Clinical Relevance of Nonvisualized Sentinel Lymph Nodes in Unselected Breast Cancer Patients during Lymphoscintigraphy

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Background: Sentinel lymph node (SLN) biopsy in breast cancer is an effective technique with a high degree of accuracy and low false-negative rate to replace axillary lymph node dissection (ALND). This study analyzed the major clinicopathological factors associated with nonvisualized sentinel nodes during preoperative lymphoscintigraphy.

Methods: Breast cancer patients who underwent preoperative lymphoscintigraphy and sentinel node biopsy between 2000 and 2003 were retrospectively reviewed. Sentinel node biopsy was performed with a two-day protocol. On day one, a filtered (45 μ m Millipore) technetium-99m sulfur colloid isotope with a mean radioactive dose of 37 MBq (1 mCi) in a diluted volume of 1 ml was injected subdermally just above the primary breast tumor site. Serial dynamic images were taken with a high-resolution collimator and a static image was acquired after the SLN was identified. No hot spot identified two hours after injection was classified as nonvisualization unless lymphatic drainage channels were viewed by the lymphoscintigraphy and a prolonged two hour scan was obtained. Sentinel nodes were harvested on day two. The cases with nonvisualized sentinel nodes were analyzed according to clinical histopathologic parameters to determine the clinical significance.

Results: A total of two hundred thirty-two breast cancer patients were enrolled in this study. Twenty-four of these cases presented with advanced breast cancer prior to neoadjuvant chemotherapy. The sentinel node was nonvisualized in twenty-seven of two hundred thrity-two cases (11.6%). Tumor size ($p = 0.025$) and lymph node metastasis ($p = 0.001$) were two factors associated with nonvisualized sentinel node in univariate analysis. Multivariate logistic regression analysis showed that more than three nodes ($p = 0.001$) and more than ten nodes ($p = 0.001$) metastasis were independent factors associated with nonvisualized sentinel node.

Conclusions: Patients with more than three axillary nodes metastasis is an independent factor associated with nonvisualized sentinel node during lymphoscintigraphy.

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Key words: sentinel lymph node, breast cancer.

Surgical treatment of breast cancer comprises resection of primary tumors and axillary lymph node dissections. Breast surgery has recently become increasingly conservative moving away from modified radical mastectomy toward more conservative treatments. However, there is to date no non-invasive procedure to replace axillary dissection in the prediction of breast cancer prognosis, and axillary dissection has remained the standard treatment of breast cancer. A limited axillary dissection, such as axillary sampling, may engender a high-risk of axillary understaging.[1,2] The increased use of mammograms in breast cancer screening has resulted in a decrease in the detected size of breast cancers. More than 50% to 70% of breast cancer patients are now tumor free in the axillary node. The routine use of axillary node dissection produces unnecessary morbidity in node-negative breast cancer patients and holds no direct benefit for the patients. Since the first report of a sentinel node biopsy in breast cancer by Krag et al. who used technetium-labeled sulfur colloid, SLN biopsy has proved to be effective and highly accurate with a low false-negative rate.[3] Only SLN biopsy without a backup ALND in SLN negative breast cancer patients is being increasingly used by numerous surgeons. Naik et al, who studied four thousand and eight randomized procedures with a median follow-up of thirty-one months, demonstrated that the risk of axillary relapse was comparable in SLN biopsy groups and axillary dissection groups.[4] The SLN biopsy is predicted to replace ALND as the preferred technique for accessing the regional nodes in all operable, clinically node-negative breast cancer patients. A preoperative SLN identification is the first step in a SLN biopsy and the principal factor of a successful SLN biopsy. Patients with a nonvisualized SLN should undergo total ALND even in node-negative cases. The majority of surgeons who perform SLN biopsy encounter the problem of nonvisualization of SLN in the lymphoscintigraphy. The clinicopathologic factors in unselected breast cancer patients related to nonvisualized lymphoscintigraphy were retrospectively analyzed in this study.

