

Correlative Study on MRI Morphologic Features, Pathology, and Molecular Biology of Breast Cancer

Rong Chen
Shuigen Gong
Weiguo Zhang
Jinhua Chen
Shuangwu He
Baohua Liu
Zengpeng Li

Department of Radiology, Daping
Hospital, Third Military Medical
University, Chongqing 400042, China.

OBJECTIVE To investigate the correlation among MRI morphologic features, pathology, and molecular biology of breast cancer.

METHODS MRI was used to analyze the morphologic features of breast cancers of 78 patients before operation. The mastectomy specimens of the breast neoplasms were immunohistochemically stained, and the expression of the estrogen (ER), progesterone receptor (PR), C-erbB-2, P53, and the distribution of microvessel density (MVD) measured. The pathologic results were compared with the MRI features.

RESULTS Among the 80 breast cancers, ER positive expression was positively correlated with the spicular contour of breast cancers ($P < 0.01$), while showing a significant inverse correlation with the T-stage ($P < 0.05$). C-erbB-2 and P53 positive expression were positively correlated with the necrotic center of the cancers ($P < 0.05$). The expression of PR was not significantly correlated with the spicular contour, obscure margin, necrotic center, and T-stage of these cancers ($P > 0.05$). Among 41 breast cancers examined with dynamic contrast enhanced MR, there was a positive correlation between the spatial distribution of the contrast agent and MVD ($P < 0.01$).

CONCLUSION To a certain extent there is some correlation among the MRI morphologic features, pathology, and molecular biological factors in breast cancer. The biological behavior and prognosis of breast cancer can be assessed based on MRI features.

KEYWORDS: breast neoplasm, magnetic resonance imaging, pathology, molecular biology.

Breast cancer, which has increased in incidence in recent years, is one of the most common malignant tumors in women. Its molecular biological markup determines its biological behavior and histopathological changes which produce features that can be displayed on images. The development of modern molecular biology provides a potential for developing correlations between genetic expression and medical imaging.^[1-3] We compared MRI features of breast cancer with its pathology and molecular biology, and studied their correlations in order to employ MRI to assess the biological behavior and prognosis of breast cancer patients.

MATERIALS AND METHODS

Received August 22, 2004; accepted
December 31, 2004.

Chinese Journal of Clinical Oncology
E-mail: 000R@ayon.com Tel(Fax): 86-22-2352-2919

Cases

From October 2000 to May 2002, 80 tumors in 78 patients (female 76, male 2; ages 28-78, average age 47) were examined by MR preoperation and verified pathologically as primary breast cancer. They were comprised of 71 infiltrating ductal carcinomas, 4 infiltrating lobular carcinomas, 2 mucinous adenocarcinomas, 1 papillary adenocarcinoma, 1 neuroendocrine carcinoma, and 1 adenoid cystic carcinoma. The patients received no anticancer therapy prior to their scanning.

Techniques

A Siemens 1.0T supraconducting MR scanner and bilateral surface coil for breasts were used. The patients lied prone on a bed and bilateral breasts were suspended in the coil. The conventional sequences were as follows: T₁WI of SE (TR 580 ms, TE 15 ms), T₂WI of TSE (TR 4250 ms, TE 90 ms), T₁W fat suppression imaging of FLASH (TR 500 ms, TE 8 ms, Flip angle 90°), T₂W fat suppression imaging of TSE (TR 4000 ms, TE 119 ms). After the cancers were found on a plain scan, contrast enhancement MR was performed with Gd-DTPA injected intravenously (0.1mmol/kg). Thirty-nine patients received static contrast enhancement and 41 dynamic contrast enhancement.

Observation indexes of MRI

Morphologic features on MRI

The features included the contour (smooth, lobulate, spicular and irregular), margin (obscure, obscure partly and well-defined), density (homogenous or heterogenous).

Staging of breast cancer

T-staging of these patients was designated T₁, T₂, T₃, and T₄, according to TNM staging criteria^[4] constituted in combination with the American Joint Committee on Cancer and International Union Against Cancer in 1988.

