Synchronous Breast Cancer: Phenotypic Similarities on MRI

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Background: Previous studies have shown discrepancies between index and synchronous breast cancer in histology and molecular phenotype. It is yet unknown whether this observation also applies to the MRI phenotype.

Purpose: To investigate whether the appearance of breast cancer on MRI (i.e. phenotype) is different from that of additional breast cancer (i.e. synchronous cancer), and whether such a difference, if it exists, is associated with prognosis.

Study Type: Retrospective.

Population: In all, 464 consecutive patients with early-stage ER+/HER2– breast cancer were included; 34/464 (7.3%) had 44 synchronous cancers in total (34 ipsilateral, 10 contralateral).

Sequence: 1.5T, contrast-enhanced T1-weighted.

Assessment: We assessed imaging phenotype using 50 quantitative features from each cancer and applied principal component analysis (PCA) to identify independent properties. The degree of phenotype difference was assessed. An association between phenotype differences and prognosis in terms of the Nottingham Prognostic Index (NPI) and PREDICT score were analyzed.

Statistical Tests: PCA; Wilcoxon rank sum test; Benjamini–Hochberg to control the false discovery rate.

Results: PCA identified eight components in patients with ipsilateral synchronous cancer. Six out of eight were significantly different between index and synchronous cancer. These components represented features describing texture (three components, \( P < 0.001, P < 0.001, P = 0.004 \)), size (\( P < 0.001 \)), smoothness (\( P < 0.001 \)), and kinetics (\( P = 0.004 \)). Phenotype differences in terms of the six components were split in tertiles. Larger phenotype differences in size, kinetics, and texture were associated significantly worse prognosis in terms of NPI (\( P = 0.019, P = 0.045, P = 0.014 \)), but not for the PREDICT score (\( P = 0.109, P = 0.479, P = 0.109 \)). PCA identified six components in patients with contralateral synchronous cancer. None were significantly different from the index cancer (\( P = 0.178, P = 0.178, P = 0.326, P = 0.739, P = 0.423 \)).

Data Conclusion: The MRI phenotype of ER+/HER2– breast cancer was different from that of ipsilateral synchronous cancer and a large phenotype difference was associated with worse prognosis. No significant difference was found for synchronous contralateral cancer.

Level of Evidence: 3
Technical Efficacy: Stage 4

Synchronous Breast Cancer refers to breast cancer detected simultaneously with an index breast cancer, but is physically separated.1 The incidence of synchronous breast cancer varies and is largely dependent on the criteria used in imaging and pathology.2,3 The synchronous breast cancer rate can reach as high as 38%.4–6 Discrepancies in prognostic markers between the index cancers and their synchronous counterparts may have impact on systemic treatment of patients.7 It has been observed that patients with discrepant prognostic markers between index and the corresponding synchronous cancer have worse long-term survival than patients with congruent markers.8–12 It is yet unknown, however, whether the imaging phenotype of the index cancer also differs from that of the synchronous cancer, and if so, whether such a difference is related to the patient’s prognosis.

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Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has been regarded as the most sensitive method for detection of breast cancer, ranging between 89% and 100%.\textsuperscript{13,14} Quantitative analysis of the phenotype of breast cancer on MRI may extract subtle but reproducible information that is imperceptible to radiologists’ eyes,\textsuperscript{15,16} thus providing more detail to compare phenotypes.\textsuperscript{17,18} The primary aim of this study was to determine whether the MRI phenotypes of index cancers and their synchronous counterparts differ in a series of consecutive patients with early breast cancer. The second aim was to explore whether this difference, if it exists, is associated with patient prognosis.

Materials and Methods

Patients and Lesions

This study was performed after approval of the Institutional Review Board and with written informed consent of all patients. In total, 628 patients were collected. We retrospectively analyzed the prospectively collected data from the MARGINS study (Multi-modality Analysis and Radiological Guidance IN breast conserving therapy), which was conducted between 2000 and 2008; patients who were included after being diagnosed with early-stage breast cancer for which breast conserving therapy was indicated based on physical examination, mammography, and ultrasound, had an additional pre-operative breast MRI. The index breast cancer was confirmed by fine-needle aspiration cytology or core needle biopsy.

We evaluated patients with pathology-proven synchronous breast cancer. To eliminate the influence of intrinsic differences in terms of immunohistochemical (IHC) subtype of the index breast cancer, and due to limitation of the sample size, we focused on patients with estrogen receptor-positive and human epidermal growth factor receptor 2-negative (ER+/HER2−) primary cancer.

