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 T_1-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 with 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 ($P = 0.178$, $P = 0.178$, $P = 0.178$, $P = 0.326$, $P = 0.739$, $P = 0.423$).
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

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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%.[13,14] Quantitative analysis of the phenotype of breast cancer on MRI may extract subtle but reproducible information that is imperceptible to radiologists' eyes,[15,16] thus providing more detail to compare phenotypes.[17,18] The primary aim of this study was to determine whether the MRI phenotypes of index cancers and their synchronous counterparts differ a in 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 preoperative 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.[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 T_1-weighted sequence; repetition time 8.1 msec; echo time 4.0 msec; isotropic voxels $1.35 \times 1.35 \times 1.35\ mm^3$, without fat suppression.

The index breast cancer and the corresponding synchronous cancer were segmented using a semiautomatic method that was previously reported.[20,21] A dedicated breast radiologist (C.L.) with more than 15 years of experience manually checked the segmentations. The imaging phenotype of each segmentation was described using 50 features: 21 features representing the size, sharpness, smoothness, and enhancement kinetics,[22,23] 28 texture features of washin and washout,[24] and one feature describing the relative distance of the cancer to the nipple in relation to breast size in the inferior–posterior direction. The position of the cancer was defined by the center of mass of the segmentation. These features were extracted using in-house-developed software in C++ and Python3.7.3; texture features were extracted using the Mahotas package.[25] These 50 features were listed in Table 1.

Phenotype Difference and Prognosis

The association between phenotype difference and prognosis in terms of the Nottingham Prognostic Index (NPI) and PREDICT score were analyzed. 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.[26] The PREDICT score was calculated through the PREDICT v. 2.1 model,[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.[28] Principal component analysis (PCA) with varimax-rotation was performed. Components describing at least 90% cumulative variance were analyzed.[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).[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

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_enhancment
9	washin_Entropy	37	top_late_enhancment
10	washin_Difference_Variance	38	vol_init_enhancment_GT100
11	washin_Difference_Entropy	39	ld_init_enhancment_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
23	washout_Entropy		
24	washout_Difference_Variance		
25	washout_Difference_Entropy		
26	washout_Measure_of_Correlation_1		
27	washout_Measure_of_Correlation_2		
28	washout_Maximal_Correlation_Coefficient		

DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging.

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

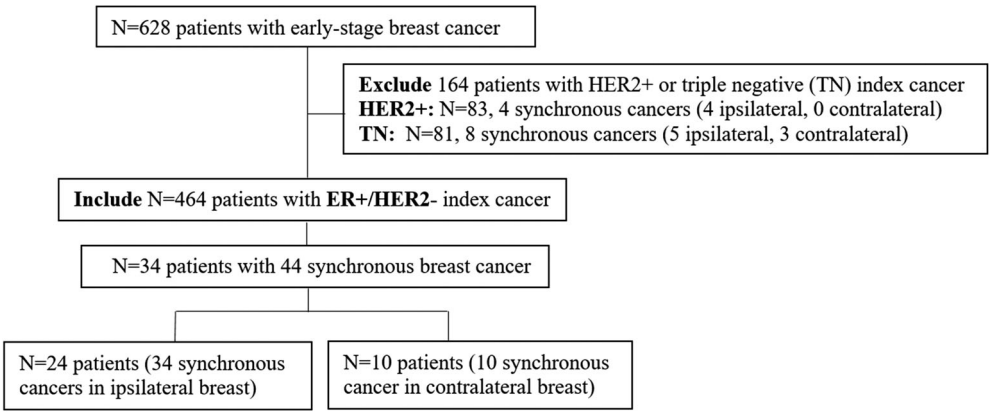

FIGURE 1: Flowchart of selection of patients included in this study.

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

TABLE 2. Characteristics of Patients and Cancers

	Features	Total ($N = 44$)	Ipsilateral ($N = 34$)	Contralateral ($N = 10$)
Patient	Age (years, mean ± SD)	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.

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.

