

REVIEW

Advanced diagnostic imaging of sentinel lymph node in early stage breast cancer

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Abstract

Sentinel lymph node biopsy has been regarded as the standard procedure for early staging breast cancer. One of the key steps is to locate the sentinel lymph node (SLN). The recommended method is the joint use of blue dye and radioisotope. However, due to radionuclide radiation and high cost, it is urgent to develop more convenient and sensitive imaging methods to accurately locate SLN. This article discusses the advancement of accurately locating SLN by isotope tracer imaging, magnetic tracer method, computed tomographic lymphography, and trans-lymphatic contrast-enhanced ultrasound, as well as proposing new propose for clinical diagnosis.

KEYWORDS

breast cancer, diagnostic imaging, lymphography, sentinel lymph node

1 | INTRODUCTION

Breast cancer is still a global challenge and the leading cause of cancer deaths and disability-adjusted life years in women.¹ Breast cancer is dominated by lymphatic metastasis. Sentinel lymph node (SLN) is the first lymph node (LN) to receive lymphatic drainage from the breast, and therefore, it has the highest probability being affected. If the SLN does not been metastasized, the possibility of the remaining axillary lymph node (ALN) metastasis is quite low. In this circumstance, axillary lymph node dissection (ALND) can be avoided. SLN metastasis is the most important indicator for the treatment of early breast cancer.² Compared with standard ALND, sentinel lymph node biopsy (SLNB) involves fewer resected LNs and has less complications.^{3,4} It has become the gold standard for the management of patients with ALN metastasis.

Precise detection and localization of SLNs is vital for SLNB. The current SLN detection method is based on staining/radionuclide method. However, the method requires intraoperative detection and biopsy. Therefore accurate and efficient preoperative examination of SLNs with image-guided minimally invasive SLNB has become hot

spot in recent years. With the development of imaging technology, more imaging methods have shown great potential in tracking and diagnosing SLN, such as isotope tracer imaging, magnetic tracer method, computed tomographic lymphography (CTLG), and trans-lymphatic contrast-enhanced ultrasound (TLCEUS), etc. We reviewed the clinical progress of these technologies in the qualitative localization and diagnosis of SLNs in early breast cancer.

2 | ISOTOPIC TRACER METHOD

The isotopic tracer method is one of the most commonly used positioning methods of SLNB. It uses planar imaging and single photon emission computed tomography (SPECT)/CT imaging to identify the preoperative SLN, and use the nuclide detector to locate the SLN during the operation. The day before operation ^{99m}Tc-labeled sulfur colloid (GE Healthcare AG, Munich, Germany) is injected into the breast tissue around the tumor by nuclear medicine physician. SPECT/CT imaging can be performed during 2 h. The nuclide tracer enters the SLN along the lymphatic channel which is the way for cancer cells

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metastasis. If the cancer has spread to that area, it will be firstly found in the SLN.² LN intake of radionuclides will display as a radioactive dark green node. The afferent lymphatic vessels is defined as SLN. If the afferent lymphatic vessels cannot be identified, the first LN that appears is defined as SLN.⁵ Regarding radioactivity, attention should be paid to the “hottest” SLN, and all nodes counted as 10% or more of the hottest node should be removed (the “10% rule”).⁶ Krzhivitskii et al.⁷ believed that increased tracer uptake with/without LN expansion can be used as markers of tumor metastasis. Taking the histopathological results as a reference, the accuracy of mixed SPECT and CT imaging in diagnosing early stage breast cancer clinically negative LN patients with axillary LN metastasis can reach 99%.⁷ Methylene blue is injected preoperatively to stain the SLN so that it can be recognized during the operation.

