Predicting sentinel lymph node metastasis in breast cancer with lymphoscintigraphy

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Predicting sentinel lymph node metastasis in breast cancer with lymphoscintigraphy

A short title: Predicting SLN metastasis

Atsushi Noguchi, Masahisa Onoguchi, Takeshi Ohnishi, Terumi Hashizume, Akiyoshi Kajita, Masahiro Funauchi, Toshizo Katsuda, Kazuyoshi Motomura

A. Noguchi, T. Ohnishi, T. Hashizume, A. Kajita, M. Funauchi
Department of Nuclear Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases,
1-3-3 Nakamichi, Higashinari, Osaka, 537-8511, JAPAN

A. Noguchi, M. Onoguchi
Department of Quantum Medical Technology, Division of Health Sciences, Kanazawa University Graduate School of Medical Science,
5-11-80 Kodatsuno, Kanazawa, 920-0942, JAPAN

T. Katsuda
Department of Radiological Technology, Seikeikai College of Medical Technology, 4-5-9 Kouryou nishimachi, Sakai, 590-0026, JAPAN

K. Motomura
Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases,
1-3-3 Nakamichi, Higashinari, Osaka, 537-8511, JAPAN

Address correspondence and reprint requests to:
Masahisa Onoguchi
Department of Quantum Medical Technology, Division of Health Sciences, Kanazawa University Graduate School of Medical Science,
5-11-80 Kodatsuno, Kanazawa, 920-0942, JAPAN
Phone&Fax: 076-265-2526
E-mail address; onoguchi@kenroku.kanazawa-u.ac.jp

Abstract

Objective Lymphoscintigraphy is an effective method for detecting sentinel lymph nodes (SLNs). However, the rate and degree of SLN detection is not uniform. We quantified SLNs detected with lymphoscintigraphy, and investigated correlations with factors that may influence detection. We then attempted to predict SLN metastasis from lymph node counts, comparing the predictions to subsequent biopsy results.

Methods We assessed lymph node counts in 100 breast cancer patients in whom a single SLN was detected with a fixed lymphoscintigraphy procedure. We examined correlations between the counts and factors known to influence lymphoscintigraphic SLN detection (age, body mass index, tumor size, and presence or absence of metastasis), and determined reference values (lymph node counts of 10.0, 19.4 and 53.0) which were used to predict SLN metastasis in 100 subsequent patients. The predictions were then compared with the SLN biopsy findings.

Results SLN counts correlated strongly with the presence or absence of metastasis, with metastasis-positive lymph nodes showing significantly lower counts than negative nodes (p < 0.001). Prediction of SLN metastasis achieved a

100% positive predictive value at a reference value of 10.0, and a 100% negative

predictive value at a reference value of 53.0. At a reference value of 19.4, the

sensitivity, specificity, and diagnostic accuracy were 77.8%, 73.2%, and 74.0%,

respectively.

Conclusions   The SLN counts detected with lymphoscintigraphy were

significantly lower in metastasis-positive lymph nodes than in metastasis-

negative lymph nodes. This suggests that prediction of SLN metastasis in breast

cancer is possible using lymphoscintigraphy.

Introduction

The presence or absence of metastasis in the axillary lymph nodes in breast cancer is a key factor for deciding the therapeutic strategy [1]. The sentinel lymph node (SLN) reflects the metastatic status of the axillary lymph nodes [2-5]. The idea that the absence of SLN metastasis indicates absence of metastasis in other axillary lymph nodes is used to decide whether to omit axillary lymph node dissection [6, 7], reducing the area of excision and enhancing the patient's quality of life. Diagnosis of SLN metastasis is made intraoperatively through biopsy. Thus, it has not been possible to determine preoperatively whether axillary lymph node dissection is necessary.

Lymphoscintigraphy is currently used preoperatively for SLN identification, though not for prediction of SLN metastasis. Previous studies have shown that SLN visualization in patients with breast cancer is influenced by several factors, including procedural variations [8-12] and such patient factors as age, body mass index (BMI), tumor size, and metastasis to the SLN [13-15]. While those studies have served to advance the SLN detection rate, the detection rates have not been uniform, and the degree of detection has not yet been assessed.

In this study, lymphoscintigraphy was conducted with a fixed procedure,

and the degree of SLN detection was quantified by assessing lymph node counts.

Correlation of the lymph node counts with patient factors showed that the counts

correlated most strongly with the presence or absence of metastasis. On that

basis, reference values derived from the lymph node counts were used to attempt

prediction of SLN metastasis. Finally, the predictions of metastasis were verified

by comparing them with the SLN biopsy findings.