Measurement of signal intensity

The slice was found that showed the cancer optimally and maximally with the statistics of our MR workstation. Then the region of interest (ROI) was set in the same slice on each time point during a dynamic scan. All of the 41 cancers that were examined with dynamic contrast enhanced MR were measured respectively in the center (the internal 1/4 part of the tumor body, avoiding hemorrhage and necrosis), periphery (the peripheral 1/4 part of the tumor body), and surrounding tissue (2 cm apart from the tumor border).

The early phase enhancement rate of signal intensity (ΔSI) was calculated with the 1st image after administration of Gd-DTPA. The formula was as follows:

$$\Delta SI(\%) = (SI_c - SI) / SI \times 100\%$$

(SI, the signal intensity before contrast enhancement; SI_c, the signal intensity after contrast enhancement.)

Collection and staining of the specimens

The lesions on the breast were marked preoperatively and the fresh breast cancer specimens were collected during the operation. The tissues were fixed in 10% formaldehyde, dehydrated, immobilized with dimethylbenzene, and imbedded in paraffin and subjected to HE and immunohistochemical staining.

For the immunohistochemical staining, antibiotin-biotin-peroxidase compound (ABC stain) was used. The first antibodies used were for the estrogen receptor (ER), progesterone receptor (PR), C-erbB-2, P53 mono-clonal antibody, and factor VIII-related antigen (VIII Rag). All of these reagents were purchased from the Beijing Zhongshan Biotechnology Co., LTD. For negative controls, PBS was used instead of the first antibody.

The evaluation of results: The expression of the antigens by the tumor cells was determined microscopically. (1) ER and PR: ER and PR were positively expressed in the nuclei of the cancer cells, which were stained with brown-yellow granules. Positive expression was defined when 25% of the nuclei were stained. (2) C-erbB-2: Positive expression was defined when 25% of the membranes were stained with a brown-yellow color. (3) P53: Brown-yellow

granules were expressed in the nuclei and positive expression was defined when more than 10% of the nuclei had definite staining. (4) Microvessel density (MVD): The expression was in the cytoplasm and membranes of vascular endothelial cells. Both single or clusters ($< 40 \mu\text{m}$) of endothelial cells were counted as a microvessel, which were well-defined and stained brown-yellow or brown by VIII — Rag. After viewing the whole section with a low power lens ($\times 40$) and finding the areas of dense microvessels (“hot spot”), 3 “hot spots” were selected respectively in the center, periphery, and surrounding tissue and the microvessels in one field of view were counted under a high power lens ($\times 200$). The average microvessels number in these spots was the MVD calculated from the respective regions.

Statistical analysis

Statistical analyses were performed using SPSS software. χ^2 tests, analysis of variance and correlation analysis were used respectively. Significance was accepted at a value of $P < 0.05$.

RESULTS

The morphologic features on MRI

The main features of the breast cancers that were observed using MRI were contours, margins, and internal structures. The contours of the breast cancers were revealed clearly in the fat suppression sequence, especially T_1 WI of FS. Out of the 80 cancers, 43 had spicular contours (53.8%), 29 were irregular contours (36.3%), and 8 were lobulate contours (10.0%). T_1 WI of SE showed the margins clearly. There were 63 (78.8%) cancers in which the margins were obscure and could not be distinguished from the surrounding tissue; 12 (15.0%) margins were clear, and 5 (6.3%) margins were partly obscured. As for the internal structure, 92.5% (74/80) of the cancers showed heterogenous signals, which showed a lower or higher signal intensity on T_2 WI, TSE T_2 WI or FS T_2 WI. After using the contrast medium, the enhancement was also heterogenous. A necrotic focus was found in 41 cancers (51.3%), showing a long T_1 and long T_2 signal

intensity. There was no enhancement in the necrotic focus. In summary, the main morphologic features of the breast cancers on MRI were spicular contour, obscure margin and necrotic center (Fig. 1, 2).

The sizes of the 80 cancers on MRI related to the pathologic results which were 18 cancers in T_1 , 31 in T_2 , 2 in T_3 , and 29 in T_4 . MRI also revealed that there were 46 patients with enlarged lymph nodes in the axillas on the affected side, while 49 axilla were verified pathologically. There were 5 patients with distant metastasis, 3 of which had lymphatic intumescence and metastasis in the homolateral supraclavicular fossa and 2 of which had multiple bilateral lung metastases.

