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Correlation study between the magnetic resonance imaging features of breast cancer and expression of immune molecular subtypes

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Abstract. – OBJECTIVE: To investigate the correlation between breast cancer magnetic resonance imaging features and immune molecular subtypes.

PATIENTS AND METHODS: A total of 129 breast cancer patients were selected as the research object. All the patients were diagnosed by histopathology. All of them had breast magnetic resonance imaging and examination data of immunohistochemical (IHC) ER, PR, HER-2, and Ki-67. The correlation of breast cancer magnetic resonance imaging features with different immune molecular subtypes was retrospectively analyzed.

RESULTS: Breast cancer is divided into different molecular subtypes. There were 72 cases with Luminal A type (55.81%), 20 cases with Luminal B type (15.50%), 14 cases with HER-2+ type (HER-2 type for over-expression) (10.85%), 23 cases with TNBC type (ER, PR and HER-2 were negative) (17.84%). The magnetic resonance imaging features of breast cancer were included, the post-enhanced morphology, margins, internal enhancement features, time-signal intensity curve (TIC) and molecular subtype expression of lesions were significantly correlated with the immune molecular subtypes (C=0.602, 0.439, 0.350 and 0.407, *p*=0.000, 0.000, 0.006 and 0.000). Lesion morphology: Luminal A type was mainly oval, accounting for 76.39% (55/76). Luminal B type and HER-2+ type was mainly irregular, accounting for 75.00% (15/20) and 64.29% (9/14) respectively. TNBC type was mainly shown as lobulation, accounting for 60.87% (14/23). Margin of the lesion: Luminal A type was mainly smooth margin, accounting for 73.61% (53/72). Luminal B type and TNBC type was mainly irregular margin, accounting for 70.00% (14/20) and 56.52% (13/23) respectively. The margin of HER-2+ type was mainly spiculation, accounting for 64.29% (9/14). The internal enhancement features: Luminal A type were mainly even enhancement, accounting for 62.50% (45/72). Luminal B type and HER-2+ type were mainly heterogeneous enhancement, accounting for 65.00% (13/20) and 64.29% (9/14) respectively. TNBC type was mainly annular enhancement, accounting for 73.91% (17/23). TIC type: Luminal A type was mainly Type II, accounting for 66.67% (48/72). Luminal B, HER-2+ type and TNBC type was mainly Type III, accounting for 70.00% (14/20), 64.29% (9/14) and 60.87% (14/23) respectively. The clinical signs include painless breast lumps, bloody breast discharge, and orange peel-like skin changes, nipple retraction and nipple elevation. There is no significant correlation between the above signs and the expression of molecular subtypes (C=0.014, 0.129, 0.154, 0.097 and 0.057, *p*=0.999, 0.533, 0.447, 0.747 and 0.935 respectively), the difference is not statistically significant (*p*>0.05).

CONCLUSIONS: The characteristics of breast cancer magnetic resonance imaging was certainly correlated with the expression of immune molecular subtypes. The breast cancer molecular subtypes can be predicted by the imaging signs, which can provide valuable information for preoperative neoadjuvant treatment of breast cancer.

Key Words:
Breast cancer, Magnetic resonance, Molecular subtypes, Correlation.

Introduction

Breast cancer is one of the most common malignant tumors in women. The incidence accounts for more than 20% of all female cancers, which is an important cause of cancer death among women[1-3]. The incidence of breast cancer