Planar imaging is limited by physical conditions, such as low resolution, noise effect, and deep anatomical structure, and its ability to identify and recognize SLNs is low. But SPECT/CT can more accurately identify and locate SLNs, which can make up for the defect of planar imaging. In addition, the mean contrast-to-noise ratio (CNR) of SPECT/CT is 1.5 times higher than that of SPECT and 3.5 times higher than that of planar imaging at depth range 1–9 cm.⁸ In 2015, a multicenter prospective study coordinated by the International Atomic Energy Agency published the added value of SPECT/CT on planar scintigraphy in various malignant tumors, including primary breast cancer, and it showed that the visualization rate of SLN increased from 87.6% to 91.3% after adding SPECT/CT.⁹ The SLN recognition

rates of ^{99m}Tc-Rituximab and ^{99m}Tc-sulfur colloid guided SPECT/CT in the axillary area were 100% and 98.4%, respectively, and 98.5% and 98.7 in all areas.¹⁰ Compared with lymphangiography alone, SPECT/CT has obvious advantages in the detection of internal breast LNs¹¹ and ipsilateral axillary external drainage.^{12,13} It is also useful for scanning invisible, unexplained, or unexpected SLNs (Figure 1).¹³ SPECT/CT can detect SLN that cannot be detected by planar imaging, resulting in upstaging and therapy change in 9.6%–21.3% of patients.^{13,14}

SPECT/CT can provide accurate anatomical information about SLN and more appropriate therapies for patients (Figure 2).¹² However, its cost is relatively higher. And it also has radiation hazards, requiring dedicated nuclear medicine facilities and strict legislations, which limits its application in more places, especially in developing countries. At present, it has been widely used in many countries in Asia, Europe and North America. The development trend of SPECT/CT in the future involves the exploration of non-radioactive tracers, molecular targeted labeling tracers,¹⁰ and mixed tracers.¹⁵

3 | MAGNETIC TRACER METHOD

Magnetic tracer method is a new SLN detection technology, which is considered to be an alternative to the radioisotope method.¹⁶ This technique involves the magnetic tracer to locate the SLN and hand-held magnetometers for intraoperative detection of SLN.¹⁷ 20 min

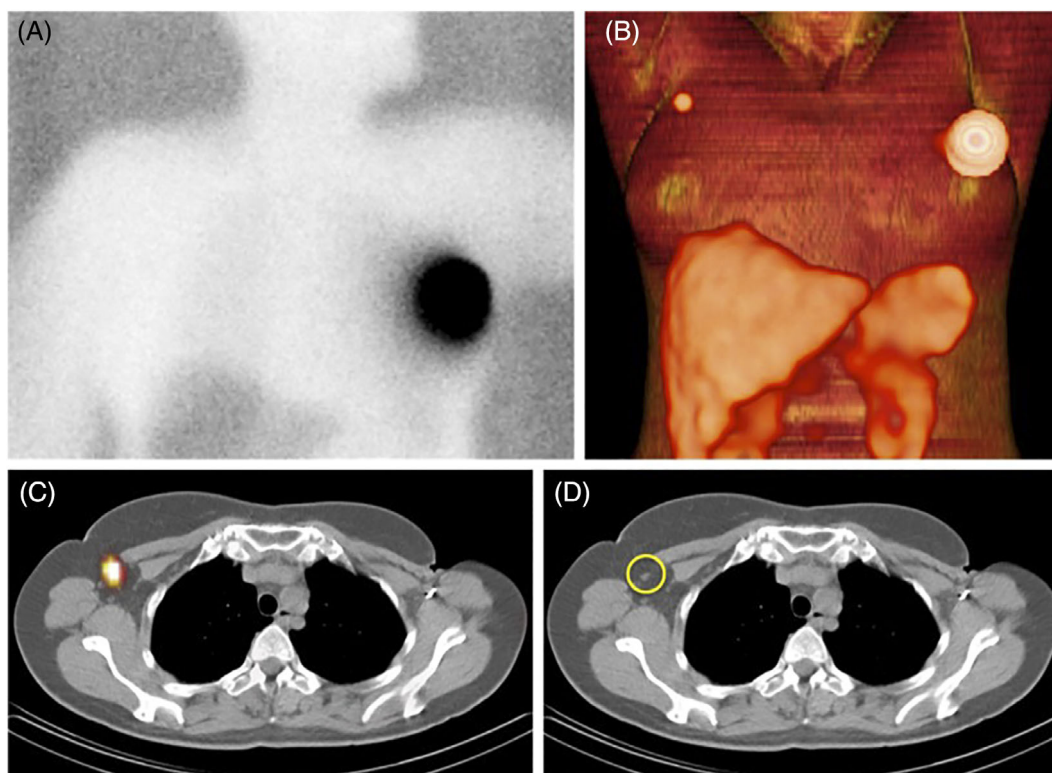


FIGURE 1 Patients with recurrence of ductal carcinoma of the left breast. (A) No SLNs visualization on planar image; (B) SPECT/CT volume imaging revealed 1 grade 1 lesion in the contralateral axillary. (C) CT showed the lesion of the contralateral axillary. (D) CT showed no enlarged LNs (circles). Source: Reference [13]. Copyright permission obtained