Correlation between features on MRI and molecular biological indices

The correlation of the MRI-produced morphologic features and T-staging of the 80 cancers with the molecular biological indices is shown on Table 1.

Table 1. The correlation between features on MRI, T staging and molecular biological indices in 80 cancers (γ value)

Index observed	ER	PR	C-erbB-2	P53
MRI features				
Speculate contour	0.423 ^①	0.157	-0.133	-0.186
Obscure margin	-0.188	-0.192	0.112	0.127
Necrotic center	-0.177	-0.148	0.273 ^②	0.233 ^②
T staging	-0.248 ^②	-0.033	0.077	0.206

Note: χ^2 correlation analysis was used, with ^① standing for $P < 0.01$, and ^② for $P < 0.05$.

The correlation between features on MRI and the expression of EP and PR

Of the 80 cancers 42 showed positive ER expression (52.5%). The ER expression rate in spicular cancers was 72.1% (31/43), while the rate in non-spicular cancers was only 29.7% (11/37). Therefore ER expression had a positive correlation with the specular contour of the breast cancers ($\gamma=0.423$, $P < 0.01$) (Fig. 3), but there were no significant correlations with the obscure margin and necrotic center ($P > 0.05$). The positive ER expression rates of T_1 , T_2 , T_3 , and T_4

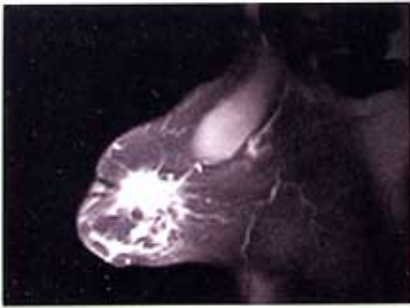


Fig.1. Cancer in the right breast. The sagittal image of FS T₂W showed the speculate mass in the right breast.



Fig.2. Cancer in the left breast. The axial image of contrast enhancement showed the non-enhancement region in the left breast cancer, which represented the necrosis.

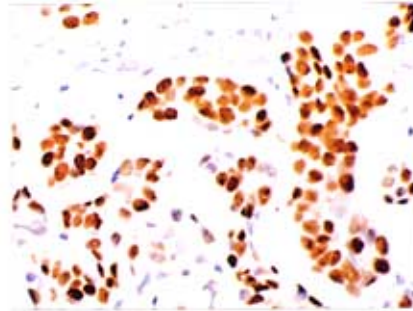


Fig.3. The same case as Fig.1. The ER expression was positive and the nuclei were brown-yellow (ABC× 400).

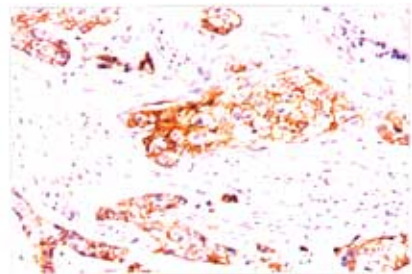


Fig.4. The same case as Fig.2. The C-erbB-2 expression was positive, and the cellular membranes were brown-yellow (ABC× 200).

cancers were 66.7% (12/18), 61.3% (19/31), 0, and 37.9% (11/29), respectively. The higher the designated T-staging, the lower the rate became. That is to say, the T-staging had a negative correlation with ER expression ($\gamma = -0.248, P < 0.05$). Additionally, ER expression in the surrounding tissues was negative.

There were 37 cancers that displayed positive PR expression (46.3%), but their PR expression failed to correlate well with the spicular contour, obscure margin and internal necrosis ($P > 0.05$). The positive PR rates of T₁, T₂, T₃ and T₄ tumors were respectively 50.0% (9/18), 45.2% (14/31), 50.0% (1/2) and 44.8% (13/29). These rates also showed no significant correlation with the T-stage ($P > 0.05$). PR expression in the surrounding tissues was all negative, too.

