Study on Sentinel Lymph Node and Its Lymphatic Drainage Pattern of Breast Cancer by Contrast-Enhanced Ultrasound

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Objectives—Sentinel lymph node (SLN) and its lymphatic drainage pattern (LDP) of breast cancer were studied by contrast-enhanced ultrasound (CEUS).

Methods—From July 2017 to December 2019, patients with SLN localization of breast cancer in Sichuan Academy of Medical Sciences-Sichuan Provincial People’s Hospital were selected. The sentinel lymph system of breast cancer was observed by CEUS before both operation and blue staining in the surgery. The location, number, and route of sentinel lymphatic channel (SLC) were recorded, along with the number, size, and the depth from skin of SLN. LDPs were summarized according to these basic characteristics of SLC and SLN.

Results—A total of 368 cases were included; 465 SLCs and 423 SLNs were detected. Most of the SLCs were originated from the outer upper quadrant of areola. Eleven LDPs were found, including 31 subtypes of LDPs. There were 6 cases of type A (1.63%), 15 cases of type B (4.08%), 223 cases of type C (57.88%), 38 cases of type D (10.33%), 2 cases of type E (0.54%), 3 cases of type F (0.82%), 50 cases of type G (13.59%), 30 cases of type H (8.15%), 2 cases of type I (0.54%), 6 cases of type J (1.63%), and 3 cases of type K (0.82%).

Conclusions—The most common LDP of breast cancer was one SLC originated from the upper quadrant of areola with one SLN. CEUS can identify the LDP before surgery to reduce the false negative rate of SLN biopsy.

Key Words—breast cancer; contrast-enhanced ultrasound; lymphatic drainage channel; lymphatic drainage pattern; sentinel lymph node

Sentinel lymph node (SLN) is the first lymph node to receive lymphatic drainage in the lymphatic system. The lymphatic vessels that drain into SLN are called sentinel lymphatic channel (SLC). Studies have shown that most SLNs of breast cancer are located in the armpit. Therefore, axillary lymph node dissection (ALND) was often used to evaluate ALN in breast cancer surgery, but complications such as edema of the affected arm, shoulder dysfunction, and loss of sensation in the intercostobrachial innervation area often occurred after ALND. For some patients with early breast cancer, sentinel lymph node biopsy (SLNB) has gradually replaced ALND to reduce post-operative complications.
SLNB usually begins with an injection of one or two tracers into the breast skin or breast gland. After the tracer is absorbed by the lymphatic system, SLN is the first lymph node to receive lymphatic drainage along the trace and then all the SLNs are resected. The blue staining method is simple and easy to operate, but it has a high false negative rate and must be performed intraoperatively. Radioisotope tracing method is expensive and radioactive, so it needs higher requirements for medical centers. Computed tomography (CT) and magnetic resonance imaging (MRI) can also identify lymph nodes, but they are rarely used relatively. Contrast-enhanced ultrasound (CEUS) is a new method to evaluate SLN of breast cancer in recent years, with the advantages of scanning and identifying at the same time. CEUS was initially used for lymphatic display of porcine melanoma model. However, many studies have confirmed that CEUS could be used to identify and locate SLN of breast cancer safely. Besides, our previous research also confirmed its feasibility.

At present, there are many studies on the evaluation of breast cancer SLN metastasis by CEUS, but only few studies have been done on lymphatic drainage pattern (LDP). This study focuses on analyzing the basic characteristics of SLN and SLC in breast cancer and summarizing the LDP to improve the accuracy of SLNB.

Material and Methods

Patient Selection
This study was approved by the institutional review board and ethics committee of Sichuan Provincial People’s Hospital, Batch Number: Ethics Review (Research) No. 272, 2018. All patients signed informed consent prior to examination.

Study candidates were patients with SLN localization of breast cancer in Sichuan Academy of Medical Sciences-Sichuan Provincial People’s Hospital from July 2017 to December 2019 based on the following selection criteria.

Inclusion criteria include: 1) female; 2) confirmed with breast malignant tumor (T1–3) by pathological biopsy before operation; 3) no abnormal lymph nodes were found in the affected axilla, including palpation, ultrasound, X-ray mammography, and/or MRI; and 4) blue staining method was used for secondary localization during operation.