Clinicohistopathological variables included age at diagnosis, location of synchronous cancer (ipsilateral or contralateral), largest diameter of index and synchronous breast cancer, number of positive axillary lymph nodes, histologic grade, and IHC subtype of index cancer.

The number of positive lymph nodes was determined by sentinel node biopsy, and combined with axillary lymph node dissection where available. The cases were grouped into three categories: none, one to three, and four or more positive lymph nodes.

Histologic grade was assessed according to the Bloom and Richardson classification.\textsuperscript{19} Tumors were classified as estrogen receptor-positive if more than 10% of the cells were stained positive. Tumors were classified as HER2-positive when scored at least 3 at IHC or when in situ hybridization demonstrated gene amplification, otherwise classified as HER2-negative.

Imaging Phenotype Identification

Patients underwent MRI in the prone position using a 1.5T scanner (Magnetom; Siemens Medical Systems, Erlangen, Germany) with a double-breast array coil. Five consecutive scans at intervals of 90 seconds were performed: one prior to and four after contrast administration. Contrast-enhanced scans were made after intravenous injection with the gadolinium-based contrast agent Gadoteridol (Prohance; Bracco-Byk Gulden, Konstanz, Germany) at 0.1 mmol/kg body weight. The following parameters were used: 3D coronal T1-weighted sequence; repetition time 8.1 msec; echo time 4.0 msec; isotropic voxels 1.35 × 1.35 × 1.35 mm\textsuperscript{3}, without fat suppression.

Phenotype Difference and Prognosis

The association between phenotype difference and prognosis was assessed using the Nottingham Prognostic Index (NPI) and PREDICT score. The NPI was defined as $(0.2×S) + N + G$, where $S$ represents the largest diameter of the index cancer in centimeter; $N$ is 1 for no positive lymph node, 2 for 1 to 3 positive lymph nodes, and 3 for more than 3 positive lymph nodes; and $G$ is the histologic grade.\textsuperscript{26} The PREDICT score was calculated through the PREDICT v. 2.1 model,\textsuperscript{27} which is a breast cancer prognostication and treatment benefit prediction model, and estimates 10-year survival probability on the basis of patient age, tumor size, tumor grade, number of positive nodes, ER status, HER2 status, Ki67 status, mode of detection, and adjuvant chemotherapy regimen.

Statistical Analysis

Outliers in feature values were winsorized to the nearest whisker.\textsuperscript{28} Principal component analysis (PCA) with varimax-rotation was performed. Components describing at least 90% cumulative variance were analyzed.\textsuperscript{29} The PCA yielded a score per component per lesion. These scores were compared between the index and synchronous cancers using the Wilcoxon rank sum test. Analysis was conducted independently for ipsilateral and contralateral synchronous cancers. Since multiple tests were performed, the Benjamini–Hochberg method was used to control the false discovery rate (FDR).\textsuperscript{30} FDR-adjusted $P$ values less than 0.05 were considered significant. The association between the differences in these PCA scores and NPI and PREDICT scores were analyzed using the Wilcoxon rank sum test. All statistical analysis was performed using R v. 3.5.2 (Vienna, Austria).

Results

Patients and Lesions

Among a total of 628 patients, 464/628 (73.9%) patients had ER+/HER2− index cancer, 34/464 (7.3%) of whom had 44 synchronous breast cancers in total; 83/628 (13.2%) patients had HER2+ index cancer, 4/83 (4.8%) of whom had
four synchronous breast cancers in total; 81/628 (12.9%) patients had triple-negative index cancer, 6/81 (7.4%) of whom had eight synchronous breast cancers in total (Fig. 1). Finally, 34 patients with 44 synchronous breast cancers in total were included. Among the 44 synchronous cancers, 34 were in the ipsilateral breast and 10 were in the contralateral breast (Fig. 1). The average age of patients at diagnosis was 54 years. The average diameter of the index cancers and the synchronous cancers was 21.7 mm and 11.9 mm, respectively (Table 2).