The correlation between features on MRI and C-erbB-2 expression

There were 27 cancers (33.8%) showing positive C-erbB-2 expression, 25 of which were infiltrating ductal carcinomas. The other 2 were mucinous adenocarcinoma and neuroendocrine carcinoma. The

positive rate of C-erbB-2 was 46.3% (19/41) in necrotic cancers, but 20.5% (8/39) in non-necrotic cancers. Therefore C-erbB-2 expression had a positive correlation with the presence of necrotic centers ($\gamma = 0.273, P < 0.05$) (Fig.4). However, C-erbB-2 had no significant correlation with the features of obscure margin and specular contour ($P > 0.05$). The positive rates in cancers from T₁ to T₄ were 22.2% (4/18), 38.7% (12/31), 50.0% (1/2), and 34.5% (10/29), respectively. The T-stage showed no obvious correlation with the C-erbB-2 expression ($P > 0.05$). C-erbB-2 expression in the surrounding tissues was all negative.

The correlation between features on MRI and P53 expression

There were 23 cancers (28.8%) in which P53 expression was positive. These were infiltrating ductal carcinoma, infiltrating lobular carcinoma, and neuroendocrine carcinoma. The positive expression rate of P53 in cancers which had internal necrosis was 39.0% (16/41), and 18.0% (7/39) in cancers with

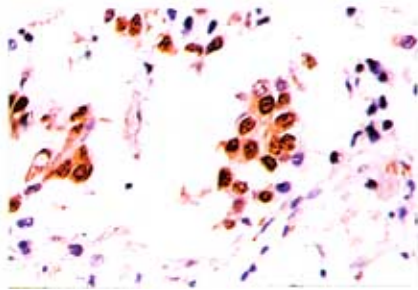


Fig.5. The same case as Fig.2. The P53 expression in breast cancer cells was positive and the nuclei were brown-yellow (ABC× 400).

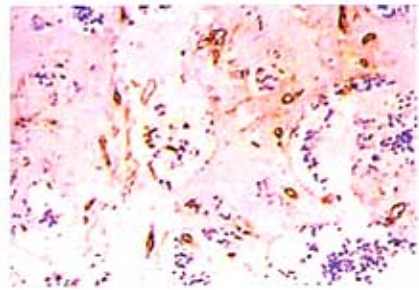


Fig.7. The same case as Fig.6. MVD was in the center and the vascular endothelial cells were brown-yellow (ABC× 100).

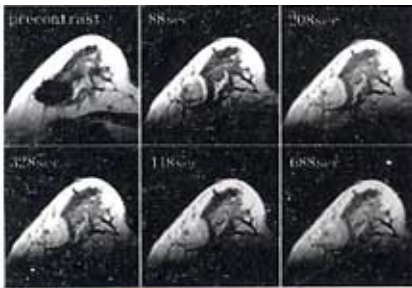


Fig.6. The infiltrative ductal cancer in the right breast. The axial image of dynamic contrast enhancement showed that the periphery of the cancer presented circular enhancement in early phase and ΔSI_{per} was higher than ΔSI_{cen} .

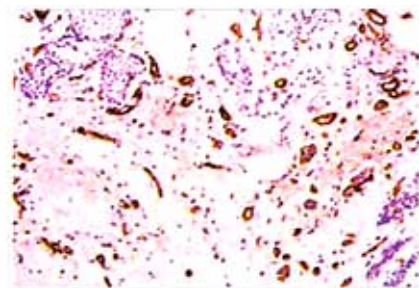


Fig.8. The same case as Fig.6. MVD was in the periphery and MVDper was higher than MVDcen (ABC× 100).

non-internal necrosis. So the P53 expression displayed a positive correlation with cancers having internal necrosis ($\gamma=0.233, P<0.05$) (Fig.5). But P53 had no significant correlation with the cancers showing an obscure margin and spicular contour ($P>0.05$). The positive rates in cancers from T1 to T4 were 16.7% (3/18), 22.6% (7/31), 100.0% (2/2), and 37.9% (11/29), respectively. These results suggest that T-staging has no correlation with P53 expression ($P>0.05$). P53 expression in the surrounding tissues was all negative.

Correlation between MVD and distribution of contrast medium during dynamic contrast enhanced MR

There were 41 breast cancers examined by dynamic contrast enhanced MR, including infiltrating ductal carcinoma (37 cases), infiltrating lobular carcinoma (2 cases), mucinous adenocarcinoma (1 case), and adenoid cystic carcinoma (1 case).