Materials and Methods

Patients

Participants in the study were T1N0M0 breast cancer patients with a

tumor size of 20 mm or less and no clinical lymph node metastasis, who

submitted written informed consent. A total of 557 patients (median age: 56

years, range: 26-84 years) completed the procedures from August 2003 through

January 2008.

The criteria for inclusion were detection with lymphoscintigraphy of only

a single SLN, and surgical removal of a single SLN. These criteria were set in

order to maintain a one-to-one correspondence between detected nodes and

SLNs removed for biopsy. Correlations between lymph node counts and patient

factors were investigated in 100 consecutive cases (from August 2003 through

July 2005, standard patients). The correlations were used to predict SLN

metastasis in the next 100 consecutive cases (from August 2005 through January

2008, predicted patients).

Lymphoscintigraphy and SLN Biopsy

In each case, lymphoscintigraphy was conducted on the day prior to

surgical resection of breast cancer using the following procedure. A total volume

of 45 MBq/0.4 mL of ^{99m}Tc-tin colloid was injected at four intradermal sites

around the tumor. At three hours after injection, the patient was placed in a

supine position with the upper extremity near the affected area elevated, the

injection sites were masked with a lead plate, and lymphoscintigraphy was

performed with an anterior oblique view of 30 degrees. The device used was a

gamma camera equipped with a low-energy high-resolution collimator (RC2500

IV, Hitachi Medical Corp., Tokyo, Japan). Static acquisition with a 256 x 256

matrix was conducted for five minutes.

During the surgical resection, the SLN was identified with a gamma probe

(neo 2000, Neoprobe, Dublin, Ohio, USA) before dissection. The biopsy

consisted of two pathological diagnoses, using imprint cytology and rapid

histology. If metastasis was detected in one or both of the diagnoses, the result

was considered positive; if no metastasis was observed, it was considered

negative.

Correlation of Lymph Node Counts and Patient Factors

To quantify the degree of SLN detection with lymphoscintigraphy, a

region of interest was set with a threshold value of 50%. The lymph node count

was defined as the mean count within the region of interest.

The patient sets were each divided into two groups at the median values

of age, BMI, and tumor size. To determine significance with respect to the

presence or absence of SLN metastasis, the lymph node counts were divided into

groups of positive and negative cases, and compared. Lymph node counts were

also compared for the positive and negative groups within each of the groups

divided by patient factors.

The differences between groups were calculated using the unequal

variance t-test (Welch's t-test), with P values < 0.05 defined as statistically

significant.

Metastasis Prediction and Verification of Predictions

From the lymph node counts in the 100 correlated cases (the standard

patients), three reference values were derived for prediction of SLN metastasis:

the maximum and mean values in the positive groups, and the minimum value in

the negative groups. In the 100 predicted cases from August 2005, counts equal

to or higher than the reference values were predicted to be metastasis-negative,

while those below the reference values were predicted to be metastasis-positive.

Those predictions were verified through comparison with the SLN biopsy

findings.

Results

Lymphoscintigraphy and SLN Biopsy

Figure 1 shows cases of SLNs with low (a) and high (b) tracer

accumulations. Figure 1a is metastasis-positive with a lymph node count of 16.6.

Figure 1b is metastasis-negative with a lymph node count of 135.2.

Table 1 lists the characteristics of the standard patients and the predicted

patients. The median age was 53 and 56 years, respectively; the median BMI

was 21.7 and 21.6, respectively; and the median tumor size was 15 mm in both

sets. The patient sets thus had similar characteristics. The number of metastasis-

positive SLN cases among the standard and predicted patients was 25 and 18,

respectively.

Correlation of Lymph Node Counts and Patient Factors

For assessment of patient factors, each patient set was divided into two at

the age of 53, BMI of 21.7, and tumor size of 15 mm, and differences of lymph

node counts between the pairs of groups were analyzed. Although there was a

difference in age between the patient sets (p = 0.0332), no significant differences

were found in BMI or tumor size. There was a clear difference between the SLN

metastasis-positive and negative groups (p < 0.0001), with lower counts in the

positive group (Fig. 2).

Comparisons of the lymph node counts between the metastasis-positive

and negative groups divided in two according to age, BMI, or tumor size,

revealed significant differences for each pair. The lymph node counts were

consistently lower in the metastasis-positive groups (Table 2).