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has increased year by year, shown as a younger trend[4,5] that it is seriously threatening the health of women. The pathogenesis of breast cancer is not yet clear. It is closely related to some high-risk factors, such as age, family history, early menarche, late menopause, unmarried status, nullipara, and mutant genes related to breast cancer[6]. Imaging examination is an important method for the diagnosis of breast cancer. Among them, magnetic resonance examination is more and more frequently used in clinic for its high sensitivity and no radiation. In the past, breast cancer was mainly treated by surgical methods based on imaging performance. In recent years, with the development of molecular biology, the endocrine therapy and targeted drugs begin to play extremely important roles in the treatment of breast cancer. Estrogen Receptor (ER), Progesterone Receptor (PR), and epidermal growth factor receptor (HER-2) are closely correlated with the biological behavior of breast cancer[7]. The biological behavior of breast cancer is determined by the expression of breast cancer-related oncogenes, and the related imaging performance is based on pathological changes. Therefore, there must be a certain correlation among molecular biology, histopathology and imaging performance of breast cancer[8-10]. It is always an important direction of breast cancer research to predict the molecular subtypes through the imaging characteristics of breast cancer, in order to evaluate and guide the clinical treatment of breast cancer. If the subtypes of breast cancer-related immune molecules can be preliminarily estimated by imaging signs before surgery, the prognosis and biological development direction of the patient can be roughly understood. Therefore, the best treatment scheme aimed at these indicators can be made for the patient before surgery or chemotherapy. The correlation between the magnetic resonance imaging features of breast cancer and the expression of tissue molecular subtypes in 129 cases were retrospectively analyzed in this study, which intended to provide a certain foundation for prognosis prediction.

Patients and Methods

A total of 129 patients with breast cancer was collected as the research objects. They were diagnosed by biopsy or post-surgery histopathology and admitted to our hospital from January 2016 to December 2018. All patients were women aged 31-78 years old, with average age as (51.23±12.67) years old. All the tumors were located in unilateral mammary glands. There were 66 cases on the left breast and 63 cases on the right breast. Pathological tissue type: there were included 91 cases with invasive ductal carcinoma, 14 cases with carcinoma *in situ*, 7 cases with mixed carcinoma, 5 cases with mucinous carcinoma, 12 cases with invasive lobular carcinoma. There were 58 cases before menopause and 71 cases after menopause. Inclusion criteria: (1) All subjects underwent breast magnetic resonance imaging examination before treatment, diagnosed as mass-like enhancement lesions, with complete immunohistochemical ER, PR, HER-2 and Ki-67 examination information and classification information of molecular subtypes. (2) All of the patients had not received anti-tumor and endocrine treatment before visiting our hospital. (3) All subjects had the right to know about the case collection and signed a written consent form, which had been reported to the Hospital Ethics Committee for approval (Yyllhao: 20151201). Exclusion criteria: (1) Patients who had contraindications for MRI examination, such as placing a pacemaker, indwelling artificial metal joints, pregnancy and so on. (2) Patients who had non-tumor MRI-enhanced lesions. (3) Patients who had bilateral multiple breast cancer. (4) Patients who had incomplete research data.

MRI Examination

Signa EXCITE 3.0T magnetic resonance imaging system produced by GE Medical Systems was used for MRI, with a surface coil dedicated to breast. Before the test, the imaging physician could introduce the inspection precautions to keep the patient calm and avoid motion artifacts. During the examination, the patient took prone position, with soundproof headphones placed on both ears, and bilateral breasts were naturally perpendicular to the coil hole. During the scan, the patients should breathe calmly. Flat scan was performed first, following T1-Weighted Imaging (T1WI) scan. The single excitation fast spin echo (FSE) scan was performed at the transverse position, TR=660 ms, TE=6.9 ms and matrix as 384×224, with 2 times of excitation. Short Tau Inversion Recovery (STIR) scan was performed at the transposition position, TR=5020 ms, TE=42 ms and the matrix as 320×192, with 2 times of excitation. The bilateral sagittal T2 Weighted Imaging of breast (T2WI) + Fat Suppression (FS)

sequence scanning was performed in parallel, TR=3800 ms, TE=75 ms and matrix as 256×192, with 2 times of excitation. Gd-DTPA contrast agent was injected through the elbow vein for enhanced scanning, with 0.1 mmol/kg of contrast agent and the injection rate as 3.0 mL/s. After injection of contrast agent, a total of 6 stages were scanned. The total scan time was about 8 min. The scanning range included the bilateral breast tissue, corresponding level of the front of the rib cage and axilla. Digital subtraction was performed while scanning. Those images were transferred to GE ADW4.2 workstation for image analysis.

