Feasibility of Sentinel Lymph Node Biopsy in Multifocal/Multicentric Breast Cancer

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Background: Sentinel lymph node (SLN) biopsy can replace axillary lymph node dissection (ALND) in prediction of nodal status in node-negative breast cancer. However, patients presenting with multifocal/multicentric (MF/MC) breast cancer are usually excluded from studies of SLN biopsy. This study evaluated the efficacy of SLN biopsy in patients with MF/MC breast cancer.

Methods: Breast cancer patients who underwent preoperative lymphoscintigraphy and SLN biopsy with backup ALND from 2004 to 2006 were retrospectively reviewed. Patients enrolled in this study had clinically node-negative unifocal or MF/MC breast cancer based on final histology. Sentinel node biopsy was performed with a 2-day protocol with intradermal radiocolloid injection on day one and SLN biopsy on day two. Histopathologic parameters and the efficacy of the SLN biopsy were compared between unifocal and MF/MC breast cancers.

Results: This study enrolled 158 breast cancer patients; one hundred and thirty-five patients were diagnosed with unifocal and 23 with MF/MC breast cancer. The mean numbers of SLNs retrieved were 1.3 for the unifocal and 1.1 for the MF/MC groups. The identification rate, sensitivity, accuracy, and false-negative rate for unifocal and MF/MC breast cancers were 94.8%, 92.6%, 98.4%, and 7.4%; and 100%, 100%, 100%, and 0%, respectively. No significant differences were observed between the two groups for SLN identification, sensitivity, accuracy, and false-negative rate.

Conclusion: Sentinel lymph node biopsy using intradermal radiocolloid injection method is feasible for MF/MC breast cancer.
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Key words: sentinel lymph node, breast cancer, multifocal/multicentric

Multifocal (MF) breast cancer has been defined as more than one separate cancer in a same quadrant and multicentric (MC) as in more than one quadrant.[1,2] MF/MC breast cancer has been reported in 9% to 75% of cases depending on the different examination methods employed.[3] Multifocal/multicentric breast cancer exhibits many differences from unifocal lesions, such as more frequent axillary lymph node metastasis, larger tumor size, more adverse outcomes, younger age distribution, modifications in surgical planning, and the feasibility of sentinel lymph node (SLN) biopsy.[1,2,4,5]

Since the first report of SLN biopsy for breast cancer by Krag et al, SLN biopsy has proven to be a feasible procedure to replace axillary lymph node dissection (ALND), with a high degree of accuracy, a low false-negative rate, low morbidity, and a low axillary relapse rate.[6-8] However, application of SLN biopsy has been limited to unifocal breast cancer, and patients with MF/MC disease are usually excluded from study.[6,7] For the peri-tumoral injection method, exclusion of MF/MC disease can prevent multiple injections to multiple tumors, which may create multiple lymphatic drainage channels, and a multiple radiotracer injection induced masking effect of the whole breast. With the introduction of dermal, subdermal, and subareolar injections, a single injection site is required, so whether MF/MC disease should be excluded from SLN biopsy needs further investigation.[9,10] In 2005, the American Society of Clinical Oncology (ASCO) conducted a systemic review of sentinel lymph node biopsy and suggested that sentinel lymph node biopsy can be applied and identified in multicentric breast cancer through intradermal, subdermal, or subareolar injection techniques. However, evidence is limited.[11] This study retrospectively evaluated the feasibility of SLN biopsy in 23 MF/MC breast cancer patients.

METHODS

Breast cancer patients who underwent radical surgery, either breast conservative treatment or a modified radical mastectomy, between Sept. 2004 and Oct. 2006 were retrospectively reviewed. Patients were enrolled in this study if they met all of the following selection criteria: clinical node-negative breast cancer, either invasive or intraductal carcinoma proved by core-needle biopsy; preoperative lymphoscintigraphy; SLN harvest with backup axillary lymph node dissection for invasive carcinoma or sampling for intraductal carcinoma; and histologically proven unifocal or MF/MC breast cancer. Patients who presented with enlarged nodes on mammography or breast ultrasound were not excluded.