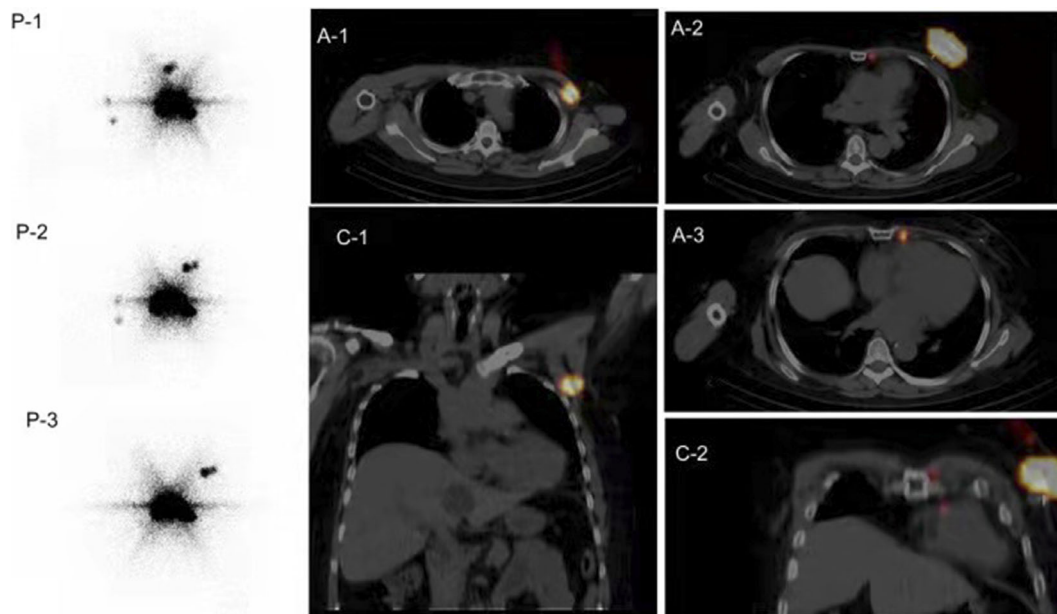


FIGURE 2 Preoperative SLN positioning with plane and SPECT/CT images of a patient with new breast cancer in the left breast. The plane images (P-1) showed two ipsilateral ALNs and two parasternal LNs. SPECT/CT images showed 1 grade 2 (Rotter) ALNs (A-1, C-1) and 2 parasternal LNs (A-2, 3, C-2). (Plane image: P-1: anterior; P-2: left anterior strabismus, 30°; P-3: left anterior strabismus, 60°. SPECT/CT image: A-1, 2, 3: axial fusion; C-1, 2: Coronary fusion). Source: Reference [12]. Copyright permission obtained

before surgery, the radiologist injects the magnetic tracer subcutaneously into the breast for MRI imaging. The magnetometer (Sentimag®, Sysmex, GmbH, Hamburg, Germany) generates an alternating magnetic field to magnetize the superparamagnetic iron oxides (SPIO) particles near the probe. The content change of the tracer can be displayed on the screen through the change of magnetization intensity.⁵ Commonly used clinical magnetic tracers are SPIO including Sienna+® (Endomagnetics Ltd, Cambridge, UK) and so on. At the same time, massage for 5 min after the tracer injection can promote lymphatic absorption.¹⁸ After injection of the tracer SPIO, the LN that shows absorption of the tracer along the lymphatic drainage channel on MRI is considered to be the SLN.¹⁹ The SLN nodules turned brown or black, and the MRI signal increased (Figure 3).²⁰ On SPIO-enhanced MRI, metastatic positive SLN showed high-signal-intensity area, and negative SLN showed low signal intensity. Studies have shown that the sensitivity, specificity and accuracy of SPIO-enhanced MRI at 1.5 T with fat-suppression sequence in diagnosing SLN metastasis are 100%, 96%, and 96%, respectively. Even 1.7 mm micrometastasis could be recognized.²¹