Image analysis: MRI images were reviewed by two highly qualified imaging physicians. When their opinions were not the same, they should organize a discussion and reach an agreement. According to the American College of Radiology Breast Imaging Report and Data System (ACR BI-RADS), the observation and classification diagnosis of the second enhanced image was performed after enhancement[11]. Tumor-like strengthening morphology included round/oval, lobulated and irregular shape. Margins included smooth, irregular and spiculation. Internal strengthening included even, heterogeneous, margin or annular strengthening.

Lesion Time-signal Intensity Curve (TIC): the Region of Interest (ROI) was set to draw the TIC in the most evident regions of lesion enhancement, with the voxels of interest region≥5. TIC was drawn and divided into three types: Type I (inflow type), Type II (platform type) and Type III (outflow type), as shown in Figure 1.

SP Immunohistochemistry (IHC) Method for ER, PR, HER-2 and Ki-67 Examination

ER, PR, HER-2 and Ki-67 antibodies and SP kits were purchased from Fuzhou Maixin Biotechnology Development Co., Ltd. The positive and negative controls was set up, with the known positive slices as positive controls, and PBS instead of primary antibodies as negative control. The operation strictly followed the instructions of the kit, and the quality control met the requirements.

The specimens of breast cancer tissue were fixed with 10% formaldehyde solution, embedded with paraffin, sliced as 5 μm thick, paved, dewaxed and examined by SP method. After completion, the specimens were checked under an optical microscope. The positive expression

