Original Article

# Sentinel lymph node metastasis diagnosis using ultrasound plus magnetic resonance lymphangiography in breast cancer

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**Background:** Ultrasound diagnosis is a highly specific tool and widely applied, but is associated with low sensitivity in detection of sentinel lymph nodes (SLNs). The diagnostic value of routine ultrasound combining magnetic resonance lymphangiography (MRL) for the detection of SLNs in breast cancer metastasis is still unclear. This study used ultrasound combined with MRL to explore the diagnostic value of detecting SLN metastasis in breast cancer.

**Methods:** This study included female breast cancer patients who received modified radical mastectomy at the Department of Breast Surgery, the First Affiliated Hospital of Zhengzhou University between January 2016 and January 2019. The gold standard of SLNs is pathological results. The patients were divided into three groups: (I) Group A: an ultrasound plus MRL (contrast agent injected outside the areola) group; (II) Group B: an ultrasound plus MRL (contrast agent injection around the areola) group; and (III) Group C: an ultrasound plus MRL group (this group comprised patients from the two aforementioned groups).

**Results:** A total of 432 patients were included. The overall detection rate and overall diagnostic accuracy of SLNs in breast cancer differed significantly among the three groups (all P<0.05). Ultrasound plus MRL showed a best overall detection rate 56.02%, and a best diagnostic accuracy 95.83%. The detection rate and diagnostic accuracy of axillary SLNs varied markedly among the three groups (P<0.05). The detection rate and diagnostic accuracy when the internal mammary node was the SLN differed notably between the ultrasound plus MRL (contrast agent injected outside the areola) and ultrasound plus MRL (contrast agent injection around the areola) groups and between the ultrasound plus MRL (contrast agent injection around the areola) and ultrasound plus MRL groups (all P<0.05).

**Conclusions:** Ultrasound plus MRL may be advantageous for the detection of SLN metastasis in breast cancer and predicting breast cancer prognosis.

**Keywords:** Breast cancer; sentinel lymph nodes (SLNs); magnetic resonance lymphangiography (MRL)

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## Introduction

Breast cancer is one of the most common malignancies among women, with the highest rates of morbidity (1). Multiple factors contribute to the occurrence of breast cancer, and unhealthy modern lifestyles including the dietary consumption of high-fat and high-sugar foods and alcohol have further promoted the increased morbidity rates of this disease (2,3). Although several advancements in medical technology and improved patient awareness have reduced the occurrence and development of breast cancer, its mortality rate remains quite high (4). A long-term study conducted by the Kaiser Permanente Washington Breast Imaging Registry identified two peaks of entry into the breast cancer registry occurring at 40 and 50 years of age. In a global population-based cancer registry data analysis, the peak ages of breast cancer were found to vary. For instance, South Korea and Cameroon had the youngest peak age of incidence at 40 years; with China, Japan, Iran, Fiji, and Morocco peaking at 55–60 years. Western countries, including the USA, Belgium, Australia, and the UK had a peak age as late as 70 years (5,6).

At present, surgical resection is still the mainstay of breast cancer treatment (7). Axillary lymph node dissection is a crucial aspect of breast cancer treatment; however, it is associated with complications such as edema of the affected upper limb lymph node, dyskinesia, numbness, and postoperative pain (8), which has prompted doctors to seek better treatment solutions. The proposition of cleaning sentinel lymph nodes (SLNs) is promising (9). An SLN is the first lymph node affected by breast cancer cell metastasis. A study by the American Society of Surgical Oncology showed that the 3-year survival rate of patients after removal of the SLN did not significantly differ from that of patients after axillary lymph node removal; however, the incidence of cancer-related complications after SLN removal was lower, illustrating the importance of the SLN in breast cancer treatment (10).