Magnetic tracer method has been proved to be an effective method. Pouw et al.⁵ demonstrated for the first time that the same magnetic tracer can be used for both preoperative imaging and intraoperative SLNB, and it has the same performance as radioisotope imaging and localization. However, the latest research has proved that the SLN detection rate of the Magnetic tracer method is higher than that of the radioisotope method (91% vs. 71.8%, $p = 0.01$).¹⁷ Magnetic tracer (Resovist or Sienna+) combined with indocyanine green fluorescence for mouse SLNB can accurately evaluate and identify the SLN intraoperatively,²² and it can significantly improve the detection

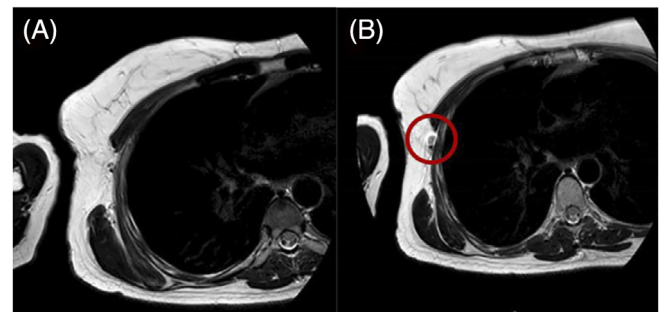


FIGURE 3 Visualization of SLN with MRI before and after SPIO injection. (A) SLN before injection. (B) SLN enhanced after injection of SPIO (red circle). Source: Reference [20]. Copyright permission obtained

of SLN. This provides a new idea to replace the radioisotope “joint technology” in clinical trials, which is worthy of further evaluation in clinical trials.

The most common adverse events following magnetic tracer use are breast discoloration or pigmentation. The incidence rate was about 15.6%–39.9%, but it subsided naturally over time.^{23,24} Besides, studies have found that deeper peritumoral injection could avoid skin staining. Moreover, the magnetic tracer method should be prohibited in patients allergic to iron or dextran compounds and patients using pacemakers or metal implants.^{18,23} Metal instruments are prohibited during operation to avoid interference with the magnetometer. Magnetic tracer technology, which does not emit radiation, is simple, relatively inexpensive¹⁷ and has been used in about 30 countries. So it is considered a good alternative to radioisotope methods.

4 | COMPUTED TOMOGRAPHY LYMPHOGRAPHY(CTLG)

CTLG utilizes the characteristics of lymphatic vessels that are composed of a single layer of endothelial cells with thin and porous walls. The contrast agent is injected locally and drained into the lymphatic system through lymphatic drainage. CT can detect this process and achieve the purpose of visualization. The most commonly used contrast agents are iodine preparations such as iopamidol 300 (Daiichi-Sankyo Company, Tokyo, Japan) and so on. The contrast agent is mainly injected into the tumor and the surrounding subcutaneous tissue. The flow direction of the contrast agent is consistent with the drainage direction of the tumor lymphatic vessels.²⁵

CTLG can be used to visualize the SLNs and breast lymphatic drainage pathways before surgery.^{26–28} CTLG is performed 1–2 h before surgery, and the radiologist performs imaging 1 min after