METHODS

Pathologically proven breast cancer patients who have undergone radical surgery, being either conservative surgery or modified radical mastectomy, and undergone preoperative lymphoscintigraphy were retrospectively reviewed. Patient data from Chang Gung Memorial Hospital covered the period from Sept. 2000 to Dec. 2003. The patients enrolled in this study had detailed clinopathologic data, including age, tumor size, biopsy method, tumor location, histologic findings, estrogen receptor (ER), progesterone receptor (PR), Her-2 and accurate pathological staging. Patients with advanced breast cancer or distant metastasis and with complete or partial response after neoadjuvant chemotherapy, and could undergo radical surgery were also included. The clinical staging and tumor sizes were recorded according to tumor status when performing the lymphoscintigraphy on neoadjuvant patients. All patients underwent total or standard axillary dissection after SLN removal. Only intraductal carcinoma patients underwent a limited axillary dissection or SLN biopsy only.

The SLN biopsy was performed with a two-day protocol. Lymphoscintigraphy was performed on day one and SLNs were harvested on day two. In the afternoon of day one, filtered (45 μm Millipore) technetium-99m sulfur colloid in a mean radioactive dose of 37 MBq (1 mCi) in a diluted volume of 1 ml was injected subdermally just above the primary breast tumor site. In non-palpable breast cancers, the injection sites were located in the same quadrant as close to the tumor as possible. In patients who had their tumors excised, the injections were administered at four points surrounding all four sides of the scar and at 0.5 cm distances from it. Serial dynamic images (fifteen minutes between frames for two hours) were taken with a high-resolution collimator, a static image was acquired in a fifteen degrees right or left anterior-oblique view after a SLN was identified. The first hot spots, viewed by lymphoscintigraphy, to arise from the primary tumor, after the radiotracer injection, was regarded as a SLN. Different hot spots arising from the primary tumor via different lymphatic pathways were recorded as different SLNs. No hot spot detection at two hours after the injection was classified as a nonvisualized SLN, except that when a lymphatic drainage channel was detected at two hours, a delayed image could be obtained at four hours after the injection. No lymphatic drainage channel at two hours and no hot spot at four hours after the injection were classified as nonvisualized SLNs.

In the morning of day two, patients underwent either modified radical mastectomy or partial mastectomy, the SLNs were harvested with the aid of a handhold gamma probe (Navigator GPS®, Norwalk Conn, USA) followed with a backup ALND. Extra-axillary SLNs detected by lymphoscintigraphy were also excised. The SLN identification rate was defined as the proportion of patients in whom a SLN was identified by lymphoscitigraphy and excised by surgeons. Sentinel node locations and numbers were first determined by nuclear medicine physicians and marked on the skin according to Mortan's definition.[5] Dynamic lymphoscintigraphy was reviewed if more than one SLN was identified or if patients had any intraoperative anatomic problems.

The SLNs were formalin-fixed, bisected, paraffin-embedded, and cut in ten serial sections: five sections were stained with hematoxylin-eosin (H&E) and five with immunohistochemical staining (IHC) for cytokeratin. An SLN was considered positive if cancer cells were identified by H&E or IHC staining.

Univariate analyses were performed to determine the correlation between variable factors of SLN identification. A multiple forward stepwise logistic regression model was then employed to analyze all variables in univariate analysis.

The Pearson chi-square and the Fisher exact test were used to compare the differences in numbers of SLN identified, identification rate, and accuracy rates according to patient characteristics including age, biopsy method, tumor location, tumor size, and tumor pathology. The identification rate of SLN was defined as a successful SLN identification via lymphoscintigraphy and the following SLN harvest. The accuracy rate of SLN was defined as the percentage of the total number of procedures without false-negative SLN biopsy divided by the total procedures performed. The false-negative rate was defined as the percentage of the number of procedures with a negative SLN divided by the procedures with positive axillary nodes.