Lymphatic mapping and SLN biopsy was performed using a radioguided 2-day protocol.[12] Briefly, in the afternoon of day 1, filtered (through a 45 μm Millipore) technetium-99m sulfur colloid isotope in a mean radioactive dose of 37 MBq (1 mCi) in a diluted volume of 1 ml was injected intradermal-ly just above the pathologically proven tumor site. In non-palpable breast cancers, the injection sites were in the same quadrant or as close as possible to the primary tumor. Serial dynamic images were taken with a high-resolution collimator; a static image was acquired after an SLN was identified. The first hot spots identified after injection on the same route from the primary tumor were defined as SLNs. Hot spots on different routes from the primary tumor were regarded as different SLNs. If multiple hot spots were presented, dynamic images were reviewed to locate the true SLNs. The location of an SLN was then marked on the skin with waterproof permanent ink. No hot spot detected within 2 hours after injection was classified as a non-visualized SLN. A delayed image 4 hours after injection was obtained if lymphatic drainage channels were seen in the 2-hour image. On the morning of day 2, the SLN was harvested under the guidance of a hand-held gamma probe (Navigator GPS®, Norwalk Conn, U.S.A.) followed by a backup ALND. All SLN biopsies were performed by the same surgeon (Lo). Each SLN was cut at an interval of 2 mm along the longitudinal axis for frozen examination and then formalin-fixed, paraffin-embedded, and cut in 10 serial sections for hematoxylin-eosin (H&E) and immuno-histochemical staining (IHC). An SLN was considered positive if cancer cells were identified by H&E or IHC staining histologically.

Unifocal or MF/MC lesions were determined on final histology according to standard pathological protocol using the same definition as mentioned above. Every mastectomy specimen was fixed in 10% formaldehyde solution, placed oriented, and serially sectioned at 1.0 cm intervals. Representative suspicious lesions, either by palpation or on image, were identified according to their numbers and were measured, embedded in tissue blocks for histological examination. Tumor size was measured as the maximal invasive component of the main primary tumor on histology. Intraductal carcinoma was classified as 0 cm. Estrogen receptor (ER) and progesterone receptor (PR) were assessed by the immuohisto-chemical method using monoclonal antibodies (Novocastra; NCL-ER-6F11 and NCL-PGR, respectively). Her2 was evaluated by immunohistochemical stain using a polyclonal antibody (Dako; Code-Nr. A0485). The histological grading for invasive carcinoma was scored using the Nottingham modification

of the Scarff-Bloom-Richardson (SBR) grading system.[13]

Univariate analysis using the chi-square test was performed to compare the following patient and tumor parameters between unifocal and MF/MC breast cancer groups: age, tumor location, tumor size, lymph node status, tumor histology, SBR grading, ER, PR, and Her2 (Table 1). Fisher's exact test was used for comparisons of SLN identification rate, sensitivity, accuracy, and false-negative rate between the two groups (Table 2). All reported p values were two tailed and $p < 0.05$ was required to reject the null hypothesis of no difference in unifocal and MF/MC breast cancer. The success of SLN identification rate, sensitivity, accuracy, and false-negative rate were reported with 95% confidence intervals (CI) using the adjusted Wald method. The identification rate was defined as successful SLN identification via lymphoscintigraphy and the subsequent SLN harvest. The statistical analyses of SLN biopsy used the following definitions: diagnostic accuracy = (true positive + true negative)/total patients, sensitivity = (true positive)/(true positive + false negative). The false-negative rate was defined as the percentage of those with no tumor identified in the SLN, but who had at least one non-SLN revealed metastasis.

RESULTS

A total of 158 patients were enrolled in this study. Of these cases, 135 (85.4%) were unifocal and 23 (14.6%) cases were classified as MF/MC breast cancer. The median age of the patients was 49 years (range, 27 to 81) in the unifocal group and 47 years (range, 33 to 66) in MF/MC breast cancer group. Of the 23 MF/MC cases, 17 were multifocal and 6 were multicentric. The median tumor size was 1.7 cm (range, 0 to 7.0 cm) in unifocal group and 1.8 cm (range 0.1 to 3.0 cm) in MF/MC group. There were no statistical differences between groups for age (mean ± standard deviation), tumor location (medial or lateral), tumor size (mean± standard deviation), tumor histology (intraductal carcinoma, invasive ductal carcinoma, or others), SBR grading, ER, PR, or Her2 (Table 1).

