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Is Blue Dye Indicated for Sentinel Lymph Node Biopsy in Breast Cancer Patients With a Positive Lymphoscintigram?

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Background: The use of isosulfan blue dye in sentinel node biopsy for breast cancer has been questioned because of its risk of allergic reaction. We hypothesized that blue dye could be safely omitted in the subgroup of patients who have evidence of successful sentinel node localization by lymphoscintigraphy.

Methods: A retrospective review of patients with breast cancer and sentinel node biopsy was conducted. Information was collected on lymphoscintigraphy results, use of blue dye, and intraoperative and pathologic findings of sentinel nodes.

Results: We identified 475 patients with breast cancer who underwent 478 sentinel node biopsies. Both dye and isotope were given in 418 cases, of which 380 had a positive lymphoscintigram. In 5 of the 380 cases with a positive lymphoscintigram, the sentinel nodes obtained were blue but not hot, for a 1.3% marginal benefit of dye in the technical success of the procedure. Sentinel nodes positive for metastasis were found in 102 of 380 cases; in 3 cases, the only positive sentinel node was blue but not hot. Omission of the blue dye tracer would have increased the false-negative rate of the sentinel node procedure by approximately 2.5%.

Conclusions: Even in sentinel node biopsy cases with a positive lymphoscintigram, the use of blue dye is beneficial for both improving the technical success of the procedure and reducing the false-negative rate of the procedure. Because the marginal benefits of dye justify its routine use, strategies to minimize the toxicity of blue dye are warranted.

Key Words: Blue dye—Sentinel lymph node biopsy—Allergic reaction—Breast neoplasms.

Sentinel lymph node biopsy (SLNB) in breast cancer has rapidly evolved as the preferred procedure for staging the axilla. Multiple techniques seem to be successful according to published reports.[1–5] The primary variations in technique surround the use of single versus dual mapping agents, the location of the tracer injection, and the use of lymphoscintigraphy. Although methylene blue has been reported for lymphatic mapping in two series of breast cancer patients,[6,7] the most commonly used blue dye tracer in the United States is isosulfan blue dye.

Isosulfan blue dye carries a small but significant risk of allergic reaction, including possible anaphylaxis.[8] One logical approach to reduce allergic reactions to isosulfan blue dye is to use the dye selectively, i.e., only in cases in which isotope mapping fails. Therefore, we investigated whether the dye provides any marginal benefit in patients with a positive lymphoscintigram. In this subgroup with successful isotope localization to the axilla, the risk of allergic

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TABLE 1. *Characteristics of surgical procedures and tumor histology*

Variable	n	Mean	Median	Range
Patients	475			
SLNB procedures	478			
Technical failures	5			
Successful SLNB procedures	473			
SNs harvested per surgeon		2.37	2	1–8
SNs found by pathologist		2.95	2	1–15
Cases with positive SN(s)	135			
Cases with completion ALND	117			
Positive nodes found at ALND		1.39	0	0–23
Nodes removed at ALND		15.7	15	5–40
Tumor histology				
Invasive ductal cancer	333			
Invasive lobular cancer	47			
DCIS (treated with mastectomy and SLNB)	34			
DCIS with microinvasion	25			
Invasive cancer, ductal and lobular	10			
Other (tubular, medullary, mucinous, papillary, Paget's, adenoid cystic, ADH)	29			

SLNB, sentinel lymph node biopsy; SN, sentinel node; ALND, axillary lymph node dissection; DCIS, ductal carcinoma-in-situ; ADH, atypical ductal hyperplasia.

reaction might be avoided without compromising the success of the procedure.

METHODS

A retrospective, institutional review board–approved chart review was performed on breast cancer patients who underwent SLNB at the University of Michigan from October 1997 to November 2002. Information was collected on isotope and lymphoscintigraphy findings, use of blue dye, and sentinel node findings. Due to evolution of technique over time, lymphatic mapping was performed with varying methods: either ^{99m}Tc 3–4 mCi, isosulfan blue dye, or both. Peritumoral injections were performed by injection of tracer at four sites surrounding the palpable or estimated site of the lesion. For peritumoral dye injections, a 4-mL volume was used. Intradermal injection of radioisotope or dye (.5 mL) was performed directly overlying a palpable lesion, at the areolar edge if the lesion was nonpalpable, or cephalad to a prior biopsy scar if one was present. Lymph nodes with evidence of blue dye uptake or radioactivity as detected with an intraoperative gamma probe (Navigator; US Surgical, Norwalk, CT) were labeled as sentinel nodes. Lymph nodes that were palpably suspicious during surgery were also labeled as sentinel nodes. The sentinel lymph nodes were processed by following current recommendations.[9,10] Briefly, each sentinel node was measured and entirely cut along its longitudinal axis into sections 1.5 to 2 mm thick. The sections were submitted in formalin for paraffin section histology, and each paraffin block was sectioned at three levels. Immunohistochemical staining for cytokeratin was performed routinely from July 1999 to June 2001. After that time, cytokeratin staining was performed only for clarification of indeterminate findings on hematoxylin and eosin stain.

