ORIGINAL ARTICLE

The Clinical Utility of Indigo Carmine in Sentinel Lymph Node Biopsy of the Breast Cancer

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Background: The selection of blue dye or technetium radioisotope depends on the surgeon's experience or the availability of the center in sentinel lymph node biopsy (SLNB). The purpose of this study is to evaluate the possibility of clinical usage of indigo carmine in SLNB in breast cancer.

Methods: From the July 2001 to the March 2004, 93 consecutive cases of Tis - T2 breast cancers without palpable axillary lymph nodes were enrolled to the SLNB. After usual preparation for the breast conserving surgery or mastectomy, the patients were intradermally injected with 5 ml of indigo carmine around the subareolar area. After 4 minutes has passed, usual axillary incision of breast conserving surgery was made, and the stained lymphatics were followed to the firstly encountered lymph nodes. The dissected nodes were sent to the department of pathology for frozen and permanent sections. After SLNB, axillary lymph node dissections (ALND) were completed regardless of the result of the frozen section.

Results: The identification rate of SLNB using Indigo carmine was 97.8% (91/93). The axillary node metastases on complete ALND were 21 cases. 18 cases were detected with SLNB, and 3 cases were falsely reported as negative on SLNB. 11 cases had metastases in the sentinel nodes only (52.4%). Among the 3 false negative cases, one case had axillary metastasis solely in a node in level III (infraclavicular node). The sensitivity of the test was 85.7% (18/21), and the specificity was 100% (70/70). False negative rate was 9.5% (2/21), and negative predictive value was 95.9% (70/73).

Conclusions: Sentinel node biopsy using indigo carmine showed similar identification rate and false negative rate with other blue dye only methods including isosulfan blue. Because indigo carmine is

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Table 1. Clinical characteristics of the patients.

Characteristics		Numbers
Mean age(range)		48.6(29~74)
Dx	IDC	73 (80.2%)
	DCIS	7 (7.7%)
	others(papillary,etc.)	11 (12.1%)
Surgery	Mastectomy	18 (19.8%)
	BCS	73 (80.2%)
Tumor size	≤2.0cm	59 (70.2%)
	2.0~5.0cm	25 (29.8%)
	Missing	7
Location	UOQ	48 (52.7%)
	UIQ	20 (21.9%)
	LOQ	6 (6.6%)
	LIQ	7 (7.7%)
	Tail	2 (2.2%)
	Central	5 (5.5%)
	Diffuse	3 (3.3%)

Dx= Pathological diagnosis of primary breast cancer; IDC= Infiltrating ductal carcinoma; DCIS= Ductal carcinoma in situ; BCS= Breast conserving surgery; UOQ= Upper outer quadrant; UIQ= Upper inner quadrant; LOQ= Lower outer quadrant; LIQ= Lower inner quadrant.

Table 2. Number of identified sentinel LN and axillary LN.

	Mean
Sentinel Lymph Node Harvested(N=91)	2.3(1~8)
Metastatic SLN(N=18)	1.17(1~3)
Total Axillary Lymph Node Harvested(N=91)	13(6~36)
Metastatic ALN(N=21)	2.95(1~19)

LN= lymph node; SLN=Sentinel lymph node; ALN=Axillary lymph node.

Table 3. Sentinel lymph node biopsy.

	Axillary lymph node status		
	Negative	Positive	Total
SLN on Permanent sections			
Negative	70(70)	3* (4)	73(75)
Positive		18(17)	18(17)
Total	70(70)	21(21)	91

Identification rate = 91/93(97.8%); Sensitivity = 18/21(85.7%) ; Specificity = 70/70(100%); False negative = 3/21(14.3%); Negative predictive value = 70/73(95.9%).
*Among 3 false negative cases, one skip metastasis was found in level III nodes and true false negative rate was 9.5% (2/21).

Table 4. Metastastic lymph nodes found in sentinel & nonsentinel lymph nodes.

Metastatic LN found in only				
No. of LN Metastasis	Sentinel	Non-sentinel	Both	Total
1	9	3	0	12
2~5	2	0	5	7
〉5	0	0	2	2
Total	11	3	7	21

LN= lymph node.

nosis of Tis - T2 breast cancers in Department of Surgery, Korea University, total 93 consecutive cases without palpable axillary lymph nodes were enrolled to the study. Patients who received prior breast or axillary surgery, or neoadjuvant chemotherapy or radiation were excluded.

Under the general anesthesia, the usual preparation of the breast cancer surgery was done. Before the main surgical procedure, 5 ml of indigo carmine (0.8%, 5 ml, United state) was intradermally injected around the subareolar area. 3, 6, 9, and 12 o'clock directions were selected for sites of injection(Fig 2). After 4 minutes have passed, usual axillary incision of the breast conserving surgery (BCS) was made. The stained lymphatics were followed to the firstly encountered lymph nodes(Fig 3). Harvested nodes were sent for frozen and permanent serial sections. If the sentinel nodes were negative for metastasis on routine examinations, their serial sections and immunohistochemical stains were executed for detection of micrometastasis. About 20 slices (range 15-25) per a sentinel node were examined.