Routine ultrasound is commonly used in SLN examinations and plays an important role in breast cancer patients with negative lymph node palpation. Ultrasound diagnosis is a highly specific tool but is associated with low sensitivity, and most breast cancer patients who have already developed SLN metastasis cannot benefit from it (11). Contrast-enhanced ultrasonography can significantly improve the accuracy of detecting SLNs in breast cancer. However, contrast agents can only observe the dynamic enhancement process of a specific section based on the site of injection and the results are easily affected by the subjective factors of the patient and the technical level of the testing doctor, thus greatly reducing the value of the test (12). Magnetic resonance lymphangiography (MRL) can perform multi-directional scanning of breast cancer SLNs; its results are reproducible and can be observed and analyzed by clinicians, and it is not affected by the subjective factors of the patient. MRL is a new magnetic resonance technology, which can completely and clearly display the physiological structure, lymph node morphology and lymphatic canal orientation of mammary gland. With convenient operation method, it is beneficial to the diagnosis of sentinel lymph node status. However, most current studies on the detection of SLN in breast cancer only focus on the axillary metastasis route, and very few studies have investigated the internal mammary node metastasis route. In addition, only some studies have investigated the effect of the contrast agent dose on the results of breast cancer detection, and even less research has investigated the diagnostic value of routine ultrasound combined with MRL for the detection of SLNs for breast cancer metastasis. We assumed that routine ultrasound combined with MRL could improve the accuracy of detecting SLN metastasis in breast cancer. In this study, we aimed to explore the diagnostic value of detecting SLN metastasis in breast cancer. We present the following article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-292/rc).

## Methods

### *Study design and subjects*

This diagnostic test study included female breast cancer patients who received modified radical mastectomy at the Department of Breast Surgery, the First Affiliated Hospital of Zhengzhou University, between January 2016 and January 2019.

Patients with breast cancer confirmed by puncture pathology and diagnosed according to the 2015 Breast Cancer Diagnosis and Treatment Guidelines and Regulations (13) were eligible for inclusion. The following patients were excluded from the analysis: (I) patients who were contraindicated for receiving magnetic resonance imaging (MRI), such as those with metal implants, claustrophobia, or allergy to contrast agents; (II) those with other tumors; (III) patients with confirmed SLN metastasis;

and (IV) patients who received systematic chemotherapy, surgery, or other treatments before enrollment. The standard diagnosis of SLN was based on pathological results.

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (No. 2020-KY-0133). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and all patients signed the informed consent.

### *Imaging examination*

All patients underwent routine ultrasound and MRL examinations. For patients who had not undergone the abovementioned examinations in the First Affiliated Hospital of Zhengzhou University, inspection reports and impact pictures from other hospitals were recorded (patient data from other hospitals were only included if they were from tertiary hospitals), and two physicians were selected to interpret the images and make a diagnosis.

The patients received a contrast agent injection at the 9 o'clock position outside of the areola and an injection of contrast agent around the areola. All patients underwent ultrasound (Toshiba SSA-270A and SSA-370A, Japan) and MRL examinations (Siemens 3.0 MRI, Germany). A total of 108 patients from the ultrasound plus MRL (contrast agent injected outside the areola) and ultrasound plus MRL (contrast agent injection around the areola) groups who received outside or inside injection were selected and placed into the ultrasound plus MRL group, whose ultrasound examination results were retrospectively collected.

The patient underwent a biopsy of the SLN during the operation, and a rapid intraoperative frozen pathological examination was performed. The tracer material was a nano-carbon suspension.

### *Data collection and definition*

The patients' ages, locations of breast cancer, distributions of the tumor on the left and right sides of the breast, the quadrants where the tumor was located, tumor sizes, tumor pathological types, numbers of metastatic lymph node vessels, long and short diameter measurements, and whether the lymphatic hilum disappeared were recorded. Patients with breast cancer metastasis were defined as pathological results, suggesting at least one cancerous SLN. The SLN biopsy criteria were used for the biopsy (14).

The calculated detection rate was the detected number of SLNs in patients with breast cancer divided by the total number of patients.

### *Statistical analysis*

The accuracy was defined as the number of true-positive patients with SLN metastasis + the number of true-negative patients divided by the total number of patients. The sensitivity was defined as the number of true-positive patients with SLN metastasis divided by the number of patients detected with SLN metastasis. The false-negative rate was defined as the number of false-negative patients with SLN metastasis divided by the number of patients detected with SLN metastasis. Statistical analysis was performed using the Statistical Package for Social Sciences version 21 (IBM, Armonk, NY, USA). The Shapiro-Wilk test was used for quantitative data, and one-way analysis of variance was used for data that conformed to normal distribution and homogeneity of variance. The Chi-square test or Fisher's test was used for categorical data, including comparison of accuracy. A two-side P value $<0.05$ was considered statistically significant.