Metastasis Prediction and Verification of Predictions

Reference values for predicting SLN metastasis were set at 10.0

(minimum value in the negative group), 19.4 (mean value in the positive group),

and 53.0 (maximum value in the positive group). For the reference value of 10.0,

all 11 cases with lymph node counts below 10.0 and a positive prediction were

found to be metastasis-positive. For the reference value of 53.0, all 28 cases with

lymph node counts equal to or higher than 53.0 and a negative prediction were

found to be metastasis-negative (Table 3). Thus, the positive predictive value of

the reference value 10.0 and the negative predictive value of the reference value

53.0 were both 100%. For the reference value 19.4, the sensitivity, specificity,

and diagnostic accuracy were 77.8%, 73.2%, and 74.0%, respectively (Table 4).

Discussion

The SLN counts observed in this study were lower in the metastasis-

positive group than in the metastasis-negative group. This finding suggests that

lymphoscintigraphy may be used preoperatively to predict SLN metastasis.

SLN detection with lymphoscintigraphy was associated with procedural

and patient factors, and correlations were made between the patient factors and

the degree of detection using a fixed procedure. While a significant difference in

lymph node counts was observed for age, the difference observed for presence

or absence of metastasis was even more significant. Higher age, BMI, or tumor

size tended to correlate with lower lymph node counts, while significant

differences were clearly observed between these groups according to the

presence or absence of metastasis (Table 2).

SLN detection most strongly reflected the presence or absence of

metastasis, with lymph node counts being lower in the metastasis-positive group

than in the negative group. To explain this finding, we may infer that radioactive

tracer does not accumulate in the metastatic lesion within an SLN. Accordingly,

metastatic prediction would be possible through lymph node assessment.

If readers predict metastasis using lymph node counts, they have to establish

reference values. Reference values have to be assessed by lymphoscintigraphy with a

fixed procedure. In addition, the reference values are assumed to be changeable by an

institution even when a fixed procedure is applied.

We established the reference values reappraised from lymph node counts

in the 100 cases. When the lymph node count was below 10 (minimum value in

the negative group), we predicted that SLN would be metastasis-positive. And

when the lymph node count was higher than 53 (maximum value in the positive

group), we predicted SLN to be metastasis-negative. In fact, in the present

investigation of 100 cases, positive metastasis was predicted in all 11 cases with

low lymph node counts, and negative metastasis was predicted in all 28 cases

with high lymph node counts, consistent with the diagnoses based on SLN

biopsies.

Wang et al. reported a lower SLN detection rate in patients with

metastasis to the axillary lymph nodes than in patients with no metastasis, but

they did not discuss the degree of SLN detection [16]. The present study also

found lower lymph node counts and less clear SLN detection in the metastasis-

positive group than in the metastasis-negative group, and made a further

comparative investigation of patients with and without SLN metastasis.

Nakashima et al. performed dynamic lymphoscintigraphy using ^{99m}Tc-

phytate, and reported that abnormal accumulation was observed near the hot

spots (SLNs) in the metastasis-positive cases [17]. In that study, patients with

abnormal accumulation near the SLN were predicted to be metastasis-positive.

In the present study, no abnormal accumulation was observed near SLNs

because the tracer was ^{99m}Tc-tin colloid, which has a larger particle size than

^{99m}Tc-phytate. As ^{99m}Tc-tin colloid takes longer to flow into the lymph channel,

it is not suitable for dynamic lymphoscintigraphy. Accordingly, for metastatic

prediction with lymphoscintigraphy using ^{99m}Tc tin colloid, lymph node counts

should be assessed. Whereas Nakashima et al. based the metastatic prediction on

visual assessment, this study used measurement and quantitative evaluation of

lymph node counts to improve the accuracy of prediction.

Preoperative prediction of SLN metastasis in breast cancer is possible

with either the dynamic lymphoscintigraphy employed by Nakashima et al., or

lymphoscintigraphy as used in the current study. Thus, although preoperative

lymphoscintigraphy was initially explored for the sole objective of SLN

detection, in the future it will likely provide information useful for metastatic

prediction.

The present study was limited to patients with only a single SLN, and

there is a need to investigate cases with two or more SLNs in the future. Martin

et al. have already reported that when metastasis-positive and metastasis-

negative lymph nodes were mixed in patients with multiple SLNs, metastasis

was found in the lymph nodes with lower counts [18]. This suggests that

metastatic prediction will also be possible in cases with multiple SLNs.

Conclusion

The SLN counts detected with lymphoscintigraphy were significantly

lower in metastasis-positive lymph nodes than in metastasis-negative lymph

nodes. This strongly suggests that prediction of SLN metastasis in breast cancer

is possible using lymphoscintigraphy.

Acknowledgments

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Figure Legends

Fig. 1: Examples of low (a) and high (b) concentrations in sentinel lymph nodes detected with lymphoscintigraphy. The injection sites T were masked with lead plates during lymphoscintigraphy.