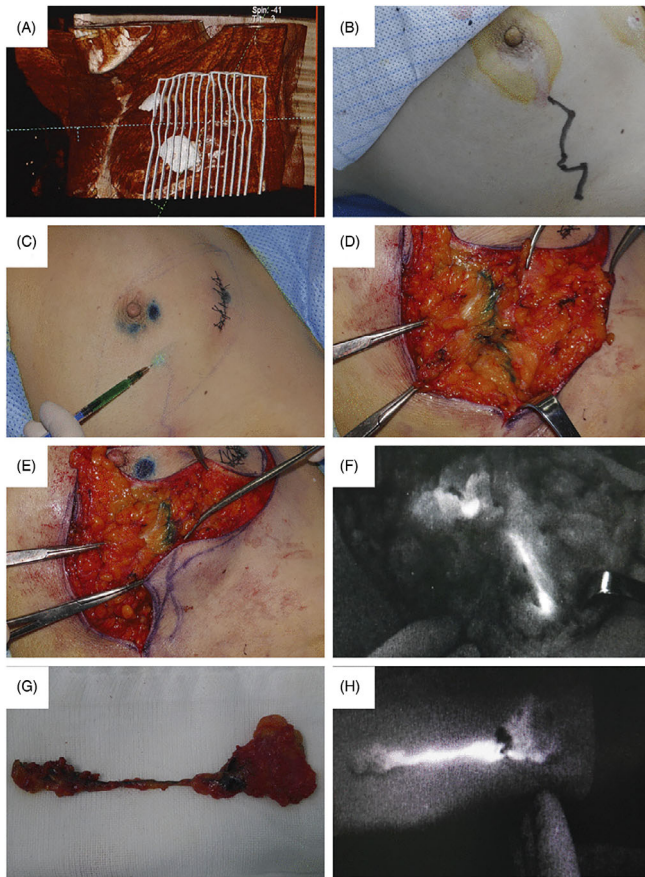


FIGURE 4 The preoperative localization of SLN based on CTLG was consistent with the intraoperative detection. (A) CTLG three-dimensional reconstruction image. (B) According to CTLG, the location of SLN and lymph vessel on the body surface before surgery. (C) Single-point injection of methylene blue and indocyanine green to evaluate CTLG efficacy. (D, E) Lymph vessel locating by CTLG before operation was consistent with blue staining during operation. (F) Lymph vessel locating by CTLG before operation was consistent with intraoperative fluorescence. (G, H) Intraoperative comparison of blue staining and fluorescence localization of SLN and lymphatic vessels. Source: Reference [29]. Copyright permission obtained

TABLE 1 Comparison of SonoVue and Sonazoid

Manufacturer	Approval indication(s)	Countries available	Shell/gas	Contraindications	Vial supplied	Storage	Typical doses	Administration recommendation	MI	Advantages	Disadvantages
SonoVue® Bracco imaging	LVO/EBD, breast ^a , liver ^a , vascular ^a , urinary tract	North America, New Zealand, Europe, Brazil, Asia	Phospholipid/sulfur hexafluoride	Hypersensitivity to sulfur hexafluoride or any inactive ingredient in lumason	10 ml vial containing 25 mg powder 5 ml saline	Room temperature	2 ml of reconstituted agent	Bolus Bolus dose can be repeated once Doses varies depending on age and indication	MI ≤0.8	Approved for use in pediatric populations Reconstitution by hand mixing	Bolus and infusion dosing are used, although package insert only describes bolus dosing
Sonazoid® GE healthcare/ daiichi sankyo	Myocardial perfusion ^a , liver ^a , breast ^a	Japan, South Korea, Norway	Phospholipid/perfluorobutane	Egg allergy	16 µl vial 2 ml solvent	Unable to identify	Weight based 15 µl/kg or 0.12 µl MB/kg	Bolus or infusion	Unable to identify	Bolus or infusion	Usually only single dose administration

Abbreviations: LVO, left ventricular opacification; EBD, endocardial border definition; MB, microbubble; MI, mechanical index. Source: Adapted from Reference 33. Copyright permission obtained.
^aOnly in certain countries.

