

Optimized Criteria for Sentinel Lymph Node Biopsy in Patients with Clinically Node Negative Breast Cancer

Jeong Suk Kim, M.D., Moo Hyun Lee, M.D., Sun Hee Kang, M.D., Ph.D., Jihyoung Cho, M.D.

Department of Surgery, Keimyung University School of Medicine, Daegu, Korea

Purpose: Sentinel lymph node biopsy (SLNB) is a well-established staging procedure for patients with early breast cancer who have clinically negative axillary lymph node. However, no consensus exists about the number of sentinel lymph nodes (SLN) that should be removed based on radioactivity counts in breast cancer. We reviewed and analyzed cases in which more than one SLN was detected and there was at least one pathologically positive node. **Methods:** We retrospectively studied breast cancer patients who underwent lymphoscintigraphy with injection of a radioactive colloid and SLNB along with intraoperative determination of radioactive counts of lymph nodes using a gamma probe between 2006 and 2018. In total 326 patients with more than one radioactive SLN were enrolled in this study. **Results:** Fifty-four patients had nodal metastases, of whom 46 (85.2%) had metastases in the hottest lymph node. All metastatic SLNs were identified as one of the first three lymph nodes dissected. The lowest radioactive count of a positive SLN corresponded to 10% of that of the hottest node. **Conclusion:** We suggest that removal of the first three lymph nodes or nodes covered by the “10% rule” is sufficient in SLNB for patients with breast cancer.

Key Words: Breast neoplasms, Lymph node excision, Sentinel lymph node biopsy

INTRODUCTION

Breast cancer prognosis is mainly determined by axillary lymph node status [1]. The sentinel lymph node (SLN) has been defined as the first lymph node to receive lymphatic drainage from a tumor bed. Commonly, there can be more than one SLN, and therefore, it is currently defined as any lymph node or first set of nodes that receives direct lymphatic drainage from a primary tumor [2].

Sentinel lymph node biopsy (SLNB) is a well-established procedure for the staging of the axilla in early stage breast cancer and has replaced axillary lymph node dissection (ALND) as the standard of care in patients with clinically negative axillary lymph node [3]. SLNB limits the extent of axillary surgery compared with complete ALND, thus reducing the associated morbidity [4]. Following the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, the role of ALND after SLNB has been further reduced [5,6]. However, because

no consensus exists about the number of SLNs that should be removed based on the relative radioactivity counts registered during surgery, the “10% of the hottest nodes rule” is often used [7,8]. To determine the frequency at which radioactivity counts can actually be used to detect malignant SLNs and to define the optimal criteria for removal of radioactive lymph nodes, we reviewed and analyzed the frequency and distribution of radioactive malignant SLNs in patients with breast cancer who had more than one radioactive SLN and at least one pathologically positive lymph node.

METHODS

We retrospectively reviewed the medical records of 1,687 patients with breast cancer who underwent lymphoscintigraphy with injection of a radioactive colloid and SLNB with intraoperative determination of the radioactive count of lymph nodes using a gamma probe (Neoprobe, Mammotome, Cincinnati, USA) at Keimyung University Dongsan Hospital between January 2006 and December 2018. The study was approved by our Institutional Review Board (IRB No. 2020-10-001-002).

SLNB was performed in all patients with early-stage breast cancer without clinically positive axillary lymph nodes or advanced disease.

Correspondence: Jihyoung Cho, M.D.

Department of Surgery, Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 41931, Korea
Tel: +82-53-258-4708, Fax: +82-53-258-4710, E-mail: chojh0404@dsmc.or.kr

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korea Government (MSIP) (no. 2018R1C1B5086617).

Received: Oct 16, 2020 **Revised:** Nov 5, 2020 **Accepted:** Jan 24, 2021

Patients with no detectable SLNs or only one SLN were excluded. A total of 326 patients who had more than one radioactive SLN were enrolled in this study. SLN-related parameters such as the number, radioactivity, order, and pathological status of SLNs were prospectively recorded. An incision was made over the hottest area identified by the gamma probe, and SLNs were retrieved for intraoperative frozen section evaluation. Patients who had positive SLNs underwent ALND. We analyzed the clinical and pathological data of patients, including data on age, tumor–node–metastasis stage, hormone receptor and human epidermal growth factor receptor type 2 (HER2) status, histologic type, number of SLNs, relative radioactivity counts, and presence of metastasis in SLNs.