The mean numbers of SLNs retrieved ± standard deviation were 1.34 ± 1.2 (range 1 to 4) in the unifocal group and 1.13 ± 0.3 (range 1 to 2) in the MF/MC group. Micrometastases in the SLNs were found in 2 cases of MF/MC (8.7%) and 7 cases of unifocal (7.0%) breast cancer ($p = 0.675$). The SLNs could not be identified on lymphoscintigraphy in 5.2% (7 of 135) of the unifocal breast cancer patients and 0% (0 of 23) of the MF/MC breast cancer patients. The identification rate, sensitivity, accuracy, and false-negative rate of SLN biopsy for MF/MC breast cancer were 100%, 100%, 100%, and 0%. There were no significant differences between groups in identification rate, sensitivity, accuracy, or

Table 1. Patients and Tumor Characteristics

Patient characteristics	Unifocal (N = 135)	MF/MC (N = 23)	p value
Age, years			
Median	49	47	
Range	27-81	33-66	
Mean age ± SD	51.25 ± 12.21	47.48 ± 7.53	0.052
Main tumor location (%)			
Medial	44 (33)	10 (43)	
Lateral	91 (67)	13 (57)	0.285
Tumor size, cm			
Median	1.7	1.8	
Range	0-7.0	0.1-3.0	
Mean tumor size ± SD	1.88 ± 1.20	1.64 ± 0.88	0.377
Lymph node status (%)			
Negative	108 (80)	16 (70)	
Positive	27 (20)	7 (30)	0.277
Histology (%)			
Intraducatal carcinoma	11 (8)	2 (9)	
Invasive ductal carcinoma	100 (74)	19 (82)	
Others	24 (18)	2 (9)	0.501
SBR grading (%)			
Grade 1	37 (37)	6 (32)	
Grade 2	41 (41)	7 (36)	
Grade 3	22 (22)	6 (32)	0.663
Estrogen receptor (%)			
Negative	49 (37)	8 (35)	
Positive	83 (63)	15 (65)	0.874
Progesterone receptor (%)			
Negative	45 (34)	10 (43)	
Positive	87 (66)	13 (57)	0.348
Her2 (%)			
Negative	99 (76)	16 (70)	
Positive	32 (24)	7 (30)	0.512

Abbreviations: MF/MC: Multifocal/multicentric; SBR: Scarff-Bloom-Richardson; CI: confidence interval; SD: standard deviation.

Table 2. Identification, Diagnostic Accuracy, and False-negative Rate of Sentinel Lymph Node Biopsy

Tumor characteristics	Sentinel lymph node biopsy											
	Identification rate (%)	95% CI	p value	Sensitivity (%)	95% CI	p value	Accuracy (%)	95% CI	p value	False-negative rate (%)	95% CI	p value
Unifocal (n = 135)	128/135 (94.8)	89.5-97.7		25/27 (92.6)	75.5-99.0		126/128 (98.4)	94.1-99.9		2/27 (7.4)	1.0-24.5	
MF/MC (n = 23)	23/23 (100.0)	87.5-100.0	0.595	7/7 (100.0)	67.8-100.0	1.000	23/23 (100.0)	87.5-100.0	1.000	0/7 (0.0)	0.0-32.2	1.000

Abbreviations: MF/MC: multifocal/multicentric; CI: confidence interval.

false-negative rate (Table 2).

DISCUSSION

In this retrospective study, we found that the intradermal radiocolloid injection technique can accurately predict and harvest SLNs in MF/MC breast cancer, and that patients with clinically node-negative MF/MC breast cancer should not be excluded from SLN biopsy. Veronesi et al was the first to advocate the use of SLN biopsy for MF/MC breast cancer. They studied radioactive subdermal injections for SLN biopsy in 163 breast cancer patients and identified 4 false-negative cases; 2 of these 4 false-negative cases were multifocal. Their explanation for the high false-negative rate for MF/MC breast cancer in SLN biopsy was that more than one lymphatic channel may arise from different breast tumors which may drain to different SLNs.[14] Years later, they studied 376 operable breast cancer patients, including 46 with MF/MC breast cancer, using the radioactive peritumoral injection method for SLN biopsy. The overall identification rate was 98.7% (371 of 376) and MF/MC breast cancer was not significantly associated with a higher false-negative rate.[15]