RESULTS

A total of two hundred thirty-two breast cancer patients were enrolled in this study from Sep 2000 to Dec 2003. Thirty patients were diagnosed with advanced breast cancer. Twenty-two of these thirty patients had locally advanced breast cancer and had undergone neoadjuvant chemotherapy. Two of the thirty patients presented with neck lymph node metastasis before neoadjuvant chemotherapy. Six of these thiryty cases showed small breast tumors with more than three axillary node metastasis after permanent pathologic report. Table 1 presents patient characteristics and univariate analysis results for visualized versus nonvisualized groups. The SLNs were nonvisualized in twenty-seven (11.6%) of the two hundred thirty-two cases and visualized in two hundred five (88.4%) cases. There was no significant statistical difference between the groups with an age range of twenty-six to eighty-five years (mean age, forty-nine years) and the visualized group with an age range of thirty to eighty-six years (mean age, fifty-two years). The identification rate for patients aged fifty and older was low and close to statistically significant ($p = 0.059$). Table 1 showed that there was no statistical difference between visualized and nonvisualized groups for factors of age, tumor histology, tumor grading, ER, PR, Her-2, neoadjuvant chemotherapy, preoperative biopsy method, or tumor location. Most diagnostic procedures in this study were echo-guided core biopsies (two hundred twenty patients, 94.8%), which could preserve intact tumor structure, performed about two weeks before lymphoscintigraphy. There were no nonvisualized cases with intraductal carcinomas and subareolar tumor locations.

Only tumor size ($p = 0.025$) and lymph node status ($p = 0.001$), both statistically significant in univariate analysis, were associated with reduced SLN identification rate (Table 1). In the nonvisualized SLN group, 70.4% of tumors sized more than two cm. In contrast, only 43.1% of tumors sized more than 2 cm in the visualized group. Patients with axillary node metastasis revealed a significantly lower SLN identification rate in the nonvisualized group than in the visualized group (36.6% vs. 70.4%). If the axillary nodal status was further divided into four categories for univariate analysis; negative, one to three nodes metastases, four to nine nodes metastases, and more than nine nodes metastases, groups with more than three axillary nodes involvement had a significantly lower identification rate in the nonvisualized group ($p = 0.0001$) (Table 2). The subsequent multivariate logistic regression analysis, enrolled the following parameters; age, tumor size, lymph node status, showed that only

Table 1. Patient Characteristics of Visualized and Nonvisualized Sentinel Lymph Nodes in Breast Cancer

Patient characteristics	Visualized (%) N = 205 (88.4)	Nonvisualized (%) N = 27 (11.6)	p value*
Age			
≦50 yrs	131 (63.9)	12 (44.4)	
>50 yrs	74 (36.1)	15 (55.6)	0.059
Biopsy method			
Pre-excision	10 (4.9)	2 (7.4)	
Core-biopsy	195 (95.1)	25 (92.6)	0.636
Tumor location			
Medial	70 (34.1)	5 (18.5)	
Lateral	128 (62.4)	22 (81.5)	
Subareola	7 (3.4)	0 (0)	0.131
Tumor size			
≦1 cm	40 (19.5)	3 (7.4)	
>1, ≦2 cm	77 (37.6)	6 (22.2)	
>2 cm	88 (43.1)	19 (70.4)	0.025
Lymph node status			
Negative	130 (63.4)	8 (29.6)	
Positive	75 (36.6)	19 (70.4)	0.001
Mean age	49 ± 12	52 ± 13	0.158
Histology			
Intraductal carcinoma	25 (12.2)	0 (0)	
Invasive ductal carcinoma	139 (67.8)	23 (85.2)	
Others	41 (20.0)	4 (14.8)	0.098
Tumor grade			
Grade 1	21 (16.2)	3 (14.3)	
Grade 2	58 (44.6)	12 (57.1)	
Grade 3	51 (39.2)	6 (28.6)	0.550
Estrogen receptor			
Positive	97 (48.7)	12 (46.2)	
Negative	102 (51.3)	14 (53.8)	0.804
Progesterone receptor			
Positive	81 (40.7)	12 (46.2)	
Negative	118 (59.3)	14 (53.8)	0.596
Her-2			
Negative or weak positive	122 (67.4)	15 (57.7)	
Strong positive	59 (32.6)	11 (42.3)	0.328
Neoadjuvant chemotherapy			
Yes	20 (9.8)	4 (14.8)	
No	185 (90.2)	23 (85.2)	0.497

* By chi-square or Fisher exact test.

more than three lymph node involvement groups were independent factors associated with a low identification rate (Table 3).