Fig. 2: Comparisons of lymph node counts between patient sets divided according to age, BMI, tumor size, and SLN metastasis.
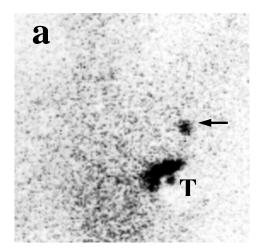
TABLES

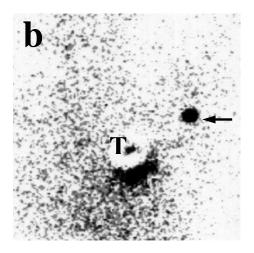Table 1: Characteristics of standard patients and predicted patients

Table 2: Comparison of metastasis-positive and metastasis-negative SLN counts in groups divided by age, BMI, and tumor size for each patient set

Table 3: Judgment of SLN metastasis with lymphoscintigraphy and results of SLN biopsies

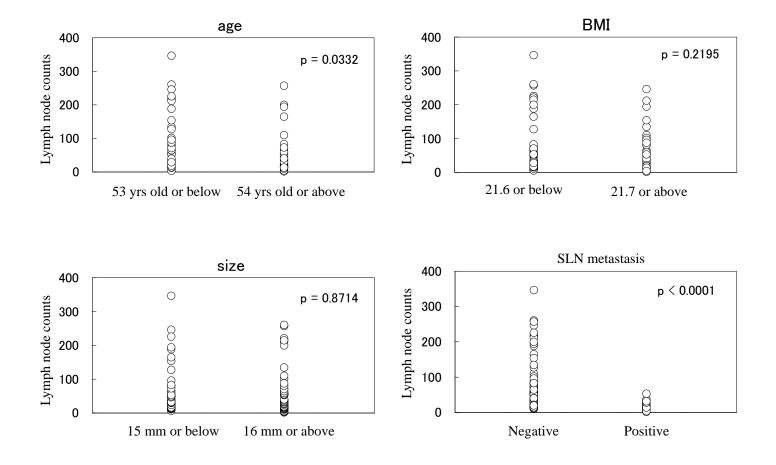Table 4: Comparison of SLN metastasis judgments at each reference value

Fig. 1

Fig. 2

Table 1

Characteristics	Standard patients (n = 100)	Predicted patients (n = 100)
Age (years): Median (Range)	53 (26-77)	56 (32-76)
BMI: Median (Range)	21.7 (16.6-30.5)	21.6 (17.0-35.4)
Tumor size (mm): Median (Range)	15 (7-20)	15 (1-20)
Tumor location (number of cases)		
Upper outer quadrant	45	54
Upper inner quadrant	27	21
Lower outer quadrant	21	16
Lower inner quadrant	7	8
Central	0	1
SLN metastasis (number of cases)		
Positive	25	18
Negative	75	82

Table 2

Factor (n)	SLN metastasis (n)	SLN counts minimum	maximum	mean	p value
Age, years					
＞53 （49）	Positive （11）	1.8	36.6	18.06	0.0009
	Negative （38）	10.0	257.0	53.77	
≤53 （51）	Positive （14）	3.6	53.0	20.36	＜0.0001
	Negative （37）	11.2	346.5	96.15	
BMI					
＞21.7 （50）	Positive （11）	1.8	53.0	17.31	＜0.0001
	Negative （39）	11.9	246.2	62.03	
≤21.7 （50）	Positive （14）	5.8	36.6	20.96	＜0.0001
	Negative （36）	10.0	346.5	88.38	
Tumor size, mm					
＞15 （52）	Positive （19）	1.8	53.0	19.53	＜0.0001
	Negative （33）	10.0	260.5	82.89	
≤15 （48）	Positive （6）	6.7	28.9	18.80	0.0002
	Negative （42）	11.2	346.5	68.22	

Table 3

Judgment of SLN metastasis	Results of SLNB	
	Positive（n=18）	Negative（n=82）
Judgment at reference value 10.0		
Metastasis predicted	11	0
Metastasis not predicted	7	82
Judgment at reference value 19.4		
Metastasis predicted	14	22
Metastasis not predicted	4	60
Judgment at reference value 53.0		
Metastasis predicted	18	54
Metastasis not predicted	0	28

Table 4

Judgment of SLN metastasis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Judgment at reference value 10.0	61.0	100.0	100.0	92.1	93.0
Judgment at reference value 19.4	77.8	73.2	38.9	93.8	74.0
Judgment at reference value 53.0	100.0	34.1	25.0	100.0	46.0