RESULTS

The clinicopathological characteristics of the 326 patients with more than one radioactive SLN are described in Table 1. The mean age of the patients was 53.0 (standard deviation, ± 11.1) years. The T

Table 1. Clinicopathological characteristics of patients with more than one radioactive sentinel lymph node (n = 326)

Characteristic	No. of patients (%)
Mean age ± SD (yr)	53.0 ± 11.1
Tumor stage	
Tis	13 (4.0)
T1	191 (58.6)
T2	117 (35.9)
T3	4 (1.2)
T4	1 (0.3)
Histology	
Invasive ductal carcinoma	287 (88.0)
Invasive lobular carcinoma	23 (7.1)
Others	16 (4.9)
Nodal stage	
N0	272 (83.4)
N1mic or N1	49 (15.0)
N2	4 (1.2)
N3	1 (0.3)
Hormone receptor status	
Negative	84 (25.7)
Positive	241 (74.0)
Unknown	1 (0.3)
HER2 status	
Negative	183 (56.1)
Equivocal	10 (3.1)
Positive	133 (40.8)

SD = standard deviation; HER2 = human epidermal growth factor-2.

stage of the primary tumor was Tis in 13 patients (4.0%), T1 in 191 patients (58.6%), T2 in 117 patients (35.9%), and T3 or T4 in 5 patients (1.5%). Invasive ductal carcinoma was the most common histological tumor type (287 of 326), and invasive lobular carcinoma was diagnosed in 23 patients. The N stage was N0 in 272 (83.4%) patients, N1mic or N1 in 49 patients (15.0%), N2 in 4 patients (1.2%), and N3 in 1 patient (0.3%). Hormone receptor status was negative in 84 patients (25.7%) and positive in 241 patients (74.0%). HER2 status was negative in 183 patients (56.1%), equivocal in 10 patients (3.1%), and positive in 133 patients (40.8%).

Among 326 patients with more than one radioactive SLN, 54 (16.6%) had nodal metastases. Among patients with metastatic SLNs, the hottest SLN showed metastasis in 85.2% (46 of 54) of cases, whereas 14.8% (8 of 54) of cases involved metastasis in SLNs other than the hottest SLN (Figure 1). Six of 256 patients (2.0%) with two radioactive SLNs showed metastasis in the non-hottest SLN and no metastasis in

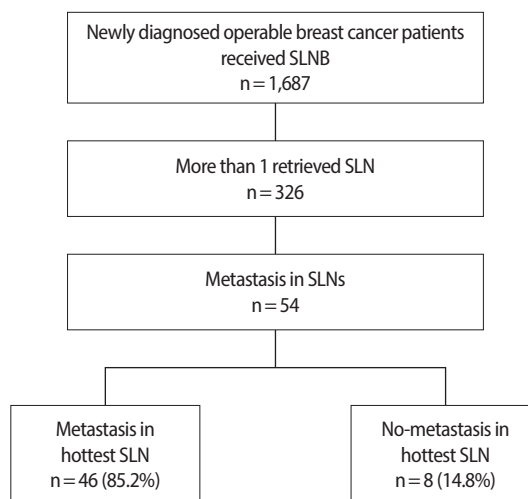


Figure 1. Study profile. SLNB = sentinel lymph node biopsy; SLN = sentinel lymph node.

Table 2. Distribution of malignancy in radioactive SLNs of patients with more than one radioactive SLNs (n = 326)

No. of radioactive SLNs	No. of patients	No. of patients with positive non-hottest SLN and negative hottest SLN (%)
2	256	6 (2.0)
3	55	2 (4.0)
4	13	0
≥ 5	2	0
Total	326	8 (2.5)

SLN = sentinel lymph node.