Exclusion criteria include: 1) metastatic carcinoma confirmed by ALN biopsy; 2) previous breast radiotherapy or chemotherapy; 3) inconsistent localization of CEUS and intraoperative blue staining; 4) advanced breast cancer (T4a–c) and inflammatory breast cancer (T4d); and 5) pregnant.

Equipment
Philips iU Elite ultrasound system (Philips Medical Systems, Bothell, WA) equipped with contrast-tuned imaging technology was selected for our examination. A 5- to 12-MHz linear array probe was used for routine two-dimensional ultrasound examination, and a 3- to 9-MHz linear array probe was used for CEUS examination. Low mechanical index (MI) values were applied (MI 0.07) to reduce microbubble destruction. Ultrasonic focus position was beneath the lesion.

Examiners
All the examinations were performed simultaneously by two experienced examiners Jun Luo and Hao Wu. Jun Luo has more than 15 years of experience in ultrasound examination and Hao Wu has more than 10 years of experience in ultrasound examination. If their diagnoses were different, the final diagnosis should be decided by Qin Chen who has more than 20 years of experience in ultrasound examination.

Ultrasound
The examination was carried out on the day of SLNB operation, and the patient was given the surgical position during the examination.

First, the routine two-dimensional ultrasound examination was performed to observe and record the basic condition of the breast tumor and affected side axilla. The location of the tumor was represented by the quadrant method. If the tumor was located behind the nipple, it was recorded as the central area.

SonoVue (Bracco spa, Milan, Italy) was used as contrast agent. It was prepared by adding 5 ml of
normal saline to the whole bottle of sulfur hexafluoride microbubbles. Shaking the bottle thoroughly for 30 seconds after preparation ensures that the contrast agent was well mixed.

The process of SLN and SLC localization by CEUS was shown in Figure 1.

Firstly, 1 ml of contrast agent was injected at 3, 6, 9, and 12 o’clock respectively at the edge of the areola with a 22-gauge needle. Intradermal injection and subcutaneous injection were performed alternately, resulting in a total of 4 injections. If the tumor was located in the outer upper quadrant of the breast, 1 ml contrast agent was added into the gland around the tumor; if the tumor was located in other quadrants and the central area, 1 ml contrast agent was added into the gland behind the nipple.

After the injection of the contrast agent, the areola was covered with sterile gauze and gently massaged at the injection point for 30 seconds to help the lymphatic system to absorb the contrast agent.

Switching the ultrasonic machine to the contrast mode, the pool of contrast agent in the areola area was found first, and we did a 360° radial scan with the nipple as the center along the pool of contrast agent. SLC and SLN showed uniform high enhancement. The location (recorded by clock position) and the number of all SLC from areola were detected and recorded. The bifurcation points and confluence points of SLC were recorded. The first lymph node to receive lymphatic drainage was regarded as SLN. If one SLC diverged to drain to multiple first lymph nodes, all these nodes were considered as SLNs. The

Figure 1. CEUS locating the SLC and SLN. 

A, Ultrasound contrast agent was injected around the areola. B, Massaging injection site. C, 360° radial scan with the nipple as the center along the pool of contrast agent. D, The lymphatic vessels showed homogeneous high enhancement during scanning. E, The SLN was localized by injection of a Carbon Nanoparticle Suspension Injection. F, Lymphatic drainage patterns were labeled on the skin surface with gentian violet solution.
number, size, and distance from skin of all SLNs were recorded. Then, all SLNs were punctured and located under the guidance of ultrasound. 0.1 ml Carbon Nanoparticle Suspension Injection (Chongqing Lummy pharmaceutical limited company, Chongqing, China) diluted with 1:10 normal saline was used as the location marker. Finally, LDPs were recorded and labeled on the skin surface with gentian violet solution.

**Blue Staining**

During the operation, blue staining was used to locate SLC and SLN. After the patients were anesthetized, 1 ml methylene blue solution was injected into the same injection site of contrast agent in areola area, and a total of 5 ml methylene blue solution was injected. The injection site was massaged for 5 minutes after injection. All the stained SLCs and SLNs were dissected and compared with the SLCs and SLNs recognized by CEUS. All SLNs were resected for pathological biopsy.

