | <3 | 7951 48.2 | 12,896 24.3 | <0.0001 | 9903 36.6 | 10,944 25.7 | <0.0001 | 6838 32.5 | 14,009 28.9 | <0.0001 |
|                      | ≥3                    | 8558 51.8            | 40,139 75.7          |                       | 17,137 63.4          | 31,560 74.3             |                         | 14,195 67.5            | 34,502 71.1            |                       |

*Chi-squared test.

bFisher's exact test.
|                  | Total (N = 69,544) | Death Event (N = 5241) | Death HR (95% CI) | Death aHR<sup>a</sup> (95% CI) | Death aHR<sup>b</sup> (95% CI) | Breast cancer-related death Event (N = 4357) | Breast cancer-related death HR (95% CI) | Breast cancer-related death aHR<sup>a</sup> (95% CI) | Breast cancer-related death aHR<sup>b</sup> (95% CI) | Recurrence Event (N = 11,676) | Recurrence HR (95% CI) | Recurrence aHR<sup>a</sup> (95% CI) | Recurrence aHR<sup>b</sup> (95% CI) |
|------------------|---------------------|------------------------|------------------|------------------|------------------|--------------------------------------------|-----------------------------------|--------------------------------------------|--------------------------------------------|---------------------|----------------------------------|----------------------------------|----------------------------------|
| Mammography <3   | 31,518              | 3179                   | 1                | 1                | 1                | 2551                                       | 1                                 | 1                                          | 1                                          | 4944                | 1                                | 1                                | 1                                |
| ≥3               | 38,026              | 2062                   | 0.53             | 0.55             | 0.53             | 1806                                       | 0.56                             | 0.59                                        | 0.59                                        | 6732                | 1.12                             | 1.08                             | 1.14                             |
| Breast MRI No    | 67,267              | 5163                   | 1                | 1                | 1                | 4284                                       | 1                                 | 1                                          | 1                                          | 11,311              | 1                                | 1                                | 1                                |
| Yes              | 2277                | 78                     | 0.60             | 0.54             | 0.66             | 73                                          | 0.66                             | 0.55                                        | 0.71                                        | 365                 | 1.17                             | 1.06                             | 1.27                             |
| Chest radiography <3 | 23,332             | 1269                   | 1                | 1                | 1                | 905                                         | 1                                 | 1                                          | 1                                          | 3001                | 1                                | 1                                | 1                                |
| ≥3               | 46,212              | 3972                   | 1.54             | (1.45–1.64)      | 1.93             | (1.74–2.15)                                 | 235                              |                              |                              | 8675                | 1.49                             | 1.42                             | 1.54                             |
| Chest CT <3      | 58,270              | 3714                   | 1                | 1                | 1                | 2932                                       | 1.89                             | 1.68                                        | 2.35                                        | 8915                | 1                                | 1                                | 1                                |
| ≥3               | 11,274              | 1527                   | 2.60             | (2.45–2.76)      | 2.39             | (2.18–2.61)                                 | 2.75                              |                              |                              | 2761                | 1.95                             | 1.79                             | 1.98                             |
| Bone scan <3     | 37,825              | 2801                   | 1                | 1                | 1                | 2171                                       | 1.16                             | 1.08                                        | 1.04                                        | 5558                | 1                                | 1                                | 1                                |
| ≥3               | 31,719              | 2440                   | 1.00             | (0.95–1.06)      | 0.89             | (0.82–0.98)                                 | 1.04                              |                              |                              | 6118                | 1.30                             | 1.22                             | 1.25                             |
| PET-CT <3        | 63,617              | 4560                   | 1                | 1                | 1                | 3711                                       | 1                                 | 1                                          | 1                                          | 9977                | 1                                | 1                                | 1                                |
| ≥3               | 5927                | 681                    | 2.16             | (1.99–2.34)      | 2.49             | (2.26–2.75)                                 | 2.83                              |                              |                              | 1699                | 2.43                             | 2.19                             | 2.96                             |
| DEXA No          | 45,052              | 4303                   | 1                | 1                | 1                | 3601                                       | 1                                 | 1                                          | 1                                          | 8705                | 1                                | 1                                | 1                                |
| Yes              | 24,492              | 938                    | 0.47             | (0.44–0.50)      | 0.51             | (0.46–0.57)                                 | 0.49                              |                              |                              | 2971                | 0.64                             | 0.60                             | 0.64                             |
| CT, PET-CT, or   | 20,847              | 1361                   | 1                | 1                | 1                | 955                                        | 1                                 | 1                                          | 1                                          | 2858                | 1                                | 1                                | 1                                |
| bone scan <3     | 48,697              | 3880                   | 1.35             | (1.27–1.44)      | 1.40             | (1.25–1.57)                                 | 1.87                              |                              |                              | 8818                | 1.44                             | 1.30                             | 1.51                             |
| ≥3               |                      |                       |                  |                  |                  |                                              |                                   |                              |                              |                    |                                   |                                   | | 

<sup>a</sup>Adjusted for age at diagnosis, treatment status (chemotherapy, radiotherapy, adjuvant hormonal therapy), and Charlson comorbidity index.