## Results

A total of 455 people were initially enrolled in this study. Of these, five patients with contraindications to MRL examination, three patients with other tumor diseases, and 15 patients with confirmed SLN metastasis were excluded. Finally, 432 patients were included in this retrospective analysis. *Table 1* presents the general conditions of patients in each group. The patients' ages, locations of breast cancer, distributions of the tumor on the left and right sides of the breast, the quadrants where the tumor was located, tumor sizes, tumor pathological types, numbers of metastatic lymph node vessels, the long and short diameter measurements, and the presence or absence of the lymphatic hilum were not significant between the three groups (all $P>0.05$).

There were 216 cases in Group A, and SLN metastasis was detected in 118 (54.63%), of which 112 cases were true positive (94.92%) and six were negative (5.08%). There were 216 cases in Group B, and 121 cases had SLN metastasis (56.02%), of which 118 cases were true positive (97.52%) and three were negative (2.48%). Group C had 216 cases, and 43 cases had SLN metastasis (19.91%), of which 41 cases were true positive (95.35%) and two were negative (4.65%). The difference in the total detection rate

**Table 1** Comparison of the general conditions of patients in each group

| Variable | Group A (n=216) | Group B (n=216) | Group C (n=216) | P value |
|---|---|---|---|---|
| Age, years, mean ± SD | 49.38±4.92 | 50.02±4.91 | 50.00±5.14 | >0.05 |
| Distribution of tumor on both sides of the breast | | | | >0.05 |
| Left breast | 111 | 115 | 109 | |
| Right breast | 105 | 101 | 107 | |
| Quadrant where the tumor was located | | | | |
| Outer upper quadrant | 56 | 55 | 59 | >0.05 |
| Inner upper quadrant | 23 | 20 | 26 | >0.05 |
| Outer lower quadrant | 12 | 14 | 9 | >0.05 |
| Inner lower quadrant | 9 | 7 | 6 | >0.05 |
| Central area, entire breast | 12 | 14 | 9 | >0.05 |
| Other location | 14 | 16 | 17 | >0.05 |
| Tumor size (cm) (14) | | | | |
| ≤2 | 70 | 73 | 68 | >0.05 |
| 2–≤5 | 72 | 74 | 76 | >0.05 |
| >5 | 74 | 69 | 72 | >0.05 |
| Tumor pathological type | | | | |
| Invasive carcinoma | 191/25 | 187 | 188 | >0.05 |
| Microinvasive carcinoma | 6/210 | 9 | 9 | >0.05 |
| Ductal carcinoma *in situ* | 8/208 | 10 | 9 | >0.05 |
| Intraductal papillary carcinoma | 5/201 | 6 | 4 | >0.05 |
| Paget's disease | 4/212 | 2 | 3 | >0.05 |
| Other rare cancer | 2/214 | 2 | 3 | >0.05 |
| Detected metastasized SLN, mean ± SD | | | | |
| Average number | 3.40±1.14 | 3.31±1.1 | 3.39±1.17 | >0.05 |
| Long lymph-vessel diameter, cm | 1.83±0.33 | 1.80±0.34 | 1.82±0.33 | >0.05 |
| Length of short diameter, cm | 1.33±0.27 | 1.35±0.29 | 1.34±0.26 | >0.05 |
| Absence of lymphatic hilum | | | | >0.05 |
| Yes | 116 | 111 | 112 | |
| No | 100 | 105 | 104 | |

Group A, ultrasound + MRL (outside areola injection) group; Group B, ultrasound + MRL (around areola injection) group; Group C, ultrasound + MRL group; MRL, magnetic resonance lymphangiography; SLN, sentinel lymph node.

of SLN in breast cancer differed significantly among the three groups (P<0.05). Moreover, the overall accuracy of SLN in breast cancer also varied notably among the three groups (P<0.05) (*Table 2*).

Metastasis to the axillary SLN was detected in 115 cases in Group A (53.24%), of which 108 were true positive (93.91%) and seven were negative (6.09%). Metastasis to the axillary SLN was detected in 117 cases in Group B