Recent large multicentre studies demonstrated that SLN can be used in clinically node-negative MF/MC breast cancer with identification rates and false-negative rates comparable with those in unifocal breast cancer. Yet, evidence remains limited.[11,16] The overall identification rates in MF/MC breast cancer and unifocal breast cancer range from 85.7% to 100% and 44% to 100%, respectively. The overall false-negative rates in MF/MC breast cancer range from 0% to 33.3%, whereas false-negative rates in unifocal disease range from 0% to 29% (Table 3).[17-20] Studies have questioned the feasibility of intratumoral or peritumoral injections for SLN mapping

and the higher false-negative rate in MF/MC.[14,15,18,19,21] However, alternative injection sites, such as subareolar, intradermal or subdermal injections, have been proved to have an SLN detection accuracy rate equal to, or better than peritumoral injection and can be applied in MF/MC breast cancer.[19,22] The identification rate and false-negative rate for MF/MC breast cancer were 87% to 100% and 0% to 8% for intradermal and subareolar injections, respectively; whereas, these rates were 85.7% to 94.7% and 0% to 33.3%, respectively, for peritumoral injections.[18,23-26]

Subareolar blue dye injection also achieved a 90% identification rate and 0% false-negative rate in MF/MC breast cancer, although subareolar blue dye injection induces skin staining, which may last for months.[27] Table 3 shows that peritumoral injections with blue dye alone seems to have poor identification rates and high false-negative rates in MF/MC breast cancer. Nevertheless, this injection alone is also associated with low identification rates and higher false-negative rates in unifocal breast SLN biopsy.[10] A combination with the radiocolloid method is required when blue dye is used in SLN biopsy for MF/MC breast cancer. However, a combination of radiocolloid and blue dye methods does not seem to have better results in the identification rate and false-negative rate than the radiocolloid method alone in MF/MC disease. Some studies, including ours, showed a 100% SLN identification rate and a 0% false-negative rate in MF/MC breast cancer. A possible explanation is the limited number of MF/MC cases in these studies.

Most studies of SLN biopsy have excluded patients with MF/MC breast cancer based on preoperative examination. According to the Veronesi hypothesis, different lymphatic drainage pathways arising from different tumors may need multiple injection sites and induce different SLN loca-

Table 3. Studies of Sentinel Lymph Node Biopsy in Multifocal/Multicentric Breast Cancer

Studies	Number of patients	Injection route	Identification rate	Sentitivity	Accuracy	False-negative rate
Veronnesi, 1999[15]	46	Peritumoral radiocolloid	NR	90.3%	93.5%	9.7%
Hill, 1999[29]	60	Peritumoral radiocolloid and blue dye	91.7%	NR	NR	Feasible (one case)
Schrenk, 2001[24]	19	Subareolar radiocolloid and blue dye	100%	100%	100%	0%
Kim, 2002[20]	5	Peritumoral or intradermal radiocolloid and blue dye	100%	100%	100%	0%
Ozmen, 2002[18]	21	Peritumoral blue dye	85.7%	60%	77.8%	33.3%
Layeeque, 2003[19]	40	Subareolar radiocolloid	100%	100%	100%	0%
Tousimis, 2003[23]	70	Intradermal radiocolloid over the tumor	100%	92%	96%	8%
Kumar, 2003[25]	59 (27 clinical; 32 histological)	Intradermal radiocolloid over the tumor; and peritumoral blue dye	87% (blue dye) 93.5% (radiocolloid)	100%	100%	0%
Kumar, 2004[27]	10	Peritumoral or subareolar radiocolloid; and subareolar blue dye	100%	100%	100%	0%
Goyal, 2004[26]	75	Peritumoral radiocolloid and blue dye	94.7%	91.2%	95.8%	8.8%
Bergkvist, 2005[21]	56	Peritumoral or intradermal or subdermal radiocolloid and blue dye	NR	85.7%	78.9%	21%
Gentilini, 2006[28]	42	Subareolar or peritumoral/subdermal radiocolloid	100%	95.2%	97.6%	4.8%
Knauer, 2006[16]	142	Multi-institute	91.5%	96.0%	97.3%	4.0%
Lo, 2007	23	Intradermal radiocolloid	100%	100%	100%	0%

Abbreviation: NR: not reported.

tions.[14,21] In fact, breast tumors in different locations will drain to the same axillary SLNs. Kim et al, using radiocolloid and blue dye injected into different tumors in multicentric breast cancer, demonstrated that multicentric tumors located in different quadrants will drain to the same SLNs in the axilla.[20] Gentilini et al studied 42 MF/MC breast cancer patients and also demonstrated that the SLN locations and numbers were determined by afferent lymphatic pathways to the axilla rather than the site or number of injections. They used a single subareolar injection for 25 cases with three or more separate invasive tumors and double peritumoral injections for cases of two separate invasive tumors. The numbers of SLNs were not modified by injection site or number.[28] Medially located breast tumors have more lymphatic drainage to the internal mammary nodes using the peritumoral radiocolloid method, and peri-