Table 3. Cases with non-metastatic hottest SLN and metastatic non-hottest SLN

Case number	Histology	Hormone receptor status	HER2 status	Staging	Activity of the hottest SLN	Relative activity of the retrieved SLNs (%)			Total number of metastatic lymph nodes
						First	Second	Third	
1	IDC	Positive	Positive	T2N1M0	2,600	100	69*		2
2	IDC	Positive	Positive	T1N1M0	780	100	32*		0
3	IDC	Positive	Positive	T2N1M0	6,000	100	65	23*	0
4	IDC	Positive	Negative	T2N3M0	1,600	100	94*		14
5	IDC	Positive	Negative	T1N1M0	10,000	100	60	55*	0
6	IDC	Positive	Negative	T2N1M0	19,000	100	23*		2
7	IDC	Positive	Negative	T1N1M0	4,000	100	10*		1
8	Metaplastic	Negative	Negative	T1N1M0	12,000	100	42*		1

SLN = sentinel lymph node; HER2 = human epidermal growth factor-2; IDC = invasive ductal carcinoma.

*Metastatic lymph node.

the hottest SLN. Of the 55 patients with three radioactive SLNs, two (4.0%) showed metastasis in non-hottest SLNs but showed no metastasis in the hottest SLN. Fifteen patients had more than three radioactive SLNs, and they showed no metastasis in the non-hottest SLN (Table 2).

The cases in which the non-hottest SLNs were metastatic and the hottest SLNs were non-metastatic are shown in Table 3. Among the eight patients with no metastasis in the hottest SLN, six showed metastasis in the second hottest SLN and two showed metastasis in the third-hottest SLN. The lowest percentage of radioactivity in a metastatic SLN was 10%, corresponding to the second hottest SLN of one of the patients.

DISCUSSION

ALND is associated with the development of lymphedema in patients with early-stage breast cancer [9]. After the ACOSOG Z0011 study, the importance of ALND after SLNB has been minimized, and several studies have shown that the number of patients undergoing ALND for pathologically positive SLNs has significantly decreased [5,6,10]. Studies that investigated the omission of SLNB for selected patients with breast cancer have also been published [11,12]. Reducing the number of dissected SLNs during SLNB is known to decrease morbidity.

SLNB has traditionally been the standard axillary staging procedure for patients with clinically node-negative breast cancer. Fortunately, the ability to identify SLNs has improved owing to increased surgical experience and refinements in nuclear imaging techniques, including injection methods and injection volume. Although the

concept is simple, there is a large variability in how the procedure is performed at different institutions and in the radioactive threshold used for SLN removal. The most popular guideline is the “10% of the hottest nodes rule,” which is used to minimize the chances of morbidity related to ALND [7]. In our study, the most metastatic SLNs had the highest radioactivity in 85.2% of cases, and the hottest lymph node was not pathologically positive in 14.8% of cases. The lowest relative radioactivity in a metastatic non-hottest SLN was 10%.

Regardless of the radioactive status of the SLN, the following question remains to be answered: How many sentinel nodes should be removed to achieve appropriate accuracy of axillary staging without negating the potential benefits of SLNB? Previously published studies have shown that 97%–98% of positive SLNs are discovered in one of the first three nodes examined and that it is rare to find a positive SLN after the first three nodes are identified as negative [2,4,13-15]. Ban et al. [2] suggested that the total number of SLNs excised should be limited to no more than four. In our study, all positive SLNs were identified as one of the first three lymph nodes dissected from patients with node-positive disease, consistent with previously reported findings.

Our study showed that there were only a few cases in which the hottest lymph node was not pathologically positive. In addition, all metastatic SLNs were identified as one of the first three lymph nodes dissected from patients with node-positive disease. To remove only the nodes that are most likely to be metastatic and to reduce the morbidity of axillary dissection, we suggest that removal of the first three lymph nodes or nodes covered by the “10% rule” is sufficient for SLNB in patients with breast cancer.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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