

## Significance of Sentinel Lymph Nodes with Low Gamma Counts in Breast Cancer Patients via Radioisotopic Sentinel Lymph Node Biopsy

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Received date: January 20, 2016; Accepted date: February 18, 2016; Published date: February 22, 2016

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### Abstract

**Objective:** Sentinel lymph node biopsy (SLNB), a standard diagnostic procedure worldwide, uses blue dye and/or radioisotopic methods to detect clinically node-negative breast cancer. With the latter method, we often experience axillary lymph nodes with extremely low levels of radioactivity, compared with the maximum radioactive nodes. Here, we investigated the significance and possibility of metastasis in low radioactive SLNs in patients with and without metastasis in maximum radioactive SLNs.

**Patients and methods:** Between 2003 and 2011, we subjected a total of 453 breasts in 443 patients with early-stage invasive ductal carcinoma to SLNB using a combination of blue dye and radioisotopic methods. All lymph nodes detected via gamma -probe were considered SLNs and resected.

**Results:** SLNs were identified in 452 (99.8%) of 453 cases; of these, SLN metastasis was pathologically diagnosed in 118 cases (26.1%). Two or more SLNs were detected in 232 (51.2%) of 453 cases; of these, 46 cases (19.8%) had SLNs with gamma counts < 10% of the maximum detected values. Metastasis was detected in these low-gamma-count SLNs in 4 of 453 cases (0.9%), even though no metastasis had been detected in SLNs with maximum radioactivity levels. Macrometastasis was pathologically demonstrated in 3 of 4 cases.

**Conclusion:** We identified several cases of metastatic SLNs with very low radioactivity, despite a lack of metastasis in SLNs with maximum radioactivity. These findings indicate that the evaluation of SLNs with gamma counts < 10% of the patient maximum would provide more precise information about the axillary status and help to maintain a low SLNB false-negative rate.

**Keywords:** Breast cancer; Sentinel lymph node biopsy; Radioisotopic method; Low gamma count; Locoregional control

### Introduction

Beginning in the late 1990s, sentinel lymph node biopsy (SLNB) was rapidly adopted worldwide as a standard diagnostic method for early-stage breast cancers with clinically negative axillary lymph nodes [1-3]. Accordingly, the risk of lymphedema in the ipsilateral arm had decreased with the elimination of axillary lymphadenectomy (ALND) for breast cancer patients without SLN metastasis.

Currently, SLNB incorporates both blue dye and/or radioisotopic methods to identify SLNs, and a combination of such methods is superior to blue dye alone with respect to SLN identification [4,5]. However, the accuracy of SLNB depends not only on the SLN identification rate, but also the false negative rate (i.e., the presence of metastases in non-SLNs without metastases in SLNs from the same patient); this latter factor must be maintained at a low rate to avoid postoperative axillary lymph node recurrence.

In many patients with multiple SLNs, some SLNs have very low levels of radioactivity, measured by gamma counts, when compared with the maximum levels in other SLNs. SLNs with maximum and high counts are easily identifiable, whereas SLNs with very low gamma counts may be difficult to detect. Notably, in melanoma cases, lymph

nodes with gamma counts < 10% of the maximum count in other nodes are generally considered to be non-SLNs [6]. However, patients who present with such findings are more likely to undergo removal of only non-metastatic SLNs with maximum counts in order to avoid ALND. As a result, the SLNB false-negative rate and the possibility of axillary lymph node recurrence may increase.

In the present study, we removed SLNs with low gamma counts (i.e., < 10% of the maximum SLN count) to the extent possible, and examined the characteristics of breast cancer patients with non-metastatic SLNs with maximum counts and metastatic SLNs with low counts to evaluate the significance of these latter SLNs.

### Patients and Methods

We studied a total of 453 breast cancers in 443 patients with invasive carcinoma (including 10 patients with bilateral breast cancers) that underwent SLNB using a technetium phytate radioisotope and indigo carmine blue dye between 2003 and 2011 at our institute. SLNB was performed in the patients with breast tumors < 3 cm in size and no detectable axillary lymph node swelling on ultrasonography and magnetic resonance imaging.

