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# Retrospective Analysis of Sentinel Node Localization in Multifocal, Multicentric, Palpable, or Nonpalpable Breast Cancer

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Multicentric or multifocal breast cancer is considered as one of the limitations for sentinel lymph node (SLN) localization. We did a retrospective analysis to evaluate the success rate, sensitivity, accuracy, and negative predictive values of SLN localization in multicentric or multifocal breast lesions. **Methods:** Fifty-nine patients with multifocal or multicentric breast lesions proven by either fine-needle aspiration (19/59), core biopsy (39/59), or lumpectomy (8/59) underwent SLN localization. Of these patients, 46 had SLN localization by both radiocolloid and blue dye, and 13 had SLN localization by radiocolloid alone. Approximately 10 MBq <sup>99m</sup>Tc-labeled unfiltered sulfur colloid in 0.3–0.4 mL were injected intradermally over the 1 or 2 breast tumor locations 2–4 h before surgery. During surgery, vital blue dye was injected intraparenchymally in 4–6 places around the tumor. All lymph nodes with counts of >10 times that of the background counts, whether or not blue dye positive, and all blue dye-positive lymph nodes, whether or not radiocolloid positive, were excised and labeled accordingly. All lymph nodes underwent frozen sectioning and were examined by hematoxylin and eosin and immunohistologic (cytokeratin) staining. **Results:** Of the 59 patients, 48 had axillary lymph node dissection irrespective of the results of pathologic examination of the SLN. The success rate, sensitivity, negative predictive value, and accuracy were 93%, 100%, 100%, and 100% using the radiocolloid probe, 87%, 100%, 100%, and 100% using blue dye, and 93.5%, 100%, 100%, and 100% using combined methods, respectively. Concordance between blue dye and radiocolloid was 91% (the incidence of the number of sentinel nodes detected was 37.5%, 30.3%, 10.7%, and 21.4% for 1, 2, 3, and 4 or more lymph nodes, respectively). Metastatic lymph node involvement was found in 39.5% of patients. **Conclusion:** The sentinel node localization approach showed a high negative predictive value in breast cancer patients with multifocal or

multicentric lesions, contrary to the common belief of significant false-negative results in these patients.

**Key Words:** multifocal or multicentric breast cancer; sentinel lymph node; <sup>99m</sup>Tc-sulfur colloid;  $\gamma$ -probe; isosulfan blue vital dye  
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**T**he management of invasive breast cancer with no clinically evident lymph node involvement (stage I or stage II) needs exact staging of axillary lymph nodes. This staging could be obtained in 2 ways, either by axillary lymph node block dissection or, selectively, by sentinel node biopsy. Axillary dissection is associated with debilitating complications such as lymphedema, seroma, and parasthesia of the ipsilateral arm (1). Mapping of the sentinel node is a new approach to avoid unnecessary axillary node dissection. The first lymph node in the lymphatic basin draining the primary tumor is called the sentinel lymph node (SLN) (2,3). When identified and biopsied it reflects the histologic characteristics of the rest of the nodes in the basin. The sentinel node can be localized by vital blue dye injected around the tumor at the time of surgery or by radiocolloid mapping, separately or simultaneously (2–4). Both radiocolloid and blue dye have their own advantages and limitations (5–7). In the literature the success rate of both procedures showed wide variations, mostly because of the difference in experience among nuclear medicine physicians and breast surgeons at this early learning phase of using this technique (8,9).

The absolute contraindications mentioned in the literature for this procedure are palpable axillary lymph nodes, multifocal breast cancer, prior breast surgery (i.e., lumpectomy or excision of breast mass), and prior axillary operations (7). Most of the studies available in the literature have excluded patients who had a multifocal breast mass on the assumption

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that it is difficult to localize the true SLN (or there may be >1 sentinel node because there is >1 tumor at different locations in the breast). This study is a retrospective analysis of the success rate, accuracy, and negative predictive value of SLN localization in multifocal or multicentric breast cancer patients using isosulfan blue vital dye and radiocolloid techniques.

## MATERIALS AND METHODS

### Patient Population

Three hundred sixty-two patients with a histologic diagnosis of breast carcinoma by biopsy (fine-needle aspiration [19/59], core biopsy [32/59], or lumpectomy [8/59]) underwent lumpectomy or mastectomy and sentinel node excision at Saint Vincent's Catholic Medical Centers of New York between July 1998 and June 2001. Of the 362 patients, retrospective analysis showed that 59 patients had a clinical or histologic diagnosis of multifocal or multicentric breast carcinoma. All patients were women (age range, 34–80 y; mean age, 55.75 y). Of these 59 patients, 46 had SLN localization by both radiocolloid and blue dye, and 13 had localization by radiocolloid only. Twenty-seven patients with palpable breast masses had SLN localization by radiocolloid, blue dye, or both. Forty-eight patients had axillary node dissection irrespective of the results of pathologic examination of the sentinel node.