injecting the contrast medium. 3D CTLG imaging showed that single path/single SLN was dominant (65%–68.2%).²⁷ Normal SLNs have good morphology, and the lymphatic vessels are completely stained. Diagnosis of SLN metastasis with CTLG is based on the morphological changes of SLN and the abnormal connection with lymphatic vessels. There are four abnormal imaging modes: (A) partial staining (stain defect, mottled or “Crab claw” stain) of SLN, (B) stagnant, (C) dilated, and (D) detour of the lymphatic route.²⁶ This is mainly related to normal SLN being occupied by tumors or lymphatic vessels being blocked by tumor embolism. It has also been found in animal studies that an uneven pattern or non-turbidity and reduced enhancement value have an important diagnostic value for SLN metastasis; the absolute density value of SLN centers lower than 444 units also has significant sensitivity and specificity.²⁸ Compared with the combined staining of methylene blue and indocyanine green, the accuracy of preoperative CTLG followed by CT three-dimensional reconstruction to locate SLN and lymphatic vessels was 92.6%, and the accuracy of SLN number was 95.2% (Figure 4).²⁹ It was reported that the preoperative recognition rate of SLN detection using liquid carbon suspension and silver wire guided CTLG was 100%, and the intraoperative recognition rate was 98.3%.³⁰ In addition, studies on gadolinium-loaded polyvinyl imide coated gold nanoparticles^{31,32} as CT/MR dual-mode contrast agents can make up for the deficiencies of single imaging examination in evaluating SLN properties. In short, CTLG has a high sensitivity and a low negative rate in the diagnosis of SLNs. It also requires almost no operation time and can be easily achieved on ordinary CT.²⁸ These methods provide novel ideas for clinical research.

In addition, CTLG does not involve the use of radioisotopes, and has been pioneered in Japan and other countries. The posture during CTLG detection is the same as that during surgery, and the position of

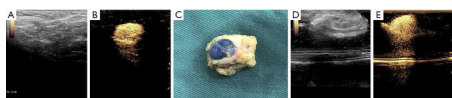


FIGURE 5 Contrast-enhanced ultrasound images of a patient with early invasive ductal carcinoma of the left breast. (A, B) The real-time dual image and macro appearance of SLN. (A) SLN cannot be observed on 2D imaging. (B) CEUS can observe enhanced SLN. (C) The excised blue dyed SLN. (D, E) Real-time dual images of sentinel lymphatic vessels and SLN soaked in physiological saline. Source: Reference [34]. Copyright permission obtained

SLNs should not change. It can well describe the lymphatic channel and can be used to visualize the SLNs and breast lymphatic drainage pathways; thus, providing important clinical significance for understanding the anatomy of the lymphatic tract and SLNs before surgery.^{26–28,30}

5 | TRANS-LYMPHATIC CONTRAST-ENHANCED ULTRASOUND (TLCEUS)

TLCEUS means that after local subcutaneous injection of ultrasound contrast agent by the sonographer, the contrast agent enters the lymphatic system and is discharged into the SLNs within seconds and minutes. Contrast-enhanced ultrasound (CEUS) images can be obtained through the ultrasonic contrast enhancement mode of ultrasound instruments to identify and perform biopsy of SLNs for non-surgical purposes.³² At present, the commonly used ultrasound contrast agents in clinical practice are SonoVue (SNV, Bracco, Milan, Italy) and Sonazoid (SNZ, GE Healthcare, Oslo, Norway), both of which are second-generation ultrasound contrast agents. SNV is a microbubble contrast agent filled with inert gas sulfur hexafluoride, while SNZ is filled with perflubutane. SNV has been widely used in liver, thyroid, lymph nodes, breast, etc. Sonazoid is mainly used in the diagnosis of hepatic space-occupying lesions, especially in Japan. The physicochemical properties and clinical applications of these two contrast agents are summarized in Table 1.³³ The imaging principles of these two contrast agents are the same. There is no significant difference between SNV and SNZ in SLN quantity detection and metastasis diagnosis (Figure 5).³⁴ In addition, Sonazoid is relatively stable and has a high rate of phagocytosis by Kupffer cells in vitro (99.00%). And SLN can be detected at least 1 h after SNZ injection,³⁵ while SNV is only 5 min.³² Therefore, SNZ has more advantages in assessing the situation after LN resection. The accuracy, sensitivity and specificity of ultrasound contrast agent subcutaneous injection through the areola are higher than peripheral injection. Probably because the lymph vessels under the areola are abundant, and the contrast agent can enter the ALNs faster with higher uptake.^{36,37} However, the dose has no effect on the identification of SLNs.³⁸ Studies have shown that using SNV's CEUS combined with blue dye to identify SLN can reach 98.5% (66/67), which is more effective than using blue dye alone (83.6%).³⁹