For radioisotope SLNB, 1.2-2.0 mCi of technetium phytate in 0.4 ml of normal saline was injected subdermally in and around the primary tumor on the day before the operation. Lymphoscintigraphy was

performed at 15 min and 2 hours post-injection. At the beginning of surgery, 2 ml of indigo carmine blue dye was injected subdermally into the primary tumor. A gamma-probe (Navigator GPS system; RMD Instruments, Corp., MA, USA) was used to intraoperatively detect and measure SLNs; the gamma counts of all removed SLNs was measured for 10 s. SLNs with very low counts were removed to the extent possible.

All SLNs were sliced at 2 mm intervals, subjected to fixation and paraffin embedding, and pathologically examined following hematoxylin and eosin staining and cytokeratin immunohistochemistry to detect micrometastases and isolated tumor cells. Clinical follow-up studies were performed to determine the ipsilateral axillary lymph node recurrence rate (i.e., false-negative rate).

## Results

SLNs were identified in 452 (99.8%) of 453 cases. A total of 875 SLNs, or an average of  $1.93 \pm 1.13$  per case, were resected. Of these 875 SLNs, 818 (93.5%) were hot nodes, and 784 (89.6%) were hot nodes stained with blue dye; 34 hot nodes (3.9% of 875) were blue dye-negative, and 57 cold nodes (6.5% of 875) were blue dye-positive (Table 1). Of the 452 cases with SLNs, 118 cases (26.1%) harbored a total of 143 histologically metastatic SLNs; 139 (97.2% of 143) were hot, blue dye-positive nodes. Notably, none of the 57 (6.5% of 875) blue dye-positive cold SLNs were metastatic (Table 2).

		Blue dye		Total (%)
		Positive (%)	Negative (%)	
Radioisotope	Positive (%)	784 (89.6)	34 (3.9)	818 (93.5)
	Negative (%)	57 (6.5)	*	57 (6.5)
Total		841 (96.1)	34 (3.9)	875

**Table 1:** Accuracy of sentinel lymph node (SLN) biopsy in the present study. \* SLNs were not identified in 1 of 453 cases (0.2%).

Findings of SLNs	Number of SLNs	Number of SLNs with metastasis
	875 (452 cases)	143 (118 cases)
Dye- stained SLNs	841 (444 cases)	139 (115 cases)
Dye-stained SLNs with radioactivity	784 (444 cases)	139 (115 cases)
Dye-stained SLNs without radioactivity	57 (36 cases)	0

**Table 2:** Dye-stained sentinel lymph nodes (SLNs) with metastasis.

Two or more SLNs were detected radioisotopically in 232 cases. SLNs with gamma counts < 10% of the maximum SLN count in the same case were resected in 46 (19.8% of 232) of these cases and in 4 such cases (0.9% of 453 total cases), metastasis was detected in these low-gamma-count nodes, despite a lack of metastasis in SLNs with maximum gamma counts. All of the very low-gamma-count metastatic SLNs were also blue dye-positive, and were thus included among the radioactive dye-stained SLNs listed in Table 2. In addition, 3 cases

harboring SLNs with very low gamma counts were found to have macrometastases (Table 3) and were subjected to ALND following the identification of metastasis during the intraoperative pathological examination. The fourth case did not undergo ALND because micrometastasis was not detected in the SLNs during the intraoperative pathological examination. The mean follow-up time in this study was 96 months (range: 57-175 months). None of these 4 cases experienced an axillary lymph node relapse or distant metastasis.

Case	Maximum count of SLN (%)	Second count of SLN (%)	Third count of SLN (%)
1	100 *	1 ***	-
2	100 *	5 ***	2 *
3	100 *	8 ***	-
4	100 *	33 *	1 **

**Table 3:** Findings of 4 patients harboring metastatic sentinel lymph nodes (SLNs) with gamma counts < 10% of the maximum gamma counts of SLNs without metastasis. \*without metastasis, \*\*with micrometastasis, \*\*\*with macrometastasis

In contrast, 2 of the 453 total patients (0.4%) experienced ipsilateral axillary lymph node recurrences at 40 and 84 months after SLNB. Both patients underwent ALND following the diagnosis of lymph node recurrence and remain alive without evidence of disease.