DISCUSSION

There are several techniques applied for breast

Table 2. Lymph Node Status of Visualized and Nonvisualized Sentinel Nodes in Breast Cancer

Lymph node status	Visualized (%)	Nonvisualized (%)	p value*
Negative	130 (63.4)	8 (27.6)	
1 to 3 nodes positive	54 (26.3)	6 (22.2)	
4 to 9 nodes positive	9 (4.4)	5 (18.5)	
More than 9 positive	12 (5.9)	8 (29.6)	0.0001

* By chi-square or Fisher exact test.

Table 3. Multiple Forward Stepwise Logistic Regression Analysis of Visualized and Nonvisualized Sentinel Nodes in Breast Cancer

Lymph node status	Odds ratio (95% CI*)	p value†
1 to 3 positive nodes/ negative node	1.78 (0.57-5.56)	0.322
4 to 9 positive nodes/ negative node	8.55 (2.26-32.26)	0.001
More than 9 positive nodes/ negative node	10.31 (3.17-33.33)	0.001

* Confidence interval
† Logistic regression analysis

cancer lymphatic mapping, including blue dye injection, intra-tumoral or peri-tumoral radioisotope injection methods, and dermal or subdermal radioisotope injection methods. The advantage of methods employing radioactive isotopes is their ability to identify the lymphatic channels and differentiate between the first and subsequent drainage lymph nodes, to differentiate between different pathways or the same pathway of a lymph node, and to localize. Of these methods, the blue dye method was first employed for melanoma and breast cancer, its identification rate in breast cancer was about 66-99%.[6-10] The limitations of the blue dye method include the following: poor visibility of internal mammary lymph nodes; risk of tumor spreading when the primary tumor is massaged after blue dye injection; without a dynamic picture the lymphatic drainage channel is not visible; and risk of allergic reaction after injections. A multi-institutional study by McMasters et al demonstrated that lymphatic mapping with blue dye alone may correlate with a low identification rate if it is not combined with a radioactive method.[11] Radioactive mapping methods were then employed and were well accepted by most surgeons. The intra-tumoral or peri-tumoral radioisotope injection method was first employed by Veronesi et al.[12,13] This technique captures on film a

clear lymphatic drainage channel and a deep injection into the breast tissue can also facilitate identification of Rotter's nodes and internal mammary lymph nodes. Combined with the blue dye method, an identification rate of 91-99% was achieved.[12,14-15] Subdermal or dermal injection lymphoscintigraphy is the most effective approach based on its rapid SLN detection, injection simplicity and a higher identification rate than that of the peritumoral injection method.[11,16-17] Dermal and subdermal injections of radiotracer are both feasible as both are of the same embryonic origin with underlying breast tissue; however, the dermal approach may be more sensitive than the subdermal.[11] Numerous studies showed that dermal, subdermal or subareolar approaches could improve SLN identification rates and decrease the false-negative rates.[11,13,18-20] A major limitation of the subdermal approach is its low internal mammary SLN detection rate as internal mammary nodes are deeply located, separated by pectoralis fascia, and arise from retromammary lymphatics.[8,16,21] Radioactive methods have been combined with the blue dye method to increase SLN identification rates and to reduce false-negative rates in some studies. For general SLN mapping, radioactive lymphoscintigraphy combined with a dermal or subdermal injection method is the preferred choice based on its simplicity for nuclear medicine physicians, rapid hot spot identification, and a higher radioactive count compared with the peritumoral method in SLNs for surgeons to harvest. This study of nonvisualized SLNs in breast cancer identified by lymphoscintigraphy includes all breast cancer patients and was not limited to early breast cancer. Consequently, an 88.4% SLN identification rate was identified in this study.

Radioactive particle size can also influence SLN visualization rates. Large particles slow down the movement of radiotracers in lymphatic channels and small particles will pass through the true SLN and cause false-negative SLN harvests.[22] Mariani et al investigated different particle sizes of radiotracer and suggested that a 100-200 nm size range would be ideal.[22] However, Paganelli et al examined three different colloid radiotracers with particle sizes ranging from less than 50 nm to 1000 nm which were injected subdermally or peri-tumorally. They found that a large particle size resulted in easier SLN detection.[23] This study employed radioactive particles passed through a 45 μm Millipore filter and achieved an acceptable identification rate (94.3%) and false-negative rate (6.3%) in early breast cancer patients.