Harvested sentinel nodes were individually characterized as hot only, blue only, both, or palpably suspicious. Pathologic evaluation of the sentinel nodes was classified as positive, negative, or cytokeratin-only positive. Data were analyzed regarding the method of tracer injection and the contribution of blue dye to the technical success of lymphatic mapping and its false-negative rate.

RESULTS

We identified 475 patients (including 4 men) with breast cancer who underwent 478 sentinel node biopsies. Histology included 333 cases (70%) of invasive ductal carcinoma, 47 (10%) invasive lobular carcinomas, 34 (7%) ductal carcinomas-in-situ, 25 (5%) ductal carcinomas-in-situ with microinvasion, and other histological findings in 39 cases (8%; Table 1). There were 473 successful SLNB procedures, with a mean of 2.37 nodes harvested according to the surgeon and a mean of 2.95 nodes identified by pathologic analysis. A positive sentinel node was found in 135 patients, of which 117 underwent completion axillary node dissection. Of the 478 cases, there were 5 (1.0%) with technical failure of the SLNB procedure. Two of these patients underwent lymphatic mapping with dye alone. Of the other three tech-

TABLE 2. *Mapping failure and method of injection*

Variable	No. of patients with no hot/blue node found[a]	%
Isotope injection method		
Peritumoral	4/54	7.4
Intradermal	5/95	5.3
Intradermal + peritumoral	5/281	1.8
Subareolar	0/4	0
Total	14/434	3.2
Dye injection method		
Peritumoral	47/239	19.7
Intradermal	4/26	15.4
Intradermal + peritumoral	14/148	9.5
Subareolar	2/20	10.0
Unknown	2/29	6.9
Total	69/462	14.9

[a] Hot node for isotope injection; blue node for dye injection.

nical failures, lymphoscintigraphy confirmed failure of the isotope to migrate to the axilla in two cases.

Mapping failures based on the method of injection are listed in Table 2. Of 434 cases that received isotope, mapping failures were infrequent (3.2% overall) but occurred regardless of the method of isotope injection. Mapping failures with dye injection (15% overall) were much more common than for isotope and occurred most frequently with peritumoral injection (19.7%) despite the majority experience with that method (239 of 462 cases). Pairwise comparisons of injection techniques confirmed that peritumoral injection had a higher mapping failure rate than peritumoral plus intradermal injection ($P = .04$ by Fisher's exact test for isotope and $P = .007$ by χ^2 analysis for dye). All other pairwise comparisons among injection techniques for either dye or isotope showed no significant differences.

Both dye and isotope were given in 418 cases, including 380 with a positive lymphoscintigram. Of these 380 cases, there were 6 cases in which a hot node was not identified during surgery. In five cases, only blue nodes were found, and in one case no sentinel node was identified with radiotracer or blue dye (Fig. 1). Therefore, the technical failure rate of the SLNB procedure with a positive lymphoscintigram was 1 (.3%) of 380, but it would have been 6 (1.6%) of 380 if dye had not been used.

One or more sentinel nodes containing metastasis were found in 102 cases of the 380 with a positive lymphoscintigram (Fig. 2). In 94 of 102 cases, the metastatic sentinel node(s) were radioactive. In three cases, one or more hot nodes were identified, but the only sentinel nodes containing metastasis were blue but not radioactive. The method of isotope injection in all three of these cases was intradermal plus peritumoral (the most successful mapping technique for isotope in this study). Therefore, the benefit of blue dye cannot be attributed to using an inferior method of isotope mapping. The blue dye injection was peritumoral in two cases and peritumoral plus intradermal in one case. These three cases of axillary metastasis would have been undetected if dye had not been used, even in the setting of a positive lymphoscintigram.

Because many of the patients with negative sentinel nodes did not undergo completion axillary dissection and because follow-up information is incomplete, the absolute change in the false-negative rate for this group of patients cannot be calculated. However, the effect of blue dye on the false-negative rate can be estimated by the following process. Assuming a false-negative rate of 5%, if we identified 102 cases with a positive sentinel node, then 5 additional cases with a truly positive axilla were missed. If we had not used dye, then we would have missed an additional 3 cases, thus increasing the number of false-negative cases to 8 (7.5%) of 107—a 2.5% increase.

In 5 of 102 cases with axillary metastasis, the only positive node found was neither hot nor blue. All five of these cases had successful technical mapping procedures, with a hot and blue sentinel node identified. However, none of these hot and blue sentinel nodes contained metastasis. In three of the five cases, the positive node was a node believed to be palpably suspicious during the procedure. In the other two cases, the positive node was an adjacent nonsentinel node that was removed incidentally.