**Imaging Phenotype**

**IPSILATERAL.** For the patients with ipsilateral synchronous breast cancer, PCA identified eight components explaining 92% cumulative variance (Table 3). Components 1, 5, and

| TABLE 1. Feature List Extracted From DCE-MRI |
|-----------------------------------------------|
| ID | Texture Feature list | ID | Conventional Feature list |
|----|---------------------|----|---------------------------|
| 1  | washin_Angular_Second_Moment | 29 | circularity |
| 2  | washin_Contrast | 30 | irregularity |
| 3  | washin_Correlation | 31 | volume |
| 4  | washin_Sum_of_Squares_Variance | 32 | largest_diameter |
| 5  | washin_Inverse_Difference_Moment | 33 | uptake_speed |
| 6  | washin_Sum_Average | 34 | washout |
| 7  | washin_Sum_Variance | 35 | SER |
| 8  | washin_Sum_Entropy | 36 | top_init_enhancement |
| 9  | washin_Entropy | 37 | top_late_enhancement |
| 10 | washin_Difference_Variance | 38 | vol_init_enhancement_GT100 |
| 11 | washin_Difference_Entropy | 39 | ld_init_enhancement_GT100 |
| 12 | washin_Measure_of_Correlation_1 | 40 | volume_late_LT0 |
| 13 | washin_Measure_of_Correlation_2 | 41 | largest_diameter_Late_LT0 |
| 14 | washin_Maximal_Correlation_Coefficient | 42 | mean_sharpness |
| 15 | washout_Angular_Second_Moment | 43 | variation_sharpness |
| 16 | washout_Contrast | 44 | mean_sharpness_frame2 |
| 17 | washout_Correlation | 45 | variation_sharpness_frame2 |
| 18 | washout_Sum_of_Squares_Variance | 46 | variation_smoothness |
| 19 | washout_Inverse_Difference_Moment | 47 | mean_smoothness |
| 20 | washout_Sum_Average | 48 | std_rgh_val_frame2 |
| 21 | washout_Sum_Variance | 49 | rad_grad_ind_frame2 |
| 22 | washout_Sum_Entropy | 50 | lesion_to_nipple_relative_distance |

DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging.
7 mainly represented texture, component 2 mainly represented texture and size of cancer, component 3 represented sharpness and uptake speed, components 4, 6, 8 represented smoothness, kinetics, and relative distance of the cancer to the nipple, respectively (Fig. S1 in the Supplemental Material, which demonstrates feature weight in eight components).

Six out of eight components were significantly different between index and the synchronous cancers after FDR adjustment. These components represented features describing texture (component 1 \( P < 0.001 \)), component 5 \( P < 0.001 \), and component 7 \( P = 0.004 \)), size (component 2, \( P < 0.001 \)), smoothness (component 4, \( P < 0.001 \)), and kinetics (component 6, \( P = 0.004 \)). Components 3 and 8 were not significantly different between index and the synchronous breast cancers \( (P = 0.859, P = 0.809) \) (Fig. 2).

**CONTRALATERAL.** For the patients with contralateral synchronous cancer, PCA identified six components explaining 92% cumulative variance (Table 4). Component 1 represented texture and cancer volume, component 2 represented texture and largest diameter of cancer, component 3 represented smoothness, component 4 represented kinetics and relative distance to the nipple, component 5 represented sharpness and texture, and component 6 represented texture (Fig. S2 in Supplemental Material, which demonstrates feature weight in six components). None of these six components were found to be significantly different between index and the

![Flowchart of selection of patients included in this study.](image)

**FIGURE 1: Flowchart of selection of patients included in this study.**

| Table 2: Characteristics of Patients and Cancers |
|-----------------------------------------------|
| **Features** | **Total** \( (N = 44) \) | **Ipsilateral** \( (N = 34) \) | **Contralateral** \( (N = 10) \) |
|-----------------|-----------------|-----------------|-----------------|
| Patient Age | 53.5 ± 7.5 | 52.5 ± 7.8 | 57.1 ± 5.4 |
| Synchronous breast cancer Largest diameter(mm, mean ± SD) | 11.9 ± 3.7 | 11.3 ± 3.4 | 13.9 ± 3.8 |
| Index breast cancer Largest diameter(mm, mean ± SD) | 21.7 ± 9.1 | 21.7 ± 8.3 | 21.6 ± 11.8 |
| **Histological grade** | | | |
| Grade I | 19 (43) | 14 (41) | 5 (50) |
| Grade II | 23 (52) | 18 (53) | 5 (50) |
| Grade III | 2 (5) | 2 (6) | 0 (0) |
| **Lymph nodes positive** | | | |
| 0 | 25 (57) | 17 (50) | 8 (80) |
| 1 to 3 | 13 (30) | 12 (35) | 1 (10) |
| 4 or more | 6 (13) | 5 (15) | 1 (10) |

SD, standard deviation. Numbers represent frequency (percentage) unless stated otherwise.
synchronous breast cancer ($P = 0.178$, $P = 0.178$, $P = 0.178$, $P = 0.326$, $P = 0.739$, $P = 0.423$). (Fig. 3). 