There are numerous factors that are potentially associated with nonvisualized lymphoscintigraphy. Patients older than fifty tend to have more nonvisualized SLNs with either blue dye, the radioisotope method or subdermal, peritumor injection methods.[11-12,19,24-26] McMasters et al. revealed that patient age could affect identification rates in univariate and multivariate analyses.[19] This study identified some relationships between unsuccessful SLN lymphatic mapping in ages older than fifty years ($p = 0.059$). However, Krausz et al. demonstrated that age did not have significant impact on nonvisualized SLN detection.[27] The reasons for the age effect remained not clear and were still under investigation. Krag et al. explained that lymph nodes may undergo fat degeneration decreasing the node's capacity to retain the radioactive colloid in aged patients.[12] Sandrucci et al. demonstrated that lymphatic flow was relatively slower in aged breast parenchyma.[18] Uren et al. described the physiology of lymphatic flow and noted that lymph nodes are not passive mechanical filters and that radiocolloids were trapped and retained in SLNs by an active physiologic process. They suggested that radioactive colloid should be firstly recognized as a foreign body and phagocytosed by macrophages or histiocytes within the lymph node.[28] The impact of age in patients on the nodal physiologic function, such as recognization and phagocytosis, requires further exploration and investigation.

The data supporting an association between tumor location and nonvisualized lymphoscintigraphy has been inconsistent. Various previous reports including the data in this study have shown that tumor location was not associated with failure to identify SLNs, and that almost all SLNs were located in axilla irrespective of tumor location.[11,20,27] However, some reports indicated that medial located tumors were associated with significantly high nonvisualized SLN.[12,25,29] A possible explanation for the high nonvisualized SLN in medial located tumors was the masking effect by the strong isotope signal on films of lymphoscintigraphy following the radiotracer injection in medial located primary tumors, particularly when lymphatic drainage flows toward internal mammary nodes. A radioactive peri-tumoral

injection method requires a higher isotope dose than the dermal or subdermal method and renders a masking effect with nonvisualized SLNs.

Krausz et al. studied seventy-four breast cancer patients with a peri-tumor injection of filtered sulfur colloid lymphoscintigraphy and univariate analysis demonstrated that tumor grade was the only factor that correlated with twenty-one nonvisualized SLNs.[27] This finding was neither apparent in this study nor any other. Tumor grade may be correlated with high degrees of lymphatic metastasis and indirectly correlated with nonvisualization. The impact of prior excision or excisional biopsy related to SLN identification is still controversial. Some reports showed a low identification rate in prior excision groups.[12,30] However, other reports, including this study, did not reveal any differences in groups between prior excision and core-biopsy groups.[11,25,27,31] A large excision or destruction area in dermal or breast parenchyma as a result of prior excision can disrupt lymphatic drainage and impair the SLN identification, especially in aged patients, or using intraparenchymal injection method. Excision followed with the intraparenchymal method has been shown to produce more nonvisualized SLNs because of the risk of intracavity injection or significantly large hematoma formation following excision.[12,30]

In univariate analysis, tumor size, especially larger than two cm, axillary lymph node metastasis, and tumor stage were significantly correlated with nonvisualized SLNs. However, in some reports, tumor size was not correlated with SLN identification.[11,25,27] This study demonstrated that tumor size did not affect SLN identification in clinical node-negative early breast cancer (data not shown). It is well known that large tumors correlate with a high rate of lymph node metastasis in breast cancer. Large tumors may have diverse lymphatic drainage pathways and increased lymph node metastasis. Distal obstruction caused by metastatic cells within lymph nodes or lymphatic channels may change the direction of lymphatic drainage or even nonvisualization of lymphoscintigraphy. The frequency of internal mammary lymph node metastasis correlated with high rates of axillary node metastasis could explain the correlation between the nonvisualization rate and the number of axillary nodal metastasis.[32] Borgstein et al described an increased internal mammary drainage of SLNs if multiple axillary nodes were involved as a result of normal axillary drainage channels being obstructed by tumors.[30] However, Bedrosian et al, showed that large tumors ($\geqq$2 cm, $\leqq$5 cm) with 59% lymph node involvement had a 99% identification rate and 2 % false-negative rate.[33]