DISCUSSION

The optimal techniques for SLNB have been debated,[11] but there is considerable support for a dual tracer technique.[4,5,12–14] Several studies have found that a dual tracer technique improves technical success by 3% to 10%[4,12–14] and reduces the false-negative rate by 2% to 6%.[4,13,14] Despite these benefits, controversy remains surrounding the routine use of blue dye because of its potential toxicity. The most widely used dye in lymphatic mapping for breast cancer is isosulfan blue dye, which carries a risk of acute inflammatory/hypersensitivity reactions, including blue urticaria, hypotension, and life-threatening anaphylaxis. These reactions have been well documented.[8,15–19] The frequency of any allergic reaction in patients who receive isosulfan blue dye for lymphatic mapping in breast cancer is reported as 1.6% to 2%,[15,16] and the risk of anaphylaxis is re-

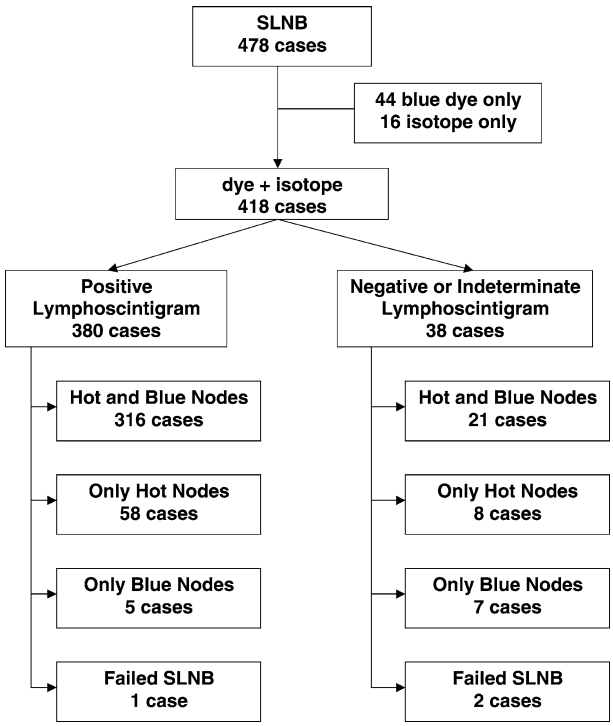

FIG. 1. Effect of blue dye use on identification of sentinel nodes. SLNB, sentinel lymph node biopsy.

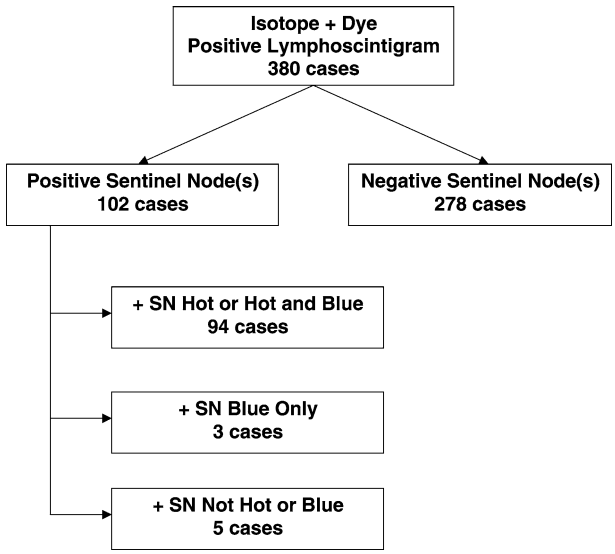

FIG. 2. Effect of blue dye use on identification of positive sentinel nodes (SN).

ported as .5% to .7%.[15,16] One approach to reduce the incidence of such reactions would be to use blue dye selectively, i.e., as a backup technique, only in cases in which lymphatic mapping with radiotracer fails.

When both blue dye and isotope are used routinely, the value of preoperative lymphoscintigraphy is questionable,[20] although it is frequently performed. We hypothesized that the blue dye, which carries much of the risk of the procedure, could be avoided in cases in which the lymphoscintigram demonstrates a sentinel lymph node. This approach rests on the assumption that lymphoscintigraphic success results in technical operative success. Before adopting a selective approach to the use of blue dye, we evaluated the utility of blue dye in our patients who had a positive lymphoscintigram. To our knowledge, the benefit of blue dye has not been reported in this subset of patients.