$\Delta SI_{per} > \Delta SI_{cen}$ was found in 29 cases (70.7%). The enhancement spread from the periphery to the center during a dynamic scan, and the peripheral enhancement was faster and more obvious than the

Table 2. The relation between ΔSI and MVD among center, periphery and surrounding tissue in 41cancers (x ± s)

Sites of breast cancer	$\Delta SI(\%)$	MVD(numbers/FOV)	Coefficient of correlation(γ)
Center	87.08 ± 18.18 ^①	54.59 ± 16.44 ^①	0.905 ^②
Periphery	92.73 ± 19.57	62.03 ± 14.41	0.823 ^②
Surrounding tissue	14.97 ± 8.69 ^①	11.49 ± 6.22 ^①	0.480 ^②
F	292.994	158.343	-

Note : Pearson correlation analysis was performed, and compared with periphery of cancer,^① stands for $P<0.01$, and ^②for $P<0.05$

center (Fig.6). The other 12 cancers (29.3%) showed $\Delta SI_{per} \leq \Delta SI_{cen}$ which displayed the whole enhancement or center enhancement. All the changes could be observed with macroscopy during a dynamic scan. The general ΔSI of the periphery was higher than that of the center, and the difference was significant ($P < 0.05$) according to the Least Significant Difference (LSD). Both ΔSI_{per} and ΔSI_{cen} were higher than ΔSI_{sur} in all cancers showing a significant difference ($P < 0.05$).

As for the MVD, 35 cancers (85.4%) showed $MVD_{per} > MVD_{cen}$, while 6 cancers (14.6%) showed $MVD_{per} \leq MVD_{cen}$. The general MVD of the periphery was higher than that of the center, and the difference was significant according to the LSD ($P < 0.05$) (Fig.7,8). Both the MVD_{per} and MVD_{cen} were higher than MVD_{sur} , and the difference was also significant ($P < 0.05$). The average MVD_{cen} and MVD_{per} of infiltrating ductal carcinoma were respectively $(55.8 \pm 17.3)/FOV$ and $(63.7 \pm 15.1)/FOV$, which was higher than that of infiltrating lobular carcinoma, mucinous adenocarcinoma, and adenoid cystic carcinoma, but the MVD_{per} and MVD_{cen} had overlapped in different histological types.

The correlation of contrast medium distribution during dynamic contrast enhancement and MVD is shown in Table 2. There was a positive correlation between the medium distribution and MVD in the center, periphery, surrounding tissue ($P < 0.01$), especially in the center ($\gamma = 0.905$) and periphery ($\gamma = 0.823$), which showed high positive correlations. Generally speaking, $MVD_{per} > MVD_{cen} > MVD_{sur}$, and $\Delta SI_{per} > \Delta SI_{cen} > \Delta SI_{sur}$ correspondingly. In other words, the MVD was higher, and the enhancement was more obvious.

DISCUSSION

To a certain extent the TNM staging, histological type and grading, lymph nodes, ER, PR, expression of C-erbB-2 and P53 can characterize the biological behavior and provide a prognosis for breast cancers.^[5] In theory, all the histopathological changes resulting

from the expression of genes and cellular factors can be imaged directly and indirectly. So the features produced by MRI must correlate with the histopathology and molecular biology.

The correlation among MRI features, pathology and molecular biology

Spicular contour

In this study, the spicular contour showed a positive correlation with ER expression, while no correlation was seen with PR, C-erbB-2 and P53 expression. Spicular contour is characterized by the short spicules radiating from the tumor to surrounding tissue seen upon histopathological examination. It represents hyperplasia of small ducts and surrounding fibrous connective tissue, which may be combined with infiltration of cancer cells. It is well known that a spicular contour is a typical sign of a malignant tumor, but its extent of malignancy is under dispute. As for the spicular contour in peripheral bronchogenic carcinoma, Peng et al.^[2] reported that tumors with spicules were highly malignant, while Liu et al.^[3] suggested that the spicules mainly resulted from a reaction of the surrounding interstitium, and did not always suggest high malignancy. Paradiso et al.^[6] studied 176 cases with infiltrating primary breast cancer and found the ER expression rates in spiculate tumors were higher than regular tumors. A spicular contour image suggested less infiltrating behavior and effective endocrinotherapy with a good prognosis. Lamb et al.^[7] suggested that a spicular contour was found mainly in tumors of a lower grade with less invasive ability. The reactive hyperplasia of the surrounding connective tissue may limit the invasion of cancer cells. Whether it is a protective mechanism in an early phase of tumor prognosis or not needs to be studied further.