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

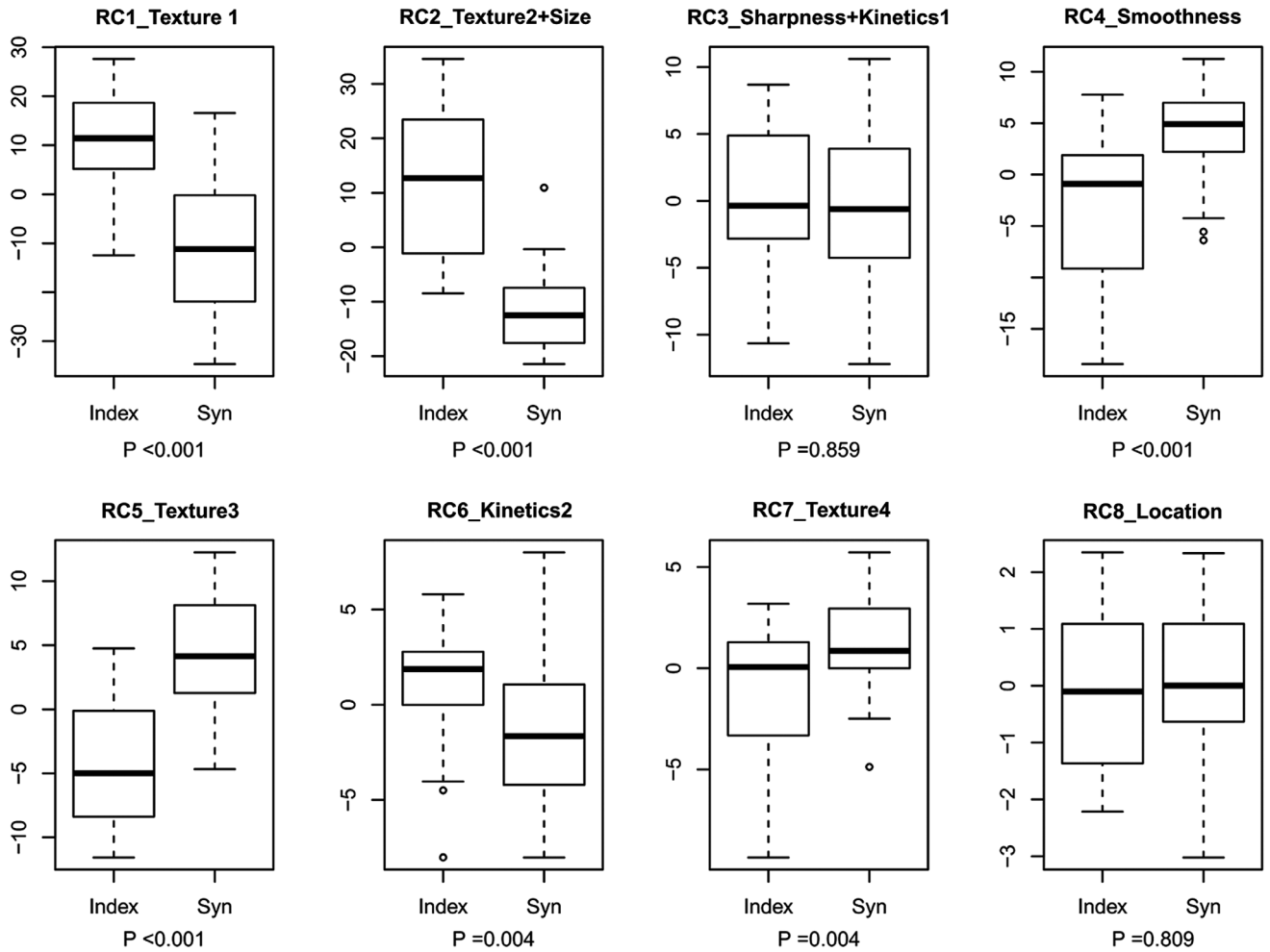

FIGURE 2: MRI phenotype of breast cancer (expressed in quantitative component score) (y-axis) for the index breast cancer and ipsilateral synchronous cancer (x-axis) (RC, rotated component; Syn, synchronous breast cancer; Index, index breast cancer).

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.