### Imaging Protocol for <sup>99m</sup>Tc-Sulfur Colloid (Radiocolloid)

Routine informed consent was obtained for all patients after the procedure was explained to them. Approximately 10 MBq <sup>99m</sup>Tc-labeled unfiltered sulfur colloid (CIS-sulfur colloid [size of particles, 160–5,600 millimicron; mean particle size, 0.3 ± 0.2 millimicron]; CIS-US, Inc., Bedford, MA) in 0.3–0.4 mL normal saline solution was injected intra- or subdermally using a tuberculin syringe with a 25-gauge fine needle over each clinically palpable tumor, or above and below the scar in case the patient had a lumpectomy or excision biopsy, 2–4 h before surgery. Patients were imaged using either a single-head or a dual-head  $\gamma$ -camera (Argus or Forte ADAC; Philips Medical Systems, Milpitas, CA) with a low-energy, high-resolution, parallel-hole collimator. Dynamic images (128 × 128 × 16 matrix) of 1 min per frame for 45 min at the lateral projection followed by static anterior and lateral images of 3 min each were obtained. The patient's arm was raised above the head. Transmission images using a <sup>67</sup>Co flood source was used to outline the body contour for the first 2 frames of the dynamic images as well as the static images. The dynamic images were reframed to 3 min per frame for review.

### Localization During Surgery

The isosulfan blue vital dye (2–5 mL) was injected intraparenchymally at 4–6 sites around the breast mass 10–15 min before

surgery. A gentle massage was performed for 5 min after the injection. During surgery, a  $\gamma$ -probe with an audible guidance system (CTC-4; Radiation Monitoring Devices, Inc., MA) was used to localize the SLN. The radioactivity counts were measured over the axilla with the  $\gamma$ -probe to confirm the location of the SLN seen on the scintigraphic images. All lymph nodes having counts  $\geq 10$  times that of the background counts were labeled as SLNs irrespective of the status of the blue dye. All lymph nodes were labeled, indicating a specific number and the blue dye status. For each serially numbered lymph node, a notation indicated whether it was blue dye positive, radiocolloid positive, or both. All sentinel nodes, plus other axillary lymph nodes, of the patients who also had axillary dissection underwent frozen sectioning, hematoxylin and eosin staining for gross metastases, and, if negative, immunohistologic (cytokeratin) staining for detection of micrometastasis.

## RESULTS

Of the 59 patients with multifocal or multicentric breast tumor, 27 patients had multiple breast lesions on clinical or mammographic examination (multifocal) and the remaining 32 patients had multicentric lesions on histopathologic examination. Forty-eight patients had axillary node dissection irrespective of the results of pathologic examination of the sentinel node. The success rate, negative predictive value, and accuracy were calculated according to the histologic report for the radiocolloid method and the blue dye method, separately and combined, as shown in Table 1. These parameters, one shown separately for multicentric patients and one for multifocal patients, are shown in Table 2 and Table 3, respectively.

Concordance between the blue dye and radiocolloid was 91% (42/46). Both techniques successfully identified the sentinel node in 85% of patients (39/46), whereas both were negative in 6% of patients (3/46). The discordance rate was 9% (4/46). Radiocolloid was positive but blue dye was negative in 3 of 46 patients (6.5%), and blue dye was positive with negative radiocolloid was in 1 of 46 patients (2%). No false-negative cases were found with either blue dye or radiocolloid. In 3 of 46 patients, both the radiocolloid method and the blue dye method failed to localize the sentinel node. All 3 patients had negative axillary node dissection for lymph node metastases.

One hundred thirty-five SLNs, ranging from 1 to 10 per patient (average, 2.4), were excised. The incidence of the number of sentinel nodes detected per patient was as follows: 1 sentinel node in 21 of 56 (37.5%), 2 sentinel nodes

**TABLE 1**  
Comparison of Success Rate, Sensitivity, Negative Predictive Value (NPV), and Accuracy in All Multicentric or Multifocal Patients

Method	Success rate (%)	Sensitivity (%)	NPV (%)	Accuracy (%)
Radiocolloid	93 (55/59)	100 (19/19)	100 (25/25)	100 (44/44)
Blue dye	87 (40/46)	100 (17/17)	100 (20/20)	100 (37/37)
Combined	93.5 (43/46)	100 (17/17)	100 (20/20)	100 (37/37)

**TABLE 2**  
Comparison of Success Rate, Sensitivity, Negative Predictive Value (NPV), and Accuracy in Patients with Multiple Breast Lesions on Clinical or Mammographic Examination

Method	Success rate (%)	Sensitivity (%)	NPV (%)	Accuracy (%)
Radiocolloid	93 (26/27)	100 (11/11)	100 (11/11)	100 (22/22)
Blue dye	95 (19/20)	100 (7/7)	100 (9/9)	100 (16/16)
Combined	100 (20/20)	100 (7/7)	100 (9/9)	100 (16/16)

in 17 of 56 (30.3%), 3 sentinel nodes in 6 of 56 (10.7%), and 4 or more sentinel nodes in 12 of 56 (21.4%) cases, respectively.