**Lymphatic Drainage Patterns**

All SLC to SLN regions were regarded as one LDP, and LDPs were counted by the combination of the number of SLC and the number of SLN. In the process of lymphatic drainage, a bifurcation point (Figure 2, D1 subtype) occurs where a single SLC sends out multiple SLCs and a confluence point (Figure 2, G2 subtype) is where multiple SLCs converge into one SLC. Both the bifurcation point and the confluence point can be regarded as the lymphatic point (LP). If a LP is both a bifurcation point and a confluence point, then the LDP is considered to have both points (Figure 2, H3 subtype).

**Statistics**

SPSS 22.0 (IBM, New York, NY) was used for statistical description of data. The data concentration of quantitative data was expressed by means of mean, and the degree of data dispersion was expressed by standard deviation. The relative number of qualitative data was expressed by the constituent ratio.

**Results**

**Patient Characteristics**

The inclusion process of the patients in the study was shown in Figure 3. A total of 368 cases were included. The consistency of CEUS localization and intraoperative blue staining localization was 95.58% (368/385).

All the patients were female, with an average age of 50.99 ± 11.04 years, the youngest age of 21 years old, and the oldest age of 85 years old, with 197 cases receiving examination on the left side of the breast and 171 cases on the right side. The characteristics of patients were shown in Table 1. The outer upper quadrant was the most common site of tumor, accounting for 53.53% (197/368). IDC/II was the most common tumor pathological type, accounting for 51.09% (188/368). Other pathological types include: invasive mucinous carcinoma, invasive micro-papillary carcinoma, tubular carcinoma, secretory carcinoma, adenoid cystic carcinoma, and mixed carcinoma. The most common T stage of tumor was T1, including T1mi, T1a, T1b, and T1c, accounting for 49.18% (181/368). Luminal B HER2 (+) was the most common molecular subtype, accounting for 44.84% (165/368).

**Sentinel Lymphatic Channel**

The recognition rate of SLC was 98.37% (362/368). A total of 465 SLCs were found from all 368 cases, with an average of 1.26 ± 0.53 cases, with a minimum of 0 and a maximum of 3, among which 242 were found from the left side and 223 from the right side. The SLC in the left breast were most located at 1 o’clock, accounting for 41.32% (100/242). The SLC in the right breast were most located at 11 o’clock, accounting for 46.19% (103/223). On average, each SLC had 0.21 ± 0.44 bifurcation points and 0.27 ± 0.51 confluence points, with a minimum of 0 and a maximum of 2. Zero bifurcation points was the most common number of bifurcation points, accounting for 84.51% (311/465). Zero bifurcation points was the most common number of confluence points, accounting for 79.35% (292/465). The characteristics of SLCs are shown in Table 2.
**Figure 2.** The subtype of LDPs.

Failed to find enhanced SLC and SLN

A  B1  B2  C1  C2  C3  D1  D2

D3  D4  E1  E2  F1  F2  G1  G2

G3  G4  G5  H1  H2  H3  H4  H5

I  J1  J2  J3  J4  J5  K

**Figure 3.** Patient inclusion process.

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408 cases

23 cases were excluded because of incomplete data

385 cases

17 cases were excluded because of the inconsistency between CEUS localization and intraoperative blue staining

368 cases enrolled in this study
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Sentinel Lymph Node

The recognition rate of SLN was 93.48% (344/368), including the aforementioned 6 cases without SLC being detected. A total of 735 lymph nodes were found in all 368 cases, with an average of 2.05/1.25 cases, with a minimum of 0 and a maximum of 8. Among them, there were 423 SLNs, with an average of 1.15/0.53, with a minimum of 0 and a maximum of 3. One SLN was the most common number of SLN, accounting for 73.10% (269/423). The average longest diameter of SLN was 10.25 ± 3.45 ml. The average shortest diameter of SLN was 5.59 ± 1.84 ml. The average depth from skin of SLN was 14.24 ± 6.25 ml. The characteristics of SLNs are shown in Table 3.