tumoral blue dye can not detect internal mammary node results in the same axillary SLNs in Kim's study.[9,20] This limitation does not necessarily influence the outcome of radioguided subdermal, intradermal, or subareolar approaches to SLN biopsy in MF/MC breast cancer. Internal mammary SLNs are not highly significant clinically in early breast cancer because internal mammary SLN identification does not necessarily indicate nodal involvement. Moreover, the use of SLN biopsy is to replace traditional axillary lymph node dissection and to avoid axillary morbidity; the detection and harvest of internal mammary nodes were another issue. Nevertheless, Gentilini et al studied 42 MF/MC breast cancers, 17 cases with two invasive tumors, using peritumoral double injection. Five patients underwent internal mammary nodes biopsy, and two had metastases. Their study suggests that for selected cases or

medially located tumors, a peritumoral injection can be performed first, followed by a subareolar injection.[28]

Tousimis et al studied 3,501 clinically node-negative breast cancer patients, including 70 with MF/MC breast cancer, using a peritumoral radiocolloid and blue dye injection approach and demonstrated a false-negative rate of 8% (3 of 38) in MF/MC breast cancer, which was comparable with the unifocal group. Two of the three tumors in the false-negative cases were larger than 5 cm, two of the three cases had N2 disease, and all three cases showed non-visible SLNs on lymphoscintigraphy.[23] For these advanced breast cancers, a high false-negative rate is expected. A recent multicentre study also demonstrated a significantly increased false-negative rate (21%) in MF/MC tumors compared with unifocal breast cancer (5.6%). However, some patients with multicentric tumors on preoperative mammograms had been excluded from SLN biopsy.[21]

An increasing number of studies have shown that SLN biopsy can accurately predict nodal status in MF/MC breast cancer.[19,21-23] Schrenk et al reported a 100% identification rate and 0% false-negative rate with subareolar blue dye and radiotracer injection techniques in 19 multicentric invasive breast cancers.[24] Kumar et al, studied 59 multicentric breast cancer patients and obtained a 93% identification rate with no false-negative results.[25] Goyal et al, investigated 75 multifocal breast cancer patients and demonstrated a 94.7% identification rate and 8.8% false-negative rate in the MF/MC group with a peritumor injection blue dye and radio-colloid approach; there were no significant differences from the unifocal group.[26] Hill et al reported a very similar identification rate for SLN mapping for multicentric and unifocal breast cancer (92% vs 93%, respectively); only 1 of 5 false-negative cases was multicentric.[29] These studies demonstrate that SLN biopsy can be applied to MF/MC breast cancer, with no statistical differences in SLN identification and false-negative rates.

Conclusions

Sentinel lymph node biopsy using intradermal radiotracer injection alone can accurately predict axillary status in clinically node-negative MF/MC breast cancer patients. The identification and false-negative rates for SLN biopsy in MF/MC breast cancer are comparable with those in unifocal breast cancer.

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前哨淋巴切除術在多發性乳癌的適用性

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背 景： 前哨淋巴切除術在預測淋巴腺的轉移有很高的正確性，但多發性乳癌常排除前哨淋巴切除術的使用，本研究探討前哨淋巴切除術在多發性乳癌的適用性。

方 法： 本研究回顧 2004 年至 2006 年有做前哨淋巴切除術的乳癌病患，這些病患必須是經超音波定位穿刺確定的早期乳癌且理學檢查無腋下淋巴腫大，經根治性手術後，再由病理做最終的確定是單發性或爲多發性乳癌。手術前一天由核醫採用皮膚內注射方式做前哨淋巴的放射線定位 (lymphoscintigraphy)，手術中再使用放射線探測器 (gamma-counter) 找尋前哨淋巴並切除之，並實施腋下淋巴廓清以比對前哨淋巴的準確性。

結 果： 總共 158 位病患符合條件，單發性乳癌 135 人，多發性乳癌 23 人。單發性乳癌及多發性乳癌前哨淋巴的發現率，靈敏度，正確性，及偽陽性率分別爲 94.8%，92.6%，98.4%，7.4% 及 100.0%，100.0%，100.0%，0%。兩組並無統計上的意義。

結 論： 多發性乳癌利用皮膚內注射方式做前哨淋巴的放射線定位做前哨淋巴切除術是可行的。

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關鍵詞：前哨淋巴，乳癌，多發性