<sup>b</sup>Adjusted for stage, age at diagnosis, treatment status (chemotherapy, radiotherapy, adjuvant hormonal therapy), and Charlson comorbidity index.
| modality                  | Death (N = 4937) | Event (N = 616) | Death (N = 575) | Event (N = 575) |
|--------------------------|------------------|----------------|----------------|----------------|
| Death                    | Death            | Death          | Death          | Death          |
| Mammography              | 2157             | 327            | 1              | 1              |
| ≥3                       | 2780             | 289            | 0.69 (0.59–0.81) | 0.72 (0.61–0.84) |
| ≥3                       | 269              | 0.69 (0.58–0.81) | 0.72 (0.61–0.84) | 1.00 (0.69–1.45) |
| Breast MRI               | No               | 4858           | 611            | 1              |
| Yes                      | 79               | 5              | 0.82 (0.34–1.97) | 0.61 (0.25–1.48) |
| Yes                      | 570              | 1              | 0.87 (0.36–2.10) | 0.63 (0.26–1.53) |
| Chest radiography        | <3               | 1430           | 180            | 1              |
| ≥3                       | 3507             | 436            | 0.96 (0.81–1.14) | 0.96 (0.80–1.14) |
| ≥3                       | 407              | 0.96 (0.80–1.15) | 0.95 (0.80–1.14) | 1.36 (0.91–2.04) |
| Chest CT                 | <3               | 4342           | 546            | 1              |
| ≥3                       | 595              | 70             | 1.28 (1.00–1.65) | 1.15 (0.90–1.48) |
| ≥3                       | 66               | 1.295 (1.00–1.68) | 1.14 (0.88–1.49) | 1.07 (0.68–1.68) |
| Bone scan                | <3               | 2532           | 327            | 1              |
| ≥3                       | 2405             | 289            | 0.90 (0.77–1.06) | 0.88 (0.75–1.03) |
| ≥3                       | 271              | 0.91 (0.77–1.07) | 0.84 (0.74–1.03) | 1.09 (0.76–1.58) |
| PET-CT                   | <3               | 4714           | 601            | 1              |
| ≥3                       | 4714             | 601            | 1              | 1              |
| ≥3                       | 452              | 1              | 0.77 (0.61–1.71) | 0.77 (0.46–1.28) |
| ≥3                       | 452              | 1              | 0.77 (0.61–1.71) | 0.77 (0.46–1.28) |
| DEXA                     | No               | 3508           | 486            | 1              |
| Yes                      | 130              | 0.83 (0.69–1.01) | 0.88 (0.72–1.07) | 0.86 (0.59–1.26) |
| Yes                      | 123              | 0.85 (0.69–1.03) | 0.90 (0.74–1.11) | 0.88 (0.60–1.30) |
| CT, PET-CT, or bone scan | <3               | 1553           | 218            | 1              |
| ≥3                       | 3384             | 398            | 0.92 (0.78–1.09) | 0.86 (0.73–1.02) |
| ≥3                       | 373              | 0.93 (0.79–1.11) | 0.85 (0.71–1.01) | 1.21 (0.77–1.91) |

<sup>a</sup> Adjusted for age at diagnosis, treatment status (chemotherapy, radiotherapy, and adjuvant hormonal therapy), and Charlson comorbidity index.

<sup>b</sup> Adjusted for stage, age at diagnosis, treatment status (chemotherapy, radiotherapy, adjuvant hormonal therapy), and Charlson comorbidity index.
in breast cancer survivors, and 70% of the patients even reported feeling more stressed and anxious when they visited clinics, especially after undergoing tests. Expert panel on breast imaging according to ACR appropriateness criteria comment that there is no role for imaging to screen for distant recurrences in asymptomatic patients with a history of stage I breast cancer that received treatment for curative intent. They recommend that routine surveillance with an annual mammogram is the only imaging test that should be performed to detect an in-breast recurrence or a new primary breast cancer in women with a history of stage I breast cancer.

This study has some limitations. First, the merged data used for the study did not include detailed information on tumor characteristics, such as hormone receptor status. To compensate, we analyzed the outcomes by adjusting for hormonal therapy status. Second, we were not able to take into account the indication for the imaging work-ups such as cancer-related symptoms, comorbidity-related causes, or other medical issues or who prescribed the work-ups (e.g., oncologists or primary physician) in our analyses. However, we considered the presence of morbid disease and the cause of death in our analysis of the effect of intensive imaging work-ups on survival. Third, this study was not randomized or a planned prospective study. However, the national health insurance data and statistics which our analyses are based on are highly specific because the KNHIS is the only public health insurer and covers at least 98% of Koreans and is the only representative national database to include cause of death.

In conclusion, this study showed that as a follow-up imaging modality, only frequent mammography and no other imaging modalities reduce overall mortality and breast cancer-related mortality in Korean female breast cancer patients. These findings provide evidence that frequent systemic imaging work-ups are not needed despite the fear of recurrence. Therefore, clinicians need to adhere to the current guidelines for surveillance after curative treatment in breast cancer patients.