Lymphatic Drainage Pattern

Combining the total number of both SLC and SLN, a total of 11 LDPs were found. According to the specific characteristics of LPs, all the LDPs can be divided into a total of 11 different types and

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**Table 1. Characteristics of Patients**

| Variable                     | No. of total (%) |
|------------------------------|------------------|
| Patient age                  |                  |
| 20–29                        | 4 (1.09%)        |
| 30–39                        | 42 (11.41%)      |
| 40–49                        | 147 (39.95%)     |
| ≥50                          | 175 (47.55%)     |
| Left or right                |                  |
| Left                         | 197 (53.53%)     |
| Right                        | 171 (46.47%)     |
| Location of tumor            |                  |
| The outer upper quadrant     | 197 (53.53%)     |
| The inner upper quadrant     | 66 (17.93%)      |
| The outer lower quadrant     | 59 (16.03%)      |
| The inner lower quadrant     | 28 (7.61%)       |
| The central                  | 18 (4.89%)       |
| Pathological types of tumor  |                  |
| DCIS/1                       | 15 (4.08%)       |
| DCIS/II                      | 13 (3.53%)       |
| DCIS/III                     | 35 (9.51%)       |
| DCIS/X                       | 10 (2.72%)       |
| IDC/1                        | 12 (3.26%)       |
| IDC/II                       | 188 (51.09%)     |
| IDC/III                      | 32 (8.70%)       |
| IDC/X                        | 24 (6.52%)       |
| ILC                          | 7 (1.90%)        |
| Others                       | 32 (8.70%)       |
| T stage of tumor             |                  |
| Tis                          | 73 (19.84%)      |
| T1mi                         | 10 (2.72%)       |
| T1a                          | 14 (3.80%)       |
| T1b                          | 33 (8.97%)       |
| T1c                          | 124 (33.70%)     |
| T2                           | 109 (29.62%)     |
| T3                           | 5 (1.36%)        |
| Molecular typing of tumor    |                  |
| Luminal A                    | 23 (6.25%)       |
| Luminal B HER2(−)            | 49 (13.32%)      |
| Luminal B HER2(+)            | 165 (44.84%)     |
| HER2 over-expression         | 37 (10.05%)      |
| Basal-like                   | 21 (5.71%)       |
| Tis                          | 73 (19.84%)      |
| Total                        | 368 (100.00%)    |

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

**Table 2. Characteristics of SLCs**

| Variable                     | No. of total (%) |
|------------------------------|------------------|
| Number of SLC                |                  |
| 0                            | 3                |
| 1                            | 151              |
| 2                            | 38               |
| 3                            | 5                |
| Location of SLC, clock position |    |
| 1                            | 100              |
| 2                            | 66               |
| 3                            | 34               |
| 4                            | 6                |
| 5                            | 0                |
| 6                            | 0                |
| 7                            | 0                |
| 8                            | 1                |
| 9                            | 23               |
| Total                        | 223              |

**Table 3. Characteristics of SLNs**

| Variable                     | No. of total (%) |
|------------------------------|------------------|
| Number of SLN                |                  |
| 0                            | 12               |
| 1                            | 141              |
| 2                            | 42               |
| 3                            | 2                |
| Total                        | 368 (100.00%)    |
31 different subtypes. The type of LDPs are shown in Table 4. The subtype of LDPs are shown in Table 5 and Figure 2.

Type C was the most common LDP type among the 11 types, accounting for 57.78% (213/368). Subtype C1 was the most common LDP subtype among the 31 subtypes, accounting for 53.53% (197/368), and its performance of CEUS and blue staining method to identify lymph nodes is shown in Figures 4 and 5. We can see one SLC draining into one SLN.

The relationship between SLC and SLN is too complicated to be used in clinical practice, so we also simplified the classification of LDPs, which can be divided into 6 categories in total. The types of simple LDPs are shown in Table 6.

### Adverse Reactions
Patients were observed immediately after the examination and kept under observation for half an hour. No adverse reactions were observed related to the

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**Table 4. The type of LDPs**

| Type of LDP | Number of SLCs’ origin | Number of SLNs | No. of total (%) |
|-------------|------------------------|----------------|------------------|
| A           | 0                      | 0              | 6 (1.63%)        |
| B           | 1                      | 0              | 15 (4.08%)       |
| C           | 1                      | 1              | 213 (57.88%)     |
| D           | 1                      | 2              | 38 (10.33%)      |
| E           | 1                      | 3              | 2 (0.54%)        |
| F           | 2                      | 0              | 3 (0.82%)        |
| G           | 2                      | 1              | 50 (13.59%)      |
| H           | 2                      | 2              | 30 (8.15%)       |
| I           | 2                      | 3              | 2 (0.54%)        |
| J           | 3                      | 1              | 6 (1.63%)        |
| K           | 3                      | 2              | 3 (0.82%)        |
| Total       |                        |                | 368 (100.00%)    |