Necrotic center

In this study, the positive expression rate of C-erbB-2 and P53 was higher in tumors with necrosis than those without necrosis resulting in necrosis having a positive correlation with expression of C-erbB-2 and P53,

while there was no correlation with expression of ER or PR. Since highly malignant breast cancers have rapid growth, the blood supply is inadequate and the tissue becomes necrotic. Some studies have shown^[8] that the grade of ductal carcinoma in situ with necrosis was higher than other cancers, and the biological behavior was more infiltrative. MR can clearly reveal tumor necrosis in vivo and evaluate the expression of C-erbB-2 and P53, so the biological behavior and prognosis can be analyzed.

Obscure margin

There were no significant correlations between an obscure margin and expression of ER, PR, C-erbB-2 or P53. From histopathology, a well-defined margin suggests distending growth, while an obscure margin represents infiltrative growth. On SE T₁WI of a plain scan, there was an obvious natural contrast between the surrounding fat tissue that shows a high signal and the tumor that shows a low signal. So the margin of the tumor was obscured partly or clear when the surrounding tissue was fat. However, the margin was often obscure when the surrounding tissue was mammary tissue. There were 3 cancers with a well-defined margin in the study, which microscopically showed the cancer cells invading the surrounding fat tissue. As a result, the location of a cancer should be considered when a correlation between the margin and a molecular biological index is analyzed.

Tumor T-staging

T-staging is based on the size of the primary tumor, and the degree of invasion of the local skin and chest wall. In our study, T-staging had a negative correlation with ER expression, but no significant correlation with PR, C-erbB-2 or P53 expression. From T₁ to T₄, the positive ER expression rates were 66.7%, 61.3%, 0, and 37.9%, respectively. That is to say, the possibility of ER expression became less with the enlargement of primary cancers and with the invasion of the local skin and chest wall, which suggested poor prognosis and no response to endocrinotherapy.

The correlation between MVD and distribution of contrast medium

In using dynamic contrast enhanced MR, the first-pass of the contrast medium through the tissue is very important for an early diagnosis of breast disease,^[9,10] because the enhancement is mainly related to the medium distribution in vasculature and there is the optimal contrast between the tumor and the parenchyma during this period. The absorption of contrast medium was heterogenous in breast cancers. In 70.7% of the tumors the periphery enhancement was greater than the center in this study, and enhancement of the periphery was faster and higher. Additionally the enhancement of the surrounding tissue was lower than that of both the center and periphery of the tumors. The general MVD of the periphery was much higher than that of the center and surrounding tissue; so there was a significant correlation between distribution of medium and MVD. From the histopathology, the cells in the periphery proliferate actively and the interstitium is abundant, so the density of microvessels is greater and the permeability increases, which results in an obvious early phase enhancement of the periphery. Because of secondary changes such as hemorrhage, cystic degeneration, necrosis and matrix fibrosis, the microvessel density of center was lower, so the enhancement is delayed or even not obvious. The surrounding tissue was mainly mammary tissue with atypical hyperplasia, adenopathy, cyst, and ductal dilation, but the microvessels were much lower than in the center and periphery of the tumors.

Peripheral enhancement is a specific sign of breast cancer. The relationship between peripheral enhancement and angiogenesis of tumors is a topic of current interest.^[11,12] Some authors have reported^[12-14] that the high microvessel density was the main cause of peripheral enhancement in dynamic contrast enhanced MR. Dynamic contrast enhanced MRI is a noninvasive method, which can show the vessel activity, and suggest general changes of cancers and reflect the characteristics of anatomy and physiology. Quantitative studies of correlations between the distribution of medium and MVD have been rare. In

our study, the distribution and the degree of microvessel development could be inferred from the early phase enhancement and distribution of the medium, which suggested the characteristics of tumor growth and blood perfusion. But the percentage of tumors that displayed greater ΔS_{Iper} than ΔS_{Icen} on MRI was lower than the percentage of tumors in which MVD_{per} was greater than MVD_{cen} from histology. It may result from other factors apart from MVD, such as vascular growth factor and the pressure gradient in the tumor. [15,16].