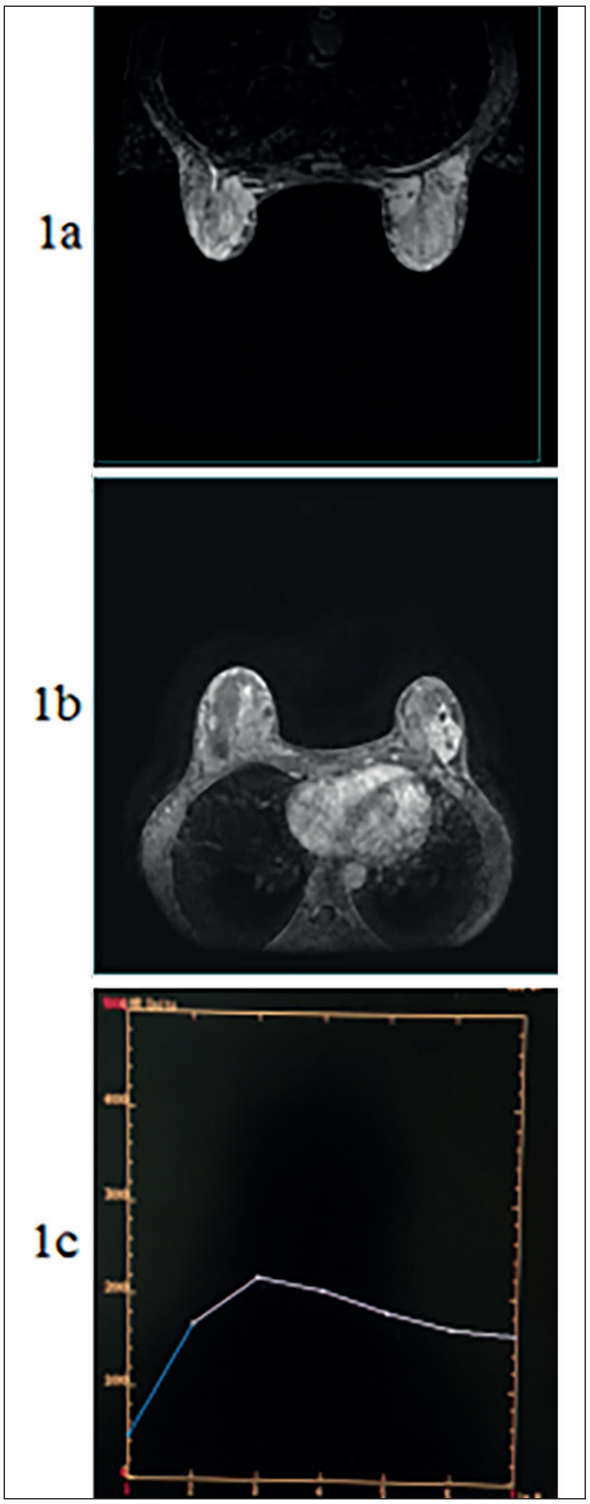

Figure 1. MRI image of breast: female for 51 years old. The left outer mammary gland of the left breast showed a mass with irregular shape and a regular margin **(A, B)**, which was significantly enhanced after dynamic enhancement, with the heterogeneous internal enhancement. The TIC was shown as type III in Figure 1c. What MRI reminded was: BI-RADS 5.

of ER, PR and Ki-67 localized the nucleus, which was brownish yellow particles. The positive expression of HER2 was localized on the cell membrane, which was brownish yellow. The judgment standard of Immune histochemical (IHC) results were[12]: ER, PR positive tumor cell nucleus ≥1% was judged as positive, while those <1% was judged as negative, as shown Figure 2A and Figure 2B. The judgment criteria of IHC result for HER-2: (-) and (+) was judged as HER-2 negative, (+++) was judged as HER-2 positive, as shown Figure 2C; (++) need to be further tested by FISH method, gene amplification was judged as HER-2 positive, otherwise it was negative. Ki-67 was positively expressed on the nucleus, and the percentage of positive cells was evaluated, as shown in Figure 2D.

The breast cancer was divided into 4 molecular subtypes[13] based on the expression of ER, PR, HER-2 and Ki-67: Luminal A type: ER+ and/or PR+, HER-2-, Ki-67≤14%; Luminal B/HER-2- type: ER+ and/or PR+, HER-2-, Ki-67>14%; Luminal B/HER-2+ type: ER+ and/or PR+, HER-2+, any Ki-67; HER-2 over-expression types: ER- and PR-, HER-2+. The triple negative breast cancer (TNBC): ER, PR and HER-2 were all shown as negative.

Evaluation

We retrospectively evaluated the value of MRI-enhanced imaging features of preoperative breast cancer lesions in predicting breast cancer immune molecular subtypes according to the preoperative MRI enhancement morphology. The imaging features include breast cancer lesions (round/ovate, lobulated and irregular), edges (smooth, irregular and burrs), internal enhancement (uniform, uneven and circular), lesion time-signal intensity curve (TIC) (type I – inflow type, type II – platform type, type III – out-