**Phenotype Difference and Prognosis**

For patients with ipsilateral synchronous cancer, the phenotype differences in the six components that were significantly different between index and the synchronous cancer were split in tertiles into small, medium, and large differences. Compared with small phenotype difference, a large phenotype difference in terms of lesion size and texture (component 2), kinetics (component 6), and texture (components 7) were associated with significantly higher NPI ($P = 0.019$, $P = 0.045$, $P = 0.014$ for components 2, 6, 7, respectively), while we did not find a significantly

| TABLE 3. Ipsilateral Group, PCA Identified Eight Components Explaining 92% Variance |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| **RC1** | **RC2** | **RC3** | **RC4** | **RC5** | **RC6** | **RC7** | **RC8** |
| **Name** | Texture1 | Texture2 + Size | Sharpness + Kinetics1 | Smoothness | Texture3 | Kinetics2 | Texture4 | Location |
| **Eigenvalue** | 23.3 | 7.4 | 6.0 | 3.3 | 2.1 | 1.7 | 1.3 | 1.0 |
| **Variance%** | 27% | 25% | 11% | 9% | 7% | 7% | 4% | 2% |
| **Cumulative variance%** | 27% | 52% | 63% | 72% | 79% | 86% | 90% | 92% |

PCA, principal component analysis; RC, rotated component.

**FIGURE 2:** MRI phenotype of breast cancer (expressed in quantitative component score) (y-axis) for the index breast cancer and ipsilateral synchronous cancer (x-axis) (RC, rotated component; Syn, synchronous breast cancer; Index, index breast cancer).
different PREDICT score between the small and large phenotype difference groups ($P = 0.109$, $P = 0.479$, $P = 0.109$ for components 2, 6, 7, respectively) (Figs. 4, 5 and Table 5).

### Discussion

In 34 patients with 44 synchronous breast cancers, we found that the imaging phenotype differed between index cancer and the corresponding synchronous cancers in the ipsilateral

#### TABLE 4. Contralateral Group, PCA Identified Six Components Explaining 92% Variance

|        | RC1   | RC2          | RC3         | RC4         | RC5          | RC6          |
|--------|-------|--------------|-------------|-------------|--------------|--------------|
| Name   | Texture1+Volume | Texture2+LD | Smoothness  | Kinetics+Location | Texture3+Sharpness | Texture4     |
| Eigenvalue | 24.7 | 7.2          | 5.8         | 4.2         | 2.4          | 1.6          |
| Variance% | 28%  | 27%          | 15%         | 9%          | 9%           | 4%           |
| Cumulative variance% | 28%  | 55%          | 70%         | 79%         | 88%          | 92%          |

PCA, principal component analysis; RC, rotated component; LD, largest diameter.

![Figure 3](image-url)  
**FIGURE 3:** MRI phenotype of breast cancer (expressed in quantitative component score) (y-axis) for the index breast cancer and contralateral synchronous cancer (x-axis) (RC, rotated component; Syn, synchronous breast cancer; Index, index breast cancer).
breast. Furthermore, patients with a large phenotype discrepancy between the index and the ipsilateral synchronous cancer had relatively inferior prognosis in terms of NPI. In patients with contralateral synchronous breast cancer, no significant difference in imaging phenotype was observed.

The proportion of synchronous tumor foci detected on MRI varies considerably. In our study, we found 34/464 (7.3%) patients with synchronous breast cancer, which is consistent with prior studies showing a frequency of 6% to 34%.31

Our results indicated that the size of ER+/HER2– index breast cancers was larger than that of ipsilateral synchronous breast cancers. PCA identified eight components; component 2 was related to size and was indeed significantly different between index and synchronous cancer. In addition to size, texture, smoothness, and kinetics were also significantly different between index and ipsilateral synchronous cancer.