**Table 2** Metastasis of SLN in breast cancer in each group

| Variable | Group A (n=216) | Group B (n=216) | Group C (n=216) | P value |
|---|---|---|---|---|
| Total SLN metastasis (%) | | | | |
| Detection rate | 54.63 | 56.02 | 19.91[ab] | <0.05 |
| Accuracy | 92.13 | 95.83 | 62.04[ab] | <0.05 |
| Sensitivity | 94.92 | 97.52 | 95.35 | >0.05 |
| False-negative rate | 5.08 | 2.48 | 4.65 | >0.05 |
| Metastasis to the axilla as the SLN (%) | | | | |
| Detection rate | 53.24 | 54.17 | 18.52[ab] | <0.05 |
| Accuracy | 93.06 | 96.30 | 63.43[ab] | <0.05 |
| Sensitivity | 93.91 | 98.29 | 97.50 | >0.05 |
| False-negative rate | 6.09 | 1.71 | 2.50 | >0.05 |
| Metastasis to the internal mammary node as the SLN (%) | | | | |
| Detection rate | 7.87 | 16.67[c] | 5.09[b] | <0.05 |
| Accuracy | 88.89 | 96.76[c] | 87.04[b] | <0.05 |
| Sensitivity | 94.12 | 91.67 | 90.91 | >0.05 |
| False-negative rate | 5.88 | 8.33 | 9.09 | >0.05 |

Group A, ultrasound + MRL (outside areola injection) group; Group B, ultrasound + MRL (around areola injection) group; Group C, ultrasound + MRL group; [a], P<0.05 Group C *vs.* Group A; [b], P<0.05 Group C *vs.* Group B; [c], P<0.05 Group B *vs.* Group A. SLN, sentinel lymph node; MRL, magnetic resonance lymphangiography.

(54.17%), of which 115 were true positive (98.29%) and two were negative (1.71%). Metastasis to the axillary SLN was detected in 40 cases in Group C (18.52%), of which 39 were true positive (97.50%) and one was negative (2.50%). The total detection rate of the axillary node as the SLN differed markedly among the three groups (P<0.05), but no obvious difference was observed between Groups A and B. The accuracy of detection of SLN metastasis to the axilla varied significantly among the three groups (P<0.05), but there were no obvious differences between Groups A and B. The overall sensitivity of detection of SLN metastasis to the axilla showed no significant differences among the three groups. Also, the false-negative rate of SLN at the axilla did not differ notably among the three groups (*Table 2*).

Metastasis to the internal mammary SLNs in Group A was detected in 36 cases (7.87%), with 33 true positive cases (94.12%) and three negative cases (5.88%). Metastasis to the internal mammary SLNs in Group B was detected in 17 cases (16.67%), of which there were 16 true positive cases (91.67%) and one negative case (8.33%). Metastasis to the internal mammary SLNs in Group C was detected in 11 cases (5.09%), with 10 true positive cases (90.91%) and one negative case (9.09%). The detection rate of metastasis to the internal mammary SLNs differed significantly between Groups A and B and between Groups B and C (all P<0.05), but the difference between Groups A and C was not statistically significant. The overall sensitivity of detection of metastasis to the internal mammary SLNs showed no obvious difference. The false-negative rate of metastasis to the internal mammary SLNs did not differ significantly among the three groups (*Table 2*).

## Discussion

The results of the present study showed no significant differences in age, tumor size, location, pathological type, and lymph node-related parameters among the three patient groups.

In the present study, the included patients with breast cancer enrolled at the First Affiliated Hospital of Zhengzhou University were aged between 41 and 64 years old. The incidence of breast cancer in the left and right breasts in our study was 52.3% and 47.68%, respectively. Most cancer sites were in the upper outer quadrant of the breast, which is consistent with findings of related studies (15). Postoperative pathological analysis revealed that most of the specimens were invasive carcinoma of the breast, which is also in line with related studies (16). The diagnosis of metastasis to SLNs using ultrasound combined with MRL is mainly based on observing the morphology of the diseased lymph node, the long and short diameters, whether the lymphatic hilum disappears, cortical eccentric thickening, whether the peripheral fat interval of the lymph node is blurred, and whether the fat echo disappears (10,17). These factors were not significantly different between the three groups in this study, which may suggest that the above factors did not have a notable impact on the detection values among the three groups.