We found greater mapping success with isotope than with dye, but there were mapping failures with isotope regardless of the method of injection. Therefore, blue dye should still provide some marginal benefit for reducing the technical failure rate and for reducing the false-negative rate, regardless of the method of isotope injection. During this study, we had very few patients with subareolar injection of tracers. Reported mapping success rates with subareolar injection are higher than those of the dye injection techniques reported here.[21] With increased mapping success from subareolar injection of dye, the benefits of complementary blue dye use may be even further enhanced.

We assumed that our technical failure rate was 0% when the lymphoscintigram confirmed uptake in an axillary node(s). This assumption was wrong, because we did not identify a hot node in every patient with a positive lymphoscintigram. Possible reasons include false-positive lymphoscintigrams and a diffusely hot axilla. Wu et al.[22] have also reported a small rate of failure to harvest sentinel lymph nodes in patients with successful preoperative lymphoscintigraphy. In that study, a sentinel node was identified in 164 of 170 patients with a positive lymphoscintigram, thus constituting a technical failure rate of 6 (3.5%) of 170. In our series of patients, the routine use of blue dye improved the technical success of lymphatic mapping by 1.3%, even when lymphatic mapping with radiotracer seemed to be successful by lymphoscintigraphy.

A second benefit of using a dual tracer technique is a reduction in the false-negative rate of SLNB. We found that blue dye allowed identification of sentinel node metastasis in three patients with positive lymphoscintigraphy. In these three patients, hot sentinel nodes were harvested and found to be negative for metastasis. With a selective use of blue dye, these nodal metastases probably would have been missed, and this would have increased the false-negative rate

by a few percentage points. DeRossis et al.[14] showed that the marginal benefit of blue dye diminished over time in accordance with experience and the technical success of the procedure, but even in their most recent 500 cases, blue dye still increased technical success by 3% and reduced the false-negative rate by 2%. DeRossis et al.[14] acknowledge that these gains are small but combine with other reasons that justify continued use of a dual tracer mapping technique.

Use of the blue dye in addition to the isotope for lymphatic mapping may also contribute to the technical ease of the procedure. The visual cues created by blue-stained channels leading to the sentinel nodes or the blue-green blush of a sentinel node that is otherwise hidden within the axillary fat pad are advantages unique to the blue dye. These subtle advantages can increase the rapidity and facility with which the sentinel lymph node is identified (whether or not there is concomitant isotope uptake), but they are not necessarily documented in the operative record.

Our findings demonstrate that a dual tracer lymphatic mapping method increases the technical success and reduces the false-negative rate of sentinel node biopsy in patients with a positive preoperative lymphoscintigram; however, the magnitude of these benefits was small ($< 5\%$). The question remains whether these small gains are worth the potential toxicity associated with the use of the blue dye, and our findings prompt exploration of other options that may still allow an optimal technique while circumventing the associated risks of administering blue dye. Investigators at the MD Anderson Cancer Center have reported on the effects of premedicating with histamine blockers and corticosteroids before isosulfan injection.[23] Although this prophylaxis reduced the severity of allergic reactions, the wound infection rate was greater in patients who received corticosteroid prophylaxis. King et al.[24] have reported a trend toward fewer allergic reactions with smaller volumes of injected dye, and they advocate the use of the smallest volume of dye necessary.

The use of an alternative dye, methylene blue, has been reported in a series of 112 patients.[6] In this retrospective review, intraparenchymal injection of 5 mL of 1% methylene blue dye was used in combination with radioisotope. The authors reported a mapping success rate of 93% by dye and 96% overall, with a dye/isotope concordance of 95%. Of patients with positive sentinel nodes, 97% demonstrated dye uptake. In a second study of methylene blue for lymphatic mapping in breast cancer,[7] a retrospective comparison of 87 patients mapped with isosulfan blue and 112 patients mapped with methylene blue showed similar performance of the 2 dyes.

Although no toxicity was attributed to methylene blue in these two series of patients, methylene blue has been anecdotally associated with local inflammatory reactions leading to skin necrosis at the site of injection. Stradling et al.[25] reported skin lesions in 5 of 24 patients who received intradermal injection of methylene blue dye for lymphatic mapping in breast cancer. The skin lesions included a variety of local inflammatory presentations, including erythematous macular lesions, superficial ulcers, and necrotic ulcerations. After injections were restricted to the deep parenchyma, no further skin lesions were noted. This local toxicity of methylene blue with superficial injection concerns surgeons who perform subareolar injection because of its potential effect on the nipple/areolar complex. Some individuals have found that dilution of methylene blue (2 mL of methylene blue and 3 mL of saline) allows successful mapping while avoiding this local toxicity (Pat Whitworth, MD, personal communication, May 2004).

Although sentinel node biopsy in breast cancer has been studied widely, continued optimization of techniques will allow patients to benefit from a dual tracer technique with minimal risks of blue dye administration. We believe that the potential gains from use of blue dye warrant its routine use, as well as continued research into strategies to reduce the toxicity of blue dye.

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