Synchronous breast cancer could result from intramammary spreading of index breast cancer with a similar phenotype. It could also develop independently, originating from separate progenitor cells and having a different phenotype.32 The discrepancy between index breast cancer and synchronous cancer observed on the ipsilateral side in our study is in agreement with the reported discrepancies in histological tumor grade,10 tumor type,33 and molecular phenotype.12

In this study we used computer-extracted descriptions of the phenotype of the breast cancers. It has been increasingly accepted that quantitative features extracted from radiological images contain more detailed information than those perceived by radiologists in qualitative studies.34 These features represent phenotypes of the tissues that might reflect underlying information such as genetics. Since we have found significant phenotype differences between index and the synchronous breast cancers, the question arose whether such phenotype differences have the potential to serve as a noninvasive indicator of long-term prognosis before treatment, so as to provide insight into individualized treatment. For the six components that significantly differ between index and the synchronous breast cancers, the results indicated that larger differences of the phenotype in terms of size, kinetics, and texture were indicative of worse prognosis in terms of NPI.

**FIGURE 4:** Association between phenotype difference (large and small group) with prognosis in terms of NPI and PREDICT score (NPI, Nottingham Prognostic Index). P value indicates the significance of Wilcoxon rank sum test (RC, rotated component; small, 1st Tertile phenotype difference; large, 3rd Tertile phenotype difference).
for ER+/HER2– breast cancer. Although the corresponding PREDICT score was not significantly different between the small and large phenotype difference, to some extent this could be attributed to the relatively small sample size.

We did not find a statistically significant discrepancy between index breast cancer and the synchronous cancer on the contralateral side. On the one hand, this may be ascribed to the small sample size in our study. On the other hand, this result is in line with the literature, describing an agreement between index cancer and synchronous cancer on the contralateral side in terms of tumor-associated antigens: bilateral breast cancers have been subjected to similar hormonal,

**TABLE 5.** For Patients With Ipsilateral Synchronous Cancer, Association Between Phenotype Difference With Prognosis

|        | NPI          | P  | PREDICT     | P  |
|--------|--------------|----|-------------|----|
|        | 1st Tertile  | 3rd Tertile |    | 1st Tertile | 3rd Tertile |    |
| RC1    | 3.5 (3.3,4.5) | 4.5 (3.3,4.7) | 0.310 | 81% (67%, 83%) | 66% (62%, 85%) | 0.975 |
| RC2    | 3.3 (3.2,3.3) | 4.5 (3.5,4.6) | **0.019** | 83% (73%, 84%) | 66% (62%, 79%) | 0.109 |
| RC4    | 3.3 (3.2,3.8) | 4.5 (4.1,4.6) | 0.139 | 82% (71%, 84%) | 63% (54%, 77%) | 0.242 |
| RC5    | 3.3 (3.2,3.7) | 3.5 (3.3,4.5) | 0.096 | 82% (71%, 84%) | 80% (66%, 85%) | 0.853 |
| RC6    | 3.3 (3.2,3.9) | 4.5 (3.4,4.7) | **0.045** | 80% (69%, 85%) | 73% (64%, 82%) | 0.479 |
| RC7    | 3.3 (3.3,6)  | 4.5 (3.5,4.6) | **0.014** | 82% (71%, 90%) | 66% (54%, 80%) | 0.109 |

Numbers represent median (Q1, Q3) Q1, First quantile, Q3, Third quantile.

1st Tertile and 3rd Tertile means first and third tertile of phenotype difference.

RC, rotated component; NPI, Nottingham Prognostic Index.
environmental, and genetic influences during tumorigenesis. Therefore, it is reasonable that tumor phenotype in synchronous bilateral breast cancer may display similar biological characteristics. It should be noted, however, that these results are based on a limited amount of data.

**Limitations**
The main limitation of this study was the small sample size. Because of this, we only investigated patients with ER+/HER2– index breast cancer that form the majority (~70%) of the breast cancer population. For patients with HER2+ and triple-negative index cancer, we lack statistical power. Nonetheless, it would be interesting to expand these analyses to HER2+ and triple-negative breast cancer patients.

**Conclusion**
The MRI phenotype of ER+/HER2– breast cancer was significantly different from that of ipsilateral synchronous breast cancer, and a large phenotype difference was associated with relatively worse prognosis in terms of NPI. Significant phenotype differences were not found for contralateral synchronous cancers.

**Conflict of Interest**
The authors declare no conflicts of interest.

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