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

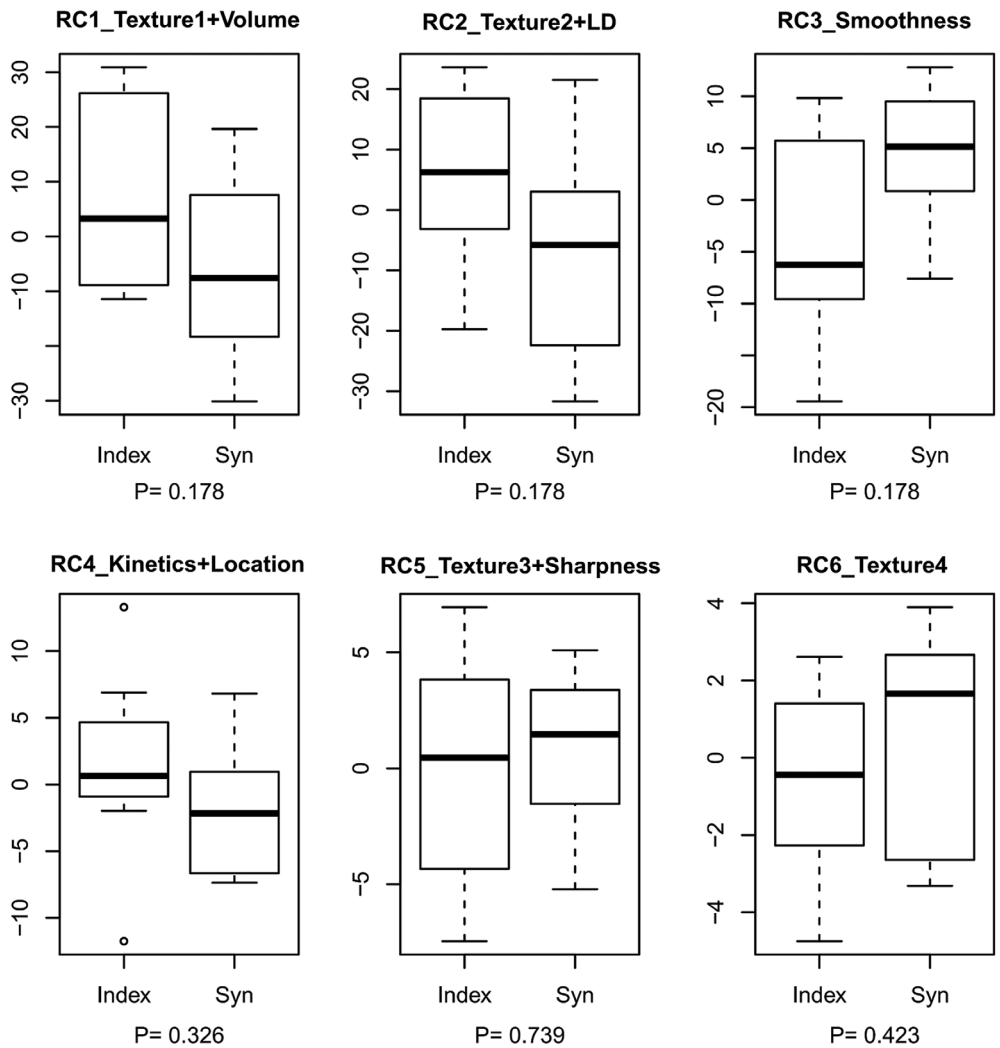

FIGURE 3: MRI phenotype of breast cancer (expressed in quantitative component score) (y-axis) for the index breast cancer and contralateral synchronous cancer (x-axis) (RC, rotated component; Syn, synchronous breast cancer; Index, index breast cancer).