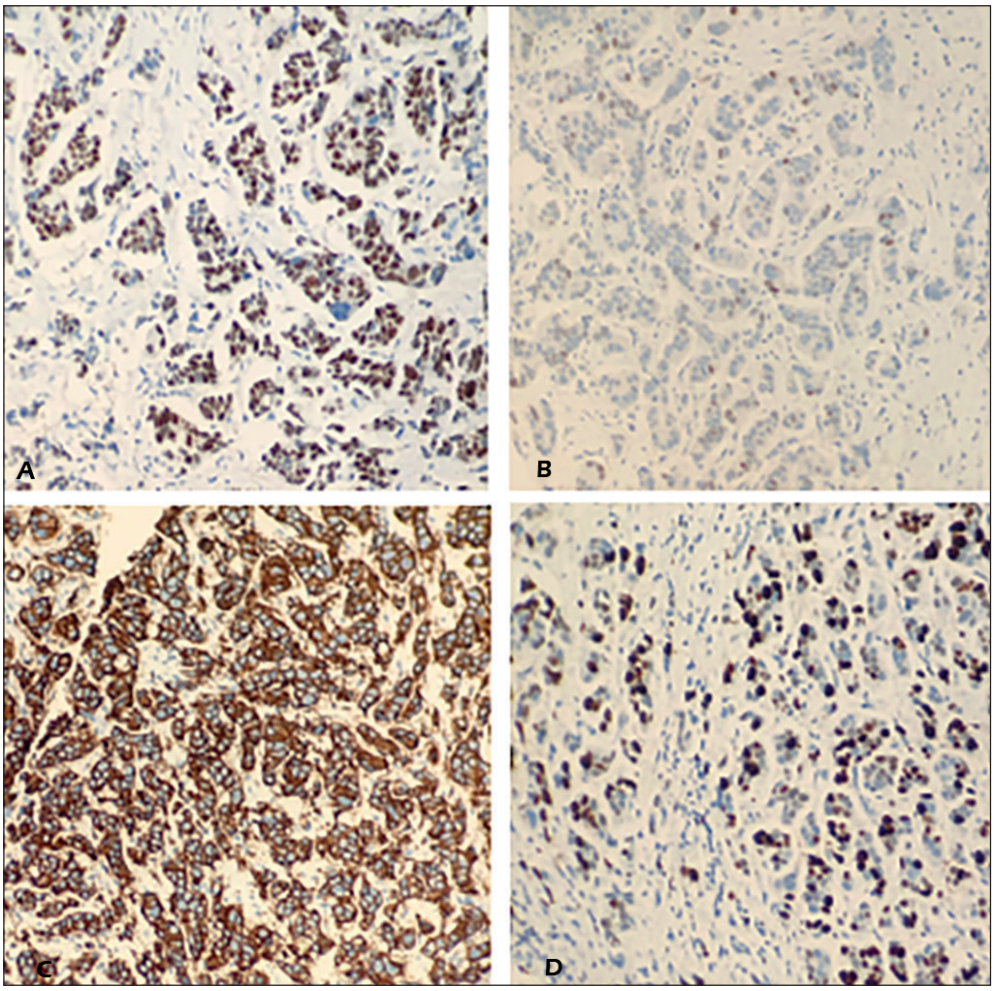

Figure 2. Female for 51 years old. Invasive ductal carcinoma of the left breast. Immunohistochemistry (×200). **A,** ER + (70% positive tumor cells). **B,** PR+ (5% positive cells). **C,** HER-2+ (+++). **D,** Ki-67 (40% positive tumor cells), immune molecular subtype: Luminal B/HER-2+ type.

flow type), accompanying clinical signs (painless breast mass, bloody breast discharge, orange peel skin changes, nipple retraction, nipple elevation). The postoperative pathological immunohistochemical ER, PR, HER-2, Ki-67 examination were used for correlation analysis with the above features.

Statistical Analysis

The Statistical Product and Service (SPSS) 23.0 (IBM Corp., Armonk, NY, USA) statistical software was performed for data processing. The x^2-test was used to compare the differences in MRI performance among all kinds of molecular subtypes. The cross-contingency table method was used to analyze the correlation between MRI image characteristics of breast cancer and molecular subtype, and to judge according to the contingency coefficient (C-value). $p<0.05$ was considered as statistically significance in difference.

Results

Comparison of Molecular Subtypes Distribution of Breast Cancer and Clinical Basic Characteristics

The immunohistochemistry of 129 cases with breast cancer were: 97 cases were ER-positive, while 32 cases were ER-negative; 78 cases were PR-positive, while 51 cases were PR-negative, 41 cases were HER-2 positive, while 88 cases were HER-2 negative. Molecular subtypes: there were 72 cases (55.81%) with Luminal A type, 20 cases (15.50%) with Luminal B type, 14 cases (10.85%) with HER-2+ type, and 23 cases (17.84%) with TNBC type. There was no statistical difference in age distribution and location distribution of breast cancer with different molecular subtypes ($p>0.05$), shown as Table I.