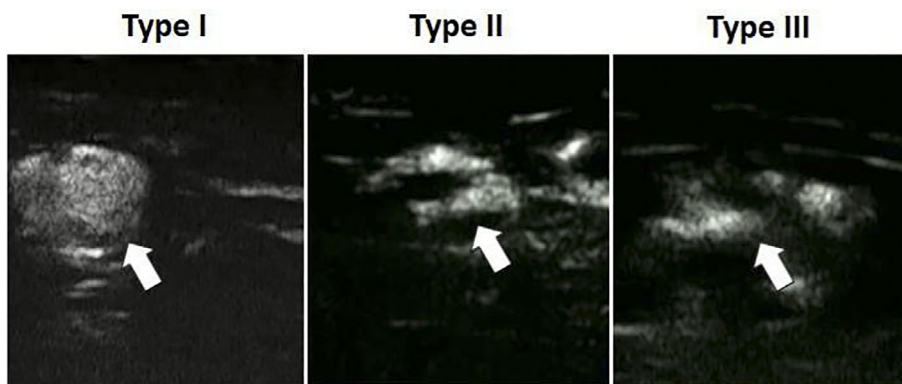


FIGURE 6 Three contrast patterns of SLNs observed by TLCEUS. Source: Reference [42]. Copyright permission obtained

CEUS not only has a high SLN recognition rate, but it can also realize real-time visualization.⁴⁰ It can be observed that in lymphatic drainage, single lymphatic pathway/single SLN type is dominant, accounting for 70.7%.⁴¹ In CEUS imaging, SLNs are classified into three enhancement types. Type II (ringed enhancement mainly at the cortex area while less in the medulla area) and type III (partial enhancement of cortex and medulla area with irregular borders) are mainly metastatic SLN (Figure 6).⁴² In addition, SLN that appears suspicious in conventional grayscale ultrasound while shows no enhancement in TLCEUS is most likely to be metastatic.⁴² The sensitivity and specificity of CEUS with SNV in diagnosing metastatic SLN were 98.04%(50/51) and 49.23%(32/65), respectively.³⁴ Micrometastasis which is defined as deposits >0.2 to ≤ 2.0 mm⁴³ may block the lymphatic vessels inside and outside the SLN, thereby prolonging the arrival time of the contrast agent in the metastatic SLN.⁴² Micrometastasis is the main reason for the false negative rate of fine needle aspiration biopsy.⁴⁴ Its detection mainly depends on pathological evaluation. Studies have shown that the effect of micrometastases on disease-free survival is very low.⁴⁵ And it is only one of the factors guiding adjuvant therapy for breast cancer.⁴⁴⁻⁴⁶

TLCEUS has a high sensitivity and specificity for the diagnosis of SLN in breast cancer. It can identify the whole process of contrast agent from tumor to lymphatic drainage to SLNs in a real-time, non-invasive and accurate manner, and has the ability to display metastatic foci in LNs. No adverse events have been reported so far. Moreover, the contrast agent can avoid the risk of excessive detection of SLNs due to the small molecular weight of methylene blue and nuclide reagents, which will lead to the expansion of surgical resection.⁴⁷ Compared with the traditional SLNB method of open surgery, TLCEUS-fine needle aspiration has high accuracy and is more in line with the direction of a precise and minimally invasive surgical operation. At present, it has entered clinical applications in Europe, Asia and North America. TLCEUS combined with methylene blue to guide SLNB will become the most potential alternative to the standard method.

6 | CONCLUSION

In summary, the above various medical imaging technologies can visualize lymphatic drainage of the breast and internal structures of SLNs through different imaging methods, especially in combination with the lymphatic system imaging technology. TLCEUS is one of the simple and effective methods, which can be used for SLN positioning and ultrasound-guided needle biopsy. We should choose the appropriate method according to the patient's condition, cost and local medical level. These imaging methods for the detection, qualitative diagnosis, location guidance, and biopsy of SLNs can efficiently promote the progress of SLNB and help to evaluate the status of LN metastasis in early breast cancer.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare

DATA AVAILABILITY STATEMENT

All data, models, and code generated or used during the study appear in the submitted article.

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