In a word, the comparative study of the morphologic features on MRI with the pathology and molecular biology showed that the features on MRI showed correlations with the expression of ER, C-erbB-2 and P53, but the correlative coefficient was small and the sensitivity was low. However, there was high a correlation between MVD and medium distribution, and the distribution of contrast medium in the early phase after its administration significantly reflected the characteristics of MVD distribution. Breast cancer features on MRI can point to the perfusion and biological behavior of the cancer and suggest a prognosis for the cancer patient. It is important for therapy selection and follow-up in producing a curative effect.

REFERENCES

- Pan P, Liu AL, Song QW, et al. Correlation of MR imaging characterizations and histologic microvessel density in hepatocellular carcinoma. *Chin J Radiol.* 2002; 36:420–424.
- Peng XB, Lin YQ, Luo YH, et al. The correlation between CT appearance and the structure and abnormal expression of P53 gene in peripheral lung cancer. *Chin J Med Imaging.* 2000; 8:210–212.
- Liu JK, Zeng JZH, Zhou JH. Study on the correlation between CT appearance and DNA contents in peripheral lung adenocarcinomas and squamous-cell carcinomas. *Chin J Radiol.* 1996; 30:15–19.
- Sobin LH, Hemanek P, Hutter RV. TNM classification of malignant tumors. A comparison between the new (1987) and the old editions. *Cancer.* 1988; 61:2310–2314.
- Fizgibbons PL, Page DL, Weaver D, et al. Prognostic factors in breast cancer. College of American Pathologists Consensus Statement. 1999. *Arch Pathol Lab Med.* 2000; 124:966–978.
- Paradiso A, Mangia A, Barletta A, et al. Mammography and morphobiologic characteristics of human breast cancer. *Tumori.* 1993; 79:422–426.
- Lamb PM, Perry NM, Vinnicombe SJ, et al. Correlation between ultrasound characteristics, mammographic findings and histological grade in patients with invasive ductal carcinoma of the breast. *Clin Radio.* 2000; 55:40–44.
- Tan PH, Ho JT, Ng EH, et al. Pathologic-radiologic correlations in screen-detected ductal carcinoma in situ of the breast: findings of the Singapore breast screening project. *Int J Cancer.* 2000; 90:231–236.
- Sardanelli F, Rescinito G, Giordano CD, et al. MR dynamic enhancement of breast lesions: high temporal resolution during the first-minute versus eight-minute study. *J Comput Assist Tomogr.* 2000; 24:724–731.
- Esseman L, Hylton N, George T, et al. Contrast-enhanced magnetic resonance imaging to assess tumor histopathology and angiogenesis in breast carcinoma. *Breast J.* 1999; 5:13–21.
- Liu PF, Bao RX, Niu Y, et al. Angiogenesis and dynamic contrast enhanced MRI of benign and malignant breast lesions: preliminary results. *Chin J Radiol.* 2002; 36:967–972.
- Buadu LD, Murakami J, Murayma S, et al. Patterns of peripheral enhancement in breast masses: correlation of findings on contrast medium enhanced MRI with histologic features and tumor angiogenesis. *J Comput Assist Tomogr.* 1997; 21:421–430.
- Buadu LD, Murakami J, Murayma S, et al. Breast lesions: correlation of contrast medium enhancement patterns on MR images with histologic findings and tumor angiogenesis. *Radiology.* 1996; 200:639–649.
- Van Dijke CF, Brasch RC, Roberts TP, et al. Mammary carcinoma model: correlation of macromolecular contrast-enhanced MR imaging characterizations of tumor microvasculature and histologic capillary density. *Radiology.* 1996; 198:813–818.
- Matsubayashi R, Matsuo Y, Edakuni G, et al. Breast masses with peripheral rim enhancement on dynamic contrast-enhanced MR images: correlation of MR findings with histologic features and expression of growth factors. *Radiology.* 2000; 217:841–848.
- Wiig H, Tveit E, Hultborn R, et al. Interstitial fluid pressure in DMBA-induced rat mammary tumors. *Scand J Clin Invest.* 1982; 42:159–164.