CONFLICT OF INTEREST
The authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request with the permission of KCCCR, Statistics Korea, and KNHIS.

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REFERENCES
1. Kang SY, Kim YS, Kim Z, et al. Basic findings regarding breast cancer in Korea in 2015: data from a breast cancer registry. J Breast Cancer. 2018;21:1-10.
2. Ferlay J, S I, E M, Dicksh, R, Eser S, Mathers C. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 International Agency for Research on Cancer. http://globocan.iarc.fr. Accessed 13 May, 2018.
3. Burstein H, Winer EP. Primary care for survivors of breast cancer. N Engl J Med. 2000;343:1086-1094.
4. Emens LA, Davidson NE. The follow-up of breast cancer. Semin Oncol. 2003;30:338-348.
5. Khatcheressian JL, Hurley P, Bantug E, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31:961-965.
6. (NCCN). NCCN. NCCN clinical practice guidelines in oncology. Breast cancer. Version 2. 2016. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breastpdf [accessed 190516].
7. Palli D, Russo A, Saieva C, et al. Intensive vs clinical follow-up after treatment of primary breast cancer: 10-year update of a randomized trial. National Research Council Project on Breast Cancer Follow-up. JAMA. 1999;281(17):1586.
8. Dalberg K, Mattsson A, Sandelin K, Rutqvist LE. Outcome of treatment for ipsilateral breast tumor recurrence in early-stage breast cancer. Breast Cancer Res Treat. 1998;49:69-78.
9. Margenthaler JA, Allam E, Chen L, et al. Surveillance of patients with breast cancer after curative-intent primary treatment: current practice patterns. J Oncol Pract. 2012;8:79-83.
10. Lafata JE, Simpkins J, Schultz L, et al. Routine surveillance care after cancer treatment with curative intent. Med Care. 2005;43:592-599.
11. Kim KS, Kim Z, Shim E-J, et al. The reality in the follow-up experience of breast cancer patients with breast cancer after curative-intent primary treatment: current practice guidelines. J Oncol Pract. 2012;8:79-83.
12. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 10th rev. Geneva: World Health Organization; 1994.
13. Ruhl J, A M, Dickie L. SEER Program Coding and Staging Manual 2016: Section V. Bethesda, MD: National Cancer Institute; 2016.
14. Shin HR, Won YJ, Jung KW, et al. Nationwide cancer incidence in Korea, 1999–2001; first result using the national cancer incidence database. Cancer Res Treat. 2005;37:325-331.
15. Jung KW, Won YJ, Hong KS, Lee ES; Community of Population-based Regional Cancer R. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2015. Cancer Res Treat. 2018;50:303-316.
16. Korean National Health Insurance Corporation. Analysis of 2009 National Health Screening Program. Seoul: National Health Insurance Corporation; 2010.
17. Korean Statistical Information Service. [Internet]. Daejeon. Statistics Korea. 2018.
18. Cardoso F, Kyrkikides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30:1674.
19. Cho KT, Wang KC, Kim SK, Shin SH, Chi JG, Cho BK. Pediatric brain tumors: statistics of SNUH, Korea (1959–2000). Childs Nerv Syst. 2002;18:30-37.
20. Schunemann HJ, Lerda D, Quinn C, et al. Breast cancer screening and diagnosis: a synopsis of the European Breast Guidelines. *Ann Intern Med.* 2020;172:46-56.

21. Mann RM, Kuhl CK, Kinkel K, Boetes C. Breast MRI: guidelines from the European Society of Breast Imaging. *Eur Radiol.* 2008;18:1307-1318.

22. Oltra A, Santaballa A, Munarriz B, Pastor M, Montalar J. Cost-benefit analysis of a follow-up program in patients with breast cancer: a randomized prospective study. *Breast J.* 2007;13:571-574.

23. Sheppard C, Higgins B, Wise M, Yiangou C, Dubois D, Kilburn S. Breast cancer follow up: a randomised controlled trial comparing point of need access versus routine 6-monthly clinical review. *Eur J Oncol Nurs.* 2009;13:2-8.

24. Lafranconi A, Pylkkanen L, Deandrea S, et al. Intensive follow-up for women with breast cancer: review of clinical, economic and patient’s preference domains through evidence to decision framework. *Health Qual Life Outcomes.* 2017;15:206.

25. Paradiso A, Nitti P, Frezza P, Scorpiglione N. A survey in Puglia: the attitudes and opinions of specialists, general physicians and patients on follow-up practice. *G.S.Bio.Ca.M. Ann Oncol.* 1995;6:53-56.

26. Expert Panel on Breast I, Lewin AA, Moy L, et al. ACR Appropriateness Criteria(R) Stage I Breast Cancer: Initial Workup and Surveillance for Local Recurrence and Distant Metastases in Asymptomatic Women. *J Am Coll Radiol.* 2019;16:S428-S439.

27. Knhi C. *Analysis of 2009 National Health Screening Program.* Seoul: National Health Insurance Corporation; 2010.

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