In this study, axillary lymph node status is significantly correlated with visualized or nonvisualized SLNs. There were more cases with axillary node metastasis in the nonvisualized group than in the visualized group (70.4% vs. 36.8%); univariate analysis identified a significant difference ($p = 0.001$). Additionally, axillary lymph node involvement or noninvolvement was also significantly different in the specified groups of the multivariate analysis ($p = 0.033$, odds ratio of lymph node positive/negative = 2.76, 95% confidence interval = 1.084-7.040). It is generally accepted that if the lymph node or the drainage pathway was obstructed by tumor cells, lymphatic drainage may follow a minor pathway.[34] To analyze the relationship between the number of the axillary node metastases and the SLN visualization rate, axillary nodes were divided into three categories, one to three, four to nine, and more than nine nodes involvement according to the 2002 American Joint Committee on Cancer (AJCC) classification. The extent of axillary lymph node involvement in this study was associated with increased risk of nonvisualized lymph nodes in the univariate analysis ($p = 0.0001$). Multivariate analysis showed that only four to nine and more than nine axillary nodes metastasis were significantly correlated with the higher risk of nonvisualization SLNs than those without node metastasis (odds ratio 8.55 and 10.31, respectively, $p = 0.001$). Brenot-Rossi et al. studied three hundred thirty-two patients with thirty nonvisualized SLN cases using intradermal and intraparenchymal injection lymphoscintigraphy. Their study showed similar results to this study, except that they found no significant difference in patients with axillary positive SLN or negative SLN.[35] Tanis et al studied four hundred ninety-five clinical node-negative breast cancer patients and showed that increased tumor-positive lymph node numbers were independently associated with nonvisualized lymph nodes.[36] Tafra et al reported a multicenter trial of SLN biopsy including five hundred twenty-nine patients. Their study showed a statistically insignificant reduced identification rate and increased false-negative rate for five or more

metastatic nodes.[24] However, in studying early breast cancer, Birdwell et al showed a higher percentage of SLN positive for metastasis in the visualized group as compared with the nonvisualized group (41% vs. 19%).[31] Dauway et al investigated twenty-five cases with nonvisualized SLN by both lymphoscintigraphic and blue dye intra-parenchymal injection methods. Their study identified no axillary node metastasis after axillary dissection in the twenty-five cases and indicated that not all nonvisualized SLNs require axillary dissection.[37]

In conclusion, this study demonstrates that breast cancer patients with a nonvisualized SLN during lymphoscintigraphy have a high risk of axillary node metastasis and require axillary lymph node dissection.

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淋巴攝影未能偵測到乳癌病患的前哨淋巴的臨床意義

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背　景： 乳癌病患腋下淋巴腺有無被侵犯是預後的重要指標，前哨淋巴切除術有很高的準確性而被用來取代腋下淋巴腺廓清術，但淋巴攝影有時候並未能成功的偵測到前哨淋巴。

方　法： 本研究回顧西元2000年至2003年所有接受淋巴攝影的乳癌病患。淋巴攝影方法係於腫瘤正上方的皮下注射 technetium-99m sulfur colloid，劑量爲 37 MBq。淋巴攝影的追蹤時間爲兩個小時，若可以看到淋巴引流的痕跡則增加至四小時。本研究收集這些淋巴攝影未能偵測到前哨淋巴的病患加以分析。

結　果： 共收集了232位乳癌病患，其中有24位有接受術前化療，有27位 (11.6％) 爲未能偵測到前哨淋巴的病患。單變異分析 (univariate analysis) 結果發現腫瘤大小與腋下淋巴腺有無被侵犯是影響前哨淋巴偵測的原因 (p 值分別爲 0.025 及 0.001)。而多變異分析 (multivariate analysis) 發現腋下淋巴腺被侵犯三顆以上及十顆以上有統計上的意義 (p 值皆爲 0.001)。

結　論： 淋巴攝影未能偵測到乳癌病患的前哨淋巴時，須懷疑有超過三顆腋下淋巴腺被侵犯。

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關鍵字： 前哨淋巴，乳癌。