**Table 5. The subtype of LDPs**

| Type of LDP | Number of SLCs’ origin | Number of SLNs | Number of bifurcation points | Number of confluence points | Subtype of LDP | No. of total (%) |
|-------------|------------------------|----------------|-------------------------------|-----------------------------|----------------|------------------|
| A           | 0                      | 0              | 0                             | 0                           | A              | 6 (1.63%)        |
| B           | 1                      | 0              | 0                             | 0                           | B1             | 14 (3.80%)       |
| C           | 1                      | 1              | 1                             | 0                           | C1             | 197 (53.53%)     |
| D           | 1                      | 2              | 2                             | 1                           | D1             | 35 (9.51%)       |
| E           | 1                      | 3              | 2                             | 0                           | E1             | 1 (0.27%)        |
| F           | 2                      | 0              | 0                             | 1                           | F1             | 2 (0.54%)        |
| G           | 2                      | 1              | 1                             | 1                           | G1             | 25 (6.81%)       |
| H           | 2                      | 2              | 2                             | 1                           | H1             | 23 (6.25%)       |
| I           | 2                      | 3              | 2                             | 1                           | I              | 2 (0.54%)        |
| J           | 3                      | 1              | 2                             | 0                           | J1             | 2 (0.54%)        |
| K           | 3                      | 2              | 0                             | 1                           | K              | 3 (0.82%)        |
| Total       |                        |                |                               |                             |                | 368 (100.00%)    |
contrast agent and Carbon Nanoparticle Suspension Injection, such as allergic reaction or skin necrosis, at the contrast agent injection point and puncture site.

**Figure 4.** The CEUS of C1 subtype. A 35-year-old female underwent CEUS for SLN localization of breast cancer. A, SLC (arrow) was originated along the areola contrast agent injection area. B, SLC (arrow) run long axis section. C, SLC (arrow) run short axis section. D, SLC (arrow) flows into SLN (triangle).

**Figure 5.** The blue staining of C1 subtype. SLC (arrow) flows into SLN (triangle), and the lymphatic drainage pattern traced by CEUS was consistent with blue staining.

**Table 6.** The type of simple LDPs

| Simplified classification         | Number | No. of total (%) |
|----------------------------------|--------|-----------------|
| Single SLC to single SLN         | 213    | 57.88%          |
| Multiple SLCs to single SLN      | 56     | 15.22%          |
| Single SLC to multiple SLNs      | 40     | 10.87%          |
| Multiple SLCs to multiple SLNs   | 35     | 9.51%           |
| Only SLCs without SLN            | 18     | 4.89%           |
| No SLC and SLN                   | 6      | 1.63%           |
| Total                            | 368    | 100%            |

**Discussion**

In our study, the patients were mainly middle-aged and elderly women, and most of the tumors were located in the outer upper quadrant of the breast. IDC was the main pathological type. The consistency of CEUS localization and intraoperative blue staining localization was 95.58%. Among them, the
recognition rate of CEUS was 98.37% for SLCs and 93.48% for SLNs. We summarized the characteristics of SLN and SLC respectively. Finally, we found 11 LDPs.

Among all the 368 cases, SLC and SLN were not found in 6 cases. Three cases had breast nodule resection before, and the operation area was located in the outer upper quadrant direction of the central breast region. CEUS found no enhancement of SLC and SLN, which may be related to previous breast surgery. Because previous surgery can permanently damage the lymphatic network of the breast, increasing difficulties to the follow-up CEUS, it was consistent with the interruption of SLC detection in Ying Wang et al.23 Two cases of detection failure were considered to be related to the injection of the contrast agent. In one case, the contrast agent failed to be injected into the lymphatic network area and accidentally entered the capillary network, which strengthened the mammary glands but did not strengthen the lymphatic system. In another case, the tumor was located in the outer upper quadrant near the areola region, and the failure of detection was related to the lymphatic network compressed by the tumor.24 For disrupted SLC, if any lymph node metastasis were confirmed after SLNB or ALND, destructions/infiltrations caused by breast carcinoma were considered. If there was no lymph node metastasis and the tumor was located near SLC interruption, compression of the lymphatics by a carcinoma was considered. Some studies had shown that25,26 SLNB can still be performed even for patients with recurrent breast cancer and previous axillary surgery. Although the success rate of SLN recognition by SLNB in those cases is lower, the accuracy of SLNB when SLN can be identified is similar to that of patients without previous axillary surgery.