Correlation Between MRI Imaging Features and Molecular Subtypes in 129 Breast Cancer

The MRI imaging lesion enhancement morphology, margin, internal enhancement characteristics, TIC type were significantly correlated with breast cancer molecular subtypes (Luminal A type, Luminal B type, HER-2+ type, TNBC type) (C=0.602, 0.439, 0.350 and 0.407, p=0.000, 0.000, 0.006 and 0.000). The shape of the lesion: Luminal A type was mainly oval, accounting for 76.39% (55/76), x^2=90.125, p=0.000. Luminal B type and HER-2+ type were mainly irregular, accounting for 75.00% (15/20) and 64.29% (9/14), x^2=23.550 and 9.214, p=0.000 and 0.010 respectively, $p<0.05$. TNBC type was mainly lobulated, accounting for 60.87% (14/23), x^2=11.870, p=0.003, $p<0.01$. The margin of the lesion: Luminal A was mainly smooth margin, accounting for 73.61% (53/72), x^2=79.625, p=0.000. Luminal B and TNBC were mainly irregular margin, accounting for 70.00% (14/20) and 56.52% (13/23), x^2=18.600 and 8.739, p=0.000 and 0.013, p <0.05. HER-2+ type was mainly spiculate, accounting for 64.29% (9/14), x^2=9.214, p=0.010, $p<0.05$. Internal strengthening characteristics: Luminal A type was mainly uniform enhancement, accounting for 62.50% (45/72), x^2=46.625, p=0.000. Luminal B type and HER-2+ type were mainly heterogeneous enhancement, accounting for 65.00% (13/20) and 64.29% (9/14), x^2=14.550 and 10.500, p=0.001 and 0.005 respectively, $p<0.01$. TNBC type was mainly annular enhancement, accounting for 73.91% (17/23), x^2=27.130, p=0.000, $p<0.01$. TIC type: Luminal A type was mainly type II, accounting for 66.67% (48/72), x^2=60.125, p=0.000, $p<0.01$. Luminal B, HER-2+ type and TNBC type were mainly type III, accounting for 70.00% (14/20), 64.29% (9/14) and 60.87% (14/23), x^2=18.600, 10.500 and 12.652, p=0.000, 0.005 and 0.002, $p<0.01$, as shown in Table II and Table III.

Table I. Comparison on the molecular subtype distribution of breast cancer and clinical basic characteristics (n).

Typing / Clinical characteristics	Luminal A Type	Luminal B Type	HER-2 + Type	TNBC Type	χ^2	p
Age (years old)					4.071	0.254
≥ 50	46	16	12	17		
< 50	26	4	2	6		
Tumor location					1.308	0.727
	39	9	8	10		
	33	11	6	13		

Table II. Correlation analysis between breast cancer MRI image characteristics and immune molecular subtypes (n).

Molecular subtype	N	Shape					Margin				
		Oval	Lobulation	Irregular	χ^2	*p*	Oval	Lobulation	Irregular	χ^2	*p*
Luminal A Type	72	55	9	8	90.125	0.000	53	7	12	79.625	0.000
Luminal B Type	20	2	3	15	23.550	0.000	2	14	4	18.600	0.000
HER-2+ Type	14	2	3	9	9.214	0.010	2	3	9	9.214	0.010
TNBC Type	23	5	14	4	11.870	0.003	4	13	6	8.739	0.013
C			0.602						0.439		
p			0.000						0.000s		

Table III. Correlation analysis between breast cancer MRI image characteristics and immune molecular subtypes (n).

Molecular subtype	N	Internal enhancement feature					TIC Typing				
		Even	Heterogeneous	Annular	χ^2	*p*	Type I	Type II	Type III	χ^2	*p*
Luminal A Type	72	45	20	7	46.625	0.000	5	48	19	60.125	0.000
Luminal B Type	20	2	13	5	14.550	0.001	2	4	14	18.60	0.000
HER-2+ Type	14	1	9	4	10.500	0.005	1	4	9	10.500	0.005
TNBC Type	23	1	5	17	27.130	0.000	3	6	14	12.652	0.002
C			0.350				0.407				
p			0.006				0.000				

Table IV. Correlation analysis between clinical signs of breast cancer and immune molecular subtypes (n).