## Discussion

The findings of the present study demonstrated the potential for metastasis in SLNs with very low gamma counts, despite a lack of metastasis in SLNs with maximum gamma counts from the same breast cancer patient, as 4 such cases were identified in our cohort. In addition, macrometastasis was identified in the 3 of these 4 cases (Table 3). These findings support the analysis of SLNs with low gamma counts to the extent possible. In such cases, an absence of metastasis in these low-gamma-count SLNs (as well as in maximum/high-gamma count SLNs), confirmed via intraoperative pathological examination, would allow patients to avoid ALND. However, failure to resect potentially metastatic SLNs with low gamma counts could increase the risk of postoperative axillary lymph node recurrence as well as the SLNB false-negative rate. Our findings indicate that the risk of axillary lymph node recurrence could be reduced in nearly 1% (0.9%, 4 of 453) of cases harboring SLNs with < 10% of the individual patient's maximum gamma count.

In our study, the SLN identification rate of 99.8%, as shown in Table 1, and the false-negative rate of 0.4%, obtained during postoperative follow-up, confirm the ability to achieve a high level of accuracy with a combination of both radioactive and dye-based methods, in agreement with earlier studies [7-9]. Previous studies have reported axillary lymph node recurrence rates after ALND omission of 2.6-3.6% for the patients in whom metastasis-negative SLNs were identified using blue dye alone [10,11], whereas a combination of blue dye and radioisotopic methods decreased the axillary recurrence rate to 0.7% [12,13]; in other words, addition of radioisotopic method would decrease the false negative rate by 2 -3%. These data appears similar to the detection rate of metastatic very low-gamma-count SLNs in the present study (0.9%). In fact, many SLNs with very low gamma counts were identified using

the radioisotopic method but would have been impossible to detect using blue dye alone, although all were blue dye-positive (Table 2).

Adjuvant breast cancer treatments, including chemotherapy, and prognostic predictions depend on a precise evaluation of the axillary status; accordingly, the accuracy and precision of SLNB techniques must be maintained. Although a false-negative SLNB result would lead to misevaluation of the axillary status and could thus affect decisions regarding adjuvant chemotherapy, the effect of a false-negative SLNB result remains controversial. Z0011, a randomized trial conducted by the American College of Surgeons Oncology Group (ACOSOG), found no differences in axillary recurrence and overall survival between SLN-positive patients in the presence and absence of ALND, and concluded that ALND omission could be acceptable even in the presence of metastatic SLNs [14]. In other words, the effect on prognosis would be small even if metastatic axillary lymph nodes other than SLNs were not resected. The metastasis rate of SLNs with very low gamma counts is small, as shown in the present study, and might be allowable especially in patients with luminal-type breast cancers, who comprised a large portion of the Z0011 cohort. However, reports of the positive impact of ALND on overall and recurrence-free survival in patients with SLN support the importance of locoregional control [15,16]. Despite these contrasting viewpoints, efforts to ensure highly accurate SLNB should be continued, especially for breast cancer patients with large primary tumors and intrinsic subtypes (including triple-negative or HER2-enriched), which are among the strong risk factors for recurrence.

In conclusion, SLNs with gamma counts < 10% of the individual breast cancer patient maximum level carry a small but notable risk of metastasis, even in the absence of metastasis in SLNs with high or maximum gamma counts. Our data indicate better accuracy with radioisotopic detection than with blue dye. SLNB technique selection is important in terms of the reduction in false-negative results; in addition, the detection of SLNs with low gamma counts would provide more precise information about the axillary status and reduce the false-negative rate among patients harboring non-metastatic SLNs with maximum gamma counts.

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