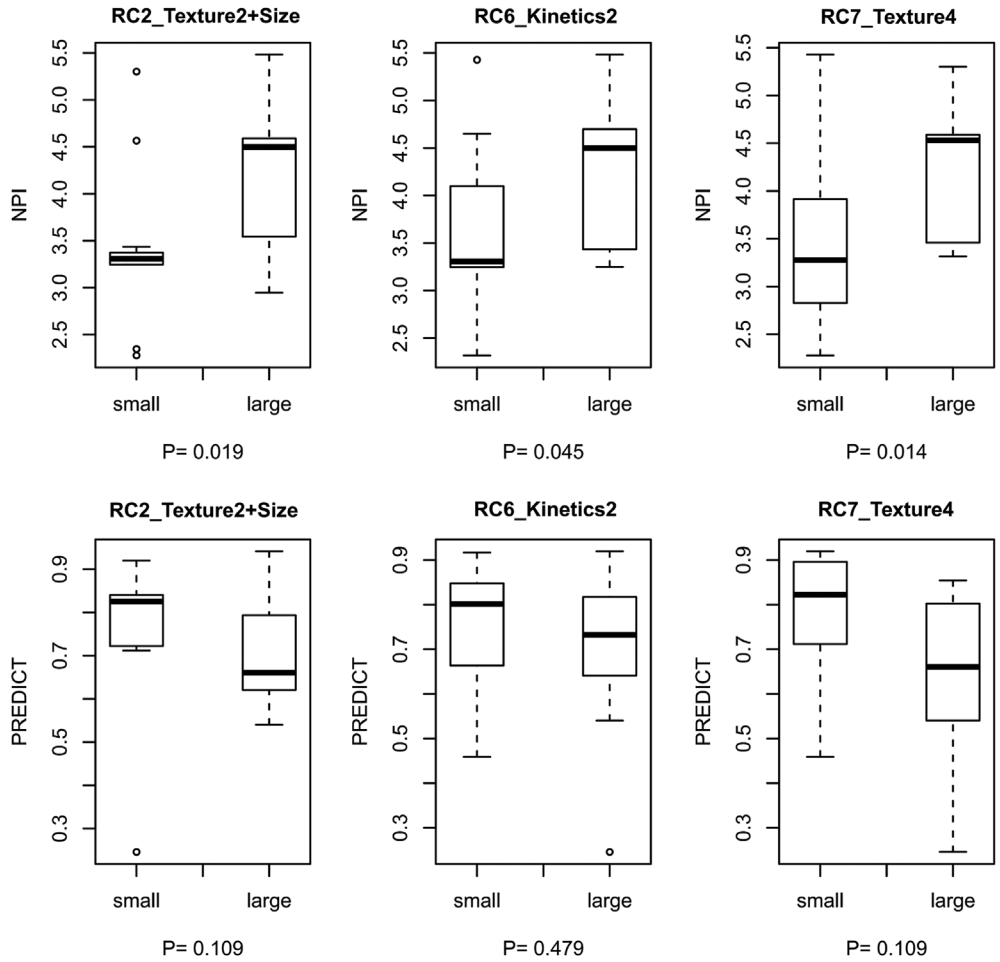

FIGURE 4: Association between phenotype difference (large and small group) with prognosis in terms of NPI and PREDICT score (NPI, Nottingham Prognostic Index). *P* value indicates the significance of Wilcoxon rank sum test (RC, rotated component; small, 1st Tertile phenotype difference; large, 3rd Tertile phenotype difference).

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

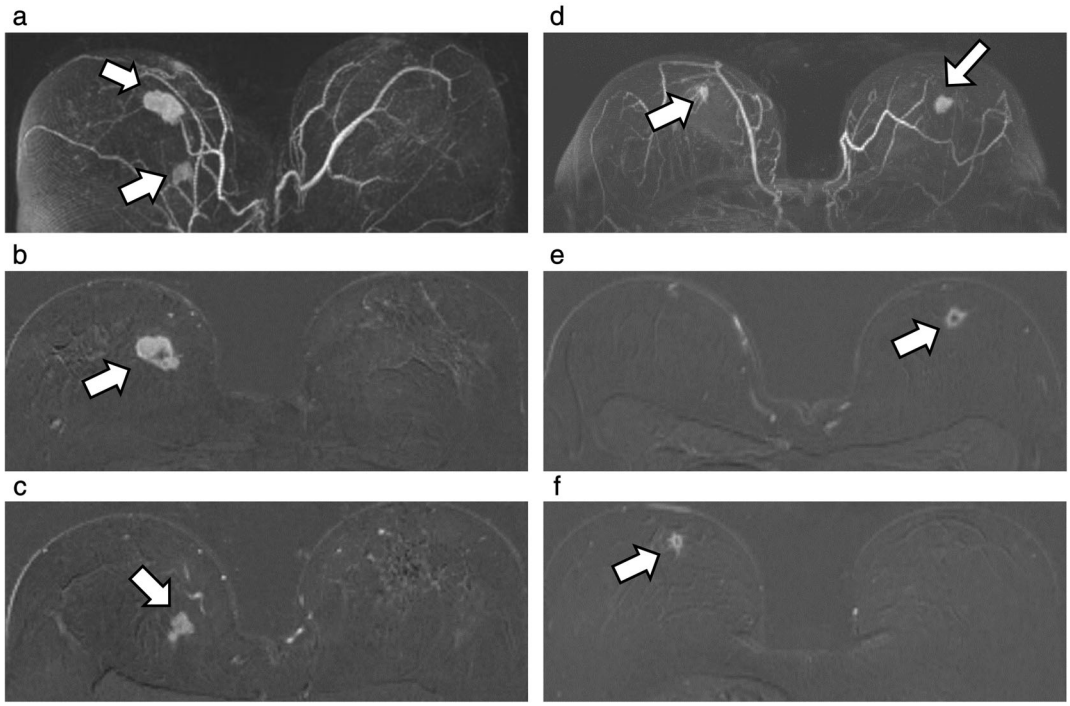

FIGURE 5: The top row shows the maximum intensity projection, the middle row shows the index breast cancer, and the third row shows the synchronous cancer. (a–c) Index breast cancer and ipsilateral synchronous breast cancer in DCE-MRI. Patient A, 52 years old; largest diameter of index cancer and ipsilateral synchronous cancer were 28 mm and 20 mm, respectively. Nottingham Prognostic Index is 4.56, and PREDICT score is 73.2% (10-year survival probability), which indicated that Patient A has a relatively bad prognosis. (d–f) Index breast cancer and contralateral synchronous breast cancer in DCE-MRI. Patient B, 61 years old, largest diameter of index cancer and contralateral synchronous cancer were 14 mm and 12 mm, respectively. Nottingham Prognostic Index is 3.28, and PREDICT score is 87.6% (10-year survival probability), which indicated that Patient B has a relatively good prognosis.

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			PREDICT		
	1st Tertile	3rd Tertile	*P*	1st Tertile	3rd Tertile	*P*
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.[6,35] 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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