Of 48 patients who had axillary dissection, 19 (39.5%) had lymph node metastasis (12 patients with lymph node gross metastases and 7 patients with lymph node micrometastases) by histopathology. Of these 19 patients, 12 (63%) had only a single positive lymph node for metastases. In 2 subgroups of multifocal (palpable) or multicentric (microscopic) breast lesion, there was a significant difference in involvement of the lymph node by the metastatic tumor (48% vs. 36%, respectively).

## DISCUSSION

There is no uniformly accepted definition of multicentricity and multifocality in breast carcinoma; however, the most widely accepted definitions were given by Silverstein et al. (10). Multifocal lesions were defined when "... separate foci of ductal carcinoma more than 2 cm from primary site were found in a mastectomy specimen." Multicentricity was defined as "... the presence of separate independent foci of carcinoma in different quadrants." The incidence of multicentricity reported varies from 15% to 47% of mastectomy specimens (10–12). The usual management of multicentric breast cancer is mastectomy plus axillary lymph node dissection. Most centers consider patients with multifocal or multicentric lesions not to be candidates for localization of the SLN by any method because it may not reflect all possible sentinel nodes from different lesions.

In this study the success rate, sensitivity, negative predictive value, and accuracy obtained in this group of patients is very much similar to those obtained in patients who are candidates for SLN localization (4,13,14). Our study found that the radiocolloid method has a higher success rate than the blue dye method (93% vs. 87%), which has been shown by several other studies (13,14). No false-negative

cases were found with either the radiocolloid or the blue dye method. No significant difference was noted between the radiocolloid and combined methods with regard to the success rate and negative predictive value; however, there was only 1 patient in whom the SLN was localized by blue dye only. The concordance rate between the radiocolloid and the blue dye was 91% in this study. Borrgstein et al. (14) found 100% concordance in SLN detection between blue dye and radiocolloid. In another study by the same author, he found 91% concordance between radiocolloid and blue dye in one group of 68 patients and 96% concordance in a second group in 85 patients. The difference could be attributable to a learning curve for the surgeons (15). We found 6.5% of SLNs (3/46) localized by radiocolloid only and not by blue dye; the reverse was true in only 1 patient (1/46 [2%]), who had a previous lumpectomy, which could have caused disruption of lymphatic drainage. Cody (16) reported that 13% of SLNs localized by radiocolloid were not identified by blue dye and, in the same study, 8% of SLNs were identified by blue dye but were radiocolloid negative. So, to achieve the maximum possible success rate and to exploit the advantage of the sentinel node localization principle, the use of both techniques simultaneously is more justified than using any 1 procedure alone. The radiocolloid procedure is safe, has no reactions, and has no side effects except for the temporary pain from the injection and exposure to a very small dose of radiation. The blue dye procedure, however, has side effects of blue urine for the first day after surgery, occasional staining of the skin, and, rarely, development of anaphylactic reactions. In the literature there are also cases of failure in 3%–8% of patients even after using both techniques simultaneously. Possible reasons of failure were attributed to prior excision of the breast tumor, prior axillary node surgery, tumor infiltrating the lymph node that entirely distorted its normal architecture and physiology, and so forth (7). In this study, radiocolloid and blue dye both failed

**TABLE 3**  
Comparison of Success Rate, Sensitivity, Negative Predictive Value (NPV), and Accuracy in Patients with Multicentric Lesions on Histopathologic Examination

Method	Success rate (%)	Sensitivity (%)	NPV (%)	Accuracy (%)
Radiocolloid	90.6 (29/32)	100 (8/8)	100 (14/14)	100 (22/22)
Blue dye	80.7 (21/26)	100 (5/5)	100 (11/11)	100 (16/16)
Combined	88.4 (23/26)	100 (5/5)	100 (11/11)	100 (16/16)

to localize the SLN in 6.5% of patients (3/46). All 3 patients had axillary node dissection that was negative for lymph node metastases. All of these patients had a previous excision biopsy.

No difference was found in the negative predictive value or accuracy between the patient groups with multicentric and multifocal lesions. However, the success rate of the combined technique was higher (100% vs. 88%) and the average incidence of detection of SLNs was greater (2.7 vs. 1.9) in patients with multicentric lesions compared with those with multifocal lesions. A possible explanation of the higher success rate and better detection of SLNs in patients with multicentric lesions is that these patients received injections at >1 site. The only limitation of this study is the small number of patients. We are adding new patients as the number of patients in our database increases. This report of our results will encourage review of these data as well.

## CONCLUSION

The results of this study are encouraging because the sentinel node localization approach maintained a high negative predictive value in breast cancer patients with multicentric or multifocal lesions, contrary to the common belief of higher false-negative results in this category of patients, and justifies its routine use to replace axillary dissection. Considering the excellent results of this study and a higher incidence of multicentricity and multifocality in breast cancer, these patients should not be denied the benefits of the sentinel node localization techniques to avoid axillary dissection.

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