In addition to the previous 6 cases, there were 15 cases only with SLC but no SLN being detected. In 9 of them, the tumor sites were the same as the SLC originating sites. Considering that the tumor compressed the adjacent SLC, the contrast agent microbubbles could not pass through the adjacent SLC.24 In 5 cases, SLC was obviously interrupted under CEUS, and the interruption was enlarged and showed inhomogeneous enhancement. Lymph node metastasis was found in all these 5 cases during axillary dissection. Therefore, metastasis was considered to cause obstruction and interruption of SLC. Wang et al also reported the same cases.23 There was another case who had undergone breast nodule resection before, so the change of SLC was considered to the former operation.

Tamaki Fujita et al and Shigeru Yamamoto et al used CT to study SLC and SLN in breast cancer,27,28 and the results showed that CT could also show LDPs. There were four patterns: single route/single SLN, multiple routes/single SLN, single route/multiple SLNs, and multiple routes/multiple SLNs. Hiroshi Ashiba et al29 showed that the accuracy of CT in detecting SLN metastasis was 93.00% to 98.00%. Naresh Kumar Saidha et al30 showed that the accuracy of CEUS in detecting SLN metastasis was 95.45%. The accuracy of SLN metastasis was similar between the two methods. Our study on LDPs by contrast ultrasound further refined the classification of drainage patterns, and there was no radiation damage to patients, in addition, SLN can be biopsied under CEUS guidance, which were the advantage of CEUS.

Li et al and Wang et al directly count the number of SLC to express the number of SLC.22,23 However, we found that detecting SLC in many cases was not straightforward and the existence of LP further complicated the detection. Simply counting the number of SLC cannot accurately represent the specific route of SLC. In addition, clinical work pays more attention to the situation of SLCs’ origin and SLNs in LDPs. Therefore, we used the original number of the SLCs from areola area to count the number of SLC.

Our data showed that the most common type of LDP was C1 subtype, accounting for 53.53% (197/368), followed by D1 subtype and G1 subtype, both accounting for 9.51% (35/368), and then by H1 subtype for 6.25% (23/368). The above four types accounted for 78.80% in total.

The origin of SLC was mostly located in the outer upper quadrant of the areola. If 3 o’clock of left areola/9 o’clock of right areola and 12 o’clock of areola were included, the original number of the SLCs in the outer upper quadrant accounted for 98.06% (456/465) of all SLCs’ origin locations. If 3 o’clock of left areola/9 o’clock of right areola and 12 o’clock of areola were excluded, the original number of the SLCs in the outer upper quadrant accounted for 67.96% (316/465) of all SLCs’ origin locations.
Li et al observed the origin of SLC in 453 cases, 85.4% of them originating from the outer upper quadrant. It can be seen that the upper outer quadrant was the most important area of lymphatic drainage in breast cancer.

LDPs of breast cancer were various. The false negative rate of SLNB may be related to the diversity of LDPs. Improving the clinicians’ knowledge understanding of LDPs may help reduce the false negative rate of SLNB. SLN was identified by CEUS before surgery to reduce intraoperative damage to SLC and improve postoperative quality of life of patients. This study also had some limitations. Due to ethical reasons, examination was only performed on patients diagnosed with breast cancer while the data of normal population could not be obtained. At the same time, this study was a single-center study, while future studies can carry out multi-center study with a larger sample size to further improve the accuracy.

Breast LDPs were complex and diverse, and the most common LDP was one SLC to one SLN, accounting for 57.78% (213/368). The origin of SLC was mostly located from the outer upper quadrant of the areola. If patients plan to perform SLNB, we should pay more attention to the location and number of both SLCs and SLNs. If patients do not plan to perform SLNB, their senological gynecologists do so. CEUS can accurately identify LDP before operation and label SLN under its guidance for assisting intraoperative formulation of surgical incision to reduce the false negative rate of SLNB and worthy of clinical promotion.

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