Meng (18) found that MRL had a detection rate of 96.8%. Serquiz *et al.* (19) reported that the detection rate of axillary SLNs using contrast-enhanced ultrasound (CEUS) was 89.6. Furthermore, in a study of 110 patients with breast cancer, the detection rate of SLNs in breast cancer was reported to be 96.4% (20). Other studies have reported the detection rate of SLNs in breast cancer to be 96–100% (21,22). The present study determined that the overall detection rates of Groups A and B were significantly higher than that of the ultrasound group. This suggests that ultrasound combined with MRL has certain advantages in the diagnosis of SLNs in breast cancer. There was no obvious difference between Groups A and B in terms of detection rate, which may be because axillary SLNs account for the majority of SLNs in breast cancer patients and internal mammary nodes as the SLN mostly tend to occur in combination with axillary SLN metastasis (23,24). Moreover, there was no significant difference in the overall accuracy between Groups A and B, and the overall accuracies of both groups were significantly higher than that of Group C. This may be related to the lower detection rate of positive SLNs in the ultrasound group. However, the specificity of ultrasound in detecting SLNs in breast cancer is relatively high, suggesting that ultrasound is an easy method to discover obvious SLNs in metastatic breast cancer. In addition, there were no obvious differences in the sensitivity of detection or false-negative rates among the three groups, which is similar to the findings of Choi *et al.* (25). Previous anatomical studies have suggested that the internal mammary node and axilla are two different pathways for breast cancer SLN metastasis (26), which also provided operability for the analysis of the contrast between the detection values of different doses of contrast agent in the present study. Our study found that using 1 mL contrast mixture (Group A) and 0.5 mL contrast mixture (Group B) for injection did not lead to differences in the overall breast cancer detection rate, accuracy, sensitivity, and false-negative rate. Taking into consideration the close association between contrast agent dosage and the incidence of side effects (27), it is recommended that a dose of 0.5 mL contrast agent be used for MLR examination of the axillary or internal mammary node pathways of breast cancer metastasis.

In this study, no significant difference was found in the detection rates of axillary SLNs in breast cancer between Groups A and B. This result could be attributed to the following reasons: (I) the contrast agent used in this study could not affect the detection rate of SLN metastasis to the axilla; and (II) breast cancer SLN metastasis to the axilla accounts for most cases of SLN metastasis (24). In the current study, Groups A and B had similar accuracies, which were both higher than that in Group C, suggesting that ultrasound combined with MRL has both a high detection rate and high accuracy. No significant differences were found in the detection sensitivity and the false-negative rates among the three groups, indicating that although ultrasound has a lower detection rate of breast cancer SLN metastasis, its sensitivity does not differ much from that of ultrasound combined with MRL.

Breast cancer metastasis with the internal mammary node as the SLN accounts for 18–33% of cases of SLN metastasis (28). In the current study, internal mammary node as the SLN accounted for 32% of cases of metastasis, and the detection rate of the internal mammary node pathway was significantly higher in Group B than in Group A. This indicated that attention was only paid to the axillary node pathway for breast cancer SLN metastasis, while the internal mammary node pathway was neglected. The findings of this study suggest that the axillary and internal mammary nodes are two different SLN pathways through which breast cancer can metastasize, and that injection of the contrast agent at the axillary lymph nodes may not be able to enter the internal mammary node circulation (26,29).

In terms of accuracy, Group B exhibited a higher accuracy than Groups A and C, but there were no differences in sensitivity among the three groups. This illustrates that ultrasound diagnosis has a lower detection rate of SLN metastasis but higher sensitivity, which may be related to the fact that SLNs with obvious lesions can be easily detected by ultrasound. Studies have shown that histological grading of breast cancer, molecular subtyping, blood metastasis, and methods for receiving radiotherapy and chemotherapy are important factors affecting the recurrence of breast cancer after surgery (30). The use of ultrasound combined with MRL in this study revealed that the 3-year recurrence rate of breast cancer metastasis to the axilla was significantly lower than that of breast cancer metastasis to the internal mammary node. This may be because the breast cancer cells that metastasize via the internal mammary node spread more easily (28). In this case, apart from the gold standard of pathological biopsy, ultrasound combined with MRL has a certain evaluative benefit for the recurrence of breast cancer after surgery.

This study has some limitations that should be noted. Firstly, this is a single-center study as patient data was only collected from one hospital. Also, due to time and energy limitations, the follow-up duration was only 3 years. More studies with a longer follow-up and observation period are required to explore the survival rates and survival times of patients.

## Conclusions

Ultrasound combined with MRL may be more advantageous in the detection of SLN metastasis in breast cancer than ultrasound alone. It is necessary to pay attention to the metastasis via the internal mammary node pathway. Ultrasound combined with MRL could be a more convenient method of evaluating the prognosis of patients with breast cancer. However, more studies are needed to further explore this subject.

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## Footnote

*Reporting Checklist*: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-292/rc

*Data Sharing Statement:* Available at https://gs.amegroups.com/article/view/10.21037/gs-22-292/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-292/coif). The authors have no conflicts of interest to declare.

*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by Ethics Committee of the First Affiliated Hospital of Zhengzhou University (No. 2020-KY-0133). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and informed consent was obtained from all participants.



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