Regardless of the results of frozen section, we proceeded to the completion axillary lymph node dissections (ALND) and compared the results with those of SLNB.

RESULTS

The mean age of the subject patients was 48.6 (range 29-74). Among the toal 93 cases, we failed to find the sentinel nodes in two cases. So the analysis was done with 91 cases. Infiltrating ductal carcinoma was 73 cases (80.2%). DCIS and other pathologic classes of breast cancer were 7 (7.7%) and 11 (12.1%) cases, respectively. The surgical treatment was BCS in 73 cases (80.2%) and mastectomy in 18 cases (19.8%). T1 breast cancers (2.0 cm or smaller) were 59 cases (70.2%) and T2 was 25 cases (29.8%). The 7 DCIS cases were not included in either size categories. The location of the tumor was most commonly in the UOQ and the UIQ was the next(Table 1).

The mean harvested sentinel lymph nodes were

DISCUSSION

SLNB in breast cancer is a promising surgical technique to confirm nodal status and minimize arm morbidity. Many investigators have demonstrated excellent results of SNB with blue dye, radionuclides, or the combined method.*(18-22)* However, there are many different ideas concerning the site of injection of the vital blue dye or radionuclides, the dose of radioactivity used, the interval between dye injection or lymphoscintiscan and SNB, and the various surgical procedures for SLNB in breast cancer. Lymphatic mapping and SLNB remain standardized. In general, SLNB is an accurate, safe procedure when used appropriately, that may save 70% of women with clinically negative axillae from undergoing a full axillary dissection and its complications. Surgeons who perform breast cancer surgery infrequently should probably not employ SLNB. Initially surgeons should perform SLNB along with axillary dissection until the sentinel node(s) can be identified accurately in more than 90% of patients, with fewer than 5% false positives on light microscopy following frozen section. In experienced hands, identification of the sentinel nodes should be achieved in more than 95% of patients, and the false negative rate should be the same.*(23)* The role of IHC is under study. For this reason, the results of IHC analysis should not determine adjuvant therapy.

The foreign publishers of isosulfan blue saled the dye only in package with the technetium radiolabled sulfur colloid. We can manage to get the chemical material by alternative means but no one has tried to get the permission of FDA of Korea for the use of that material in human bodies. In addition, adverse effects of isosulfan blue are piling in the literature. Several vital dyes have been already used in clinical practice. We started SLNB with methylene blue but switched to indigo carmine after 2 cases of skin lesions. So we selected indigo carmine as our validation study of SLNB.

The 97.8% identification rate of this study using only Indigo carmine is higher compared to usual 95% and 9.5% false negative rate is higher than less than 5%. However, surgeon's experiences in SLNB overcomes the difference in the technical aspects and more than 20 to 30 SLNB experiences can give credit in the validity of SLNB results.*(23,24)* The 3 false negative cases are shown in table 5. All 3 cases had masses in UOQ, and the sizes were all larger than 1.5cm. According Noguchi et al, mass size larger than 1.5cm is a factor related with high false negative rate.*(17)*

We tried to find the factors related with the false negative results(Table 6). But 3 cases were too small to show any statistically significant differences. A multicenter trial like that of Japanese breast cancer society are needed to address these issues.*(17, 25)*

Table 7. Published experiences with sentinel lymph node biopsy.

Study	Year	N	Technique	Injection site	MSNH	ID rate	FN Rate
Kern*(13)*	1999	40	IB alone	Subareolar	2±1.5	39/40(97.5%)	0/15(0%)
Imoto et al*(19)*	1999	88	IC alone	Peritumoral	2.0	65/88(74%)	4/29(14%)
Aihara et al*(14)*	2003	60	IC alone	NA	NA	60/60(100%)	0/20(0%)
Yang et al*(20)*	1999	140	IB alone	Peritumoral	NA	42/53(79.2%)	12.2%
			DA			10/10(100%)	8.3%
Choi et al*(21)*	2002	157	RC alone	Peritumoral	1.6	173/178(97.2%)	4/89(4.5%)
Park et al*(22)*	2002	55	DA	Subdermal	3.45	47/55(85.4%)	1/13(7.7%)
Kim et al*(23)*	2003	162	RC alone	Subareolar	1.83	127/132(96.2%)	8/38(21.1%)
Kang et al*(24)*	2003	176	DA	Subdermal	NA	164/176(93.2%)	14/85(16.5%)
Lee et al*(15)*	2003	30	IB(endoscopy)	subareolar	2.2	28/30(93.3%)	0/10(0%)
Current Study		94	IC alone	Subareolar	2.3	92/94(97.9%)	3/21(14.3%)

MSLH=Mean number of sentinel lymph node harvested; ID =identification; FN=false negative; IB=Isosulfan blue; IC=Indigo carmine; NA=Not applicable; RC=Radioactive colloid; DA=Dual agent.

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