Molecular subtype	N	Painless breast lumps		Bloody breast discharge		Orange peel changes on skin		Nipple retraction		Nipple elevation	
		Yes	No	Yes	No	Yes	No	Yes	No	χ^2	*p*
Luminal A Type	72	41	31	32	40	21	51	12	60	9	63
Luminal B Type	20	11	9	6	14	5	15	4	16	2	18
HER-2+ Type	14	8	6	4	10	3	11	2	12	1	13
TNBC Type	23	13	10	9	14	8	15	6	17	3	20
C		0.014		0.129		0.154		0.097		0.057	
p		0.999		0.533		0.447		0.747		0.935	

There were no significant correlation between Luminal A type, Luminal B type, HER-2+ type, TNBC type and the clinical signs of painless breast lumps, bloody breast discharge, orange peel changes on skin, nipple retraction and nipple elevation (C=0.014, 0.129, 0.154, 0.097 and 0.057, p=0.999, p=0.533, 0.447, 0d747 and 0.935), the differences were not statistically significant (p>0.05), as shown in Table IV.

Discussion

Breast cancer is a heterogeneous disease with various imaging manifestations, histological and molecular biological typing, and corresponding disease progression[14]. Breast cancer occurs in breast epithelial tissues, mostly pathogeny in women, which is regulated by estrogen and progesterone[15,16]. With the development of molecular biology, the current treatment of cancer has gradually developed from the original cellular level to the molecular level[17]. ER and PR-positive breast cancer is a hormone-dependent tumor, which needs to be maintained by a specific hormonal environment for growth. When the targeted anti-hormonal drugs are administered, the receptor is inactivated so that the cancer tissue loses the ability to bind hormones, thereby inhibiting the growth of cancer cells. ER and PR-positive breast cancers are generally more differentiated, with slow development. They were mainly euploid, which have low hyperplasia scores and low probability of metastasis and recurrence. Conversely, the efficacy of anti-hormonal treatment is poor in patients with negative ER and PR[18,19]. HER-2 belongs to epidermal growth factor receptor, which is a proto-oncogene with the highest frequency of genetic abnormalities in breast cancer. Moreover, its overexpression suggests that the cells strong proliferation and strong invasiveness are positively correlated with high tumor tissue grade, lymph node metastasis, and late stage. According to statistics, HER-2 over-expression may occur in 15% to 25% of invasive breast cancers, and it is related to poor prognosis. However, the response to HER-2 targeted drugs is good[20]; the triple negative breast cancer (TNBC type) is sensitive to chemotherapy drugs[21]. In the current era of molecular typing therapy, there is marked difference in the clinical treatment response and survival of breast cancers among different molecular subtypes. Therefore, it is great significance to study the correlation between breast cancer imaging characteristics and molecular typing for the treatment scheme before surgery.

Breast MRI scan has high resolution of soft tissue, multi-azimuth and multi-parameter imaging. MRI enhanced scan has great advantages in observing morphology, margin, internal enhancement features and others, which is an important supplement of the ultrasound and molybdenum target X-ray examination[22]. MRI has a high sensitivity in the diagnosis of breast cancer[23]. At present, the correlation between breast cancer magnetic resonance imaging characteristics and immune molecular typing is a hotspot of research[24-26]. Different molecular subtypes were found among the 129 cases of breast cancer in this study. There were 72 cases with Luminal A type (55.81%), 20 cases with Luminal B type (15.50%), 14 cases with HER-2 over-expression type (10.85%), and 23 cases with TNBC type (17.84 %), which is basically consistent with the literature reported[27,28]. There is no statistical difference in age distribution and location distribution of breast cancer with different molecular subtypes (p>0.05).

In this study, the characteristics of breast cancer MRI imaging lesions have a significant correlation with immune molecular subtypes. Different imaging features corresponded to different molecular subtypes. According to the statistical analysis of MRI imaging lesion morphology, Luminal A type was mainly oval, accounting for 76.39% (55/76). Luminal B type and HER-2+ type were mainly irregular, accounting for 75.00% (15/20) and 64.29% (9/14), respectively. TNBC mainly showed lobulation, accounting for 60.87% (14/23). The different morphology of the lesion may be related to the different growth modes of the tumor[29]. Statistical analysis from the margin of the lesion: Luminal A type was mainly smooth, accounting for 73.61% (53/72). The endocrine treatment showed a good efficacy on Luminal A type of breast cancer. Luminal B type and TNBC type mainly showed irregular margins, accounting for 70.00% (14/20) and 56.52% (13/23), respectively. It may be related to the slow growth of the lesion and many fibrous components in histological. Kawashima et al[30] showed that most of HER-2+ type was spiculation, accounting for 64.29% (9/14), which may be related to the invasive growth mode of the tumor[31]. The internal enhancement modes of the tumor-like lesions were even, heterogeneous and

annular enhancement. Among the three modes, the internally lesions with even enhancement had the highest degree of differentiation and the lowest malignancy, while the internally lesions with annular enhancement had low degree of differentiation and high malignancy[31]. Jeh et al[32] showed that Luminal A type mainly showed even enhancement, accounting for 62.50% (45/72), indicating that Luminal A breast cancer had a high degree of differentiation and low malignancy. TNBC type mainly showed annular enhancement, accounting for 73.91% (17/23). The annular enhancement was mainly related to regional microvessel density of tumor margins, central necrosis, or increased fibrosis. Garimiella et al[33] reported that in the time-signal intensity curve, the benign lesions were mainly inflow type, breast cancer was mainly outflow type and platform type. In this study, Luminal A type was mainly Type II (platform type) 66.67% (48/72), while Luminal B type, HER-2+ type and TNBC type were mainly Type III (outflow type), accounting for 70.00% (14/20), 64.29% (9/14) and 60.87% (14/23) respectively.

To sum up, in recent years, some scholars[34,35] have analyzed the association between the MRI imaging features of breast cancer and its molecular subtypes, but there is little clear evidence for other subtypes except for triple-negative breast cancer. In this study, the MRI imaging characteristics of breast cancer and the expression of immune molecular subtypes have a certain trend according to the data distribution. The characteristics of Luminal A type are: the mass morphology shows oval by MRI enhancement, with smooth margin, internal even enhancement and IHC with Type II molecular subtypes. The characteristics of Luminal B type are: the mass with irregular morphology, irregular margins, heterogeneous internal strengthening and IHC with Type III molecular subtypes. The characteristics of TNBC Type are: the mass with morphology of lobulation shape, annular strengthening, IHC with Type III. The characteristics of HER-2+ type are: the mass margin with spiculation shape, heterogeneity strengthening and IHC with Type III. The above results indicate that MRI imaging features have certain guiding significance in distinguishing the molecular subtypes of breast cancer. Different immune molecular subtypes of breast cancer have different treatment plans and prognosis. Therefore, the immune molecular subtypes could be predicted based on the preoperative MRI imaging characteristics of breast cancer, so as to formulate treatment plans before surgery (including hormone therapy, neoadjuvant chemotherapy, and a chance for breast preservation) and provide a reference for judging the prognosis.

Conclusions

The MRI manifestations of different molecular subtypes of breast cancer are different, and there is a certain association between molecular subtypes and some MRI signs. Some MRI signs can predict the molecular subtypes of breast cancer, which can be used to determine the prognosis of breast cancer patients and initially determine the treatment plan. The preoperative endocrine and targeted drug therapy have high prospective guiding significance.

There are some limitations in this study. Only the mass-like strengthening lesions and immune molecular subtypes were selected for correlation analysis, without involved non-tumor-like enhanced lesions. In the future, the research in this field should be strengthened.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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