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RESEARCH ARTICLE

The Omission of Axillary Lymph Node Dissection in Sentinel Node-Positive Breast Cancer Patients Requires Careful Consideration

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Abstract

Sentinel Node Biopsy (SNB) is used to accurately assess axillary lymph node status in patients with node-negative breast cancer. The purpose of this study was to assess the association between Non-Sentinel Node (SN) metastasis and clinicopathological findings in patients with one or two SN-positive breast cancer.

We evaluated 132 patients with one or two SN-positive breast cancer and 25 patients (19%) had metastatic non-SNs. Positive non-SN metastasis was associated with the HER2 positive (P = 0.035), tumor size (P = 0.06) and equal number of excisional SN and positive SN (P = 0.003).

When considering omitting the dissection in SN-positive patients, it is essential to carefully consider the number of removed SNs. Moreover, particular caution is required when considering whether to omit the dissection in patients with tumors exhibiting diameters of > 2 cm or HER2-overexpressing.

Keywords

Sentinel lymph node biopsy, Non-sentinel lymph node metastasis, Axillary lymph node dissection

Introduction

Sentinel Lymph Node Biopsy (SNB) is coming to replace axillary lymph node dissection as a method of accurately assessing axillary nodes in clinically lymphatic metastasis-negative breast cancer patients [1-3]. The omission of axillary lymph node dissection is recommended if a patient is Sentinel Lymph Node (SN) metastasis-negative. Furthermore, several recent prospective randomized comparative studies have showed an improved prognosis after omitting axillary node dissection, even in the presence of micrometastases or two or fewer macrometastases in the SN [4-7]. However, the samples in these clinical studies were inadequate (e.g., a small number of enrolled patients and events and biased enrolled patients), thereby leaving room for debate on this topic in Japan [8].

The purpose of the present study was to retrospectively examine the association among non-SN metastasis status, clinicopathological factors, the number of metastatic SNs, and the number of removed SNs in patients with one or two metastatic SNs from the prospective SNB database in our department.

Methods

Patients

Out of the 996 total clinically axillary lymph node metastasis-negative breast cancer patients at our facility between April 2007 and December 2013, 132 patients with one or two SN metastases who underwent dissection were enrolled. Patients who underwent preoperative chemotherapy were excluded. This study was

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Table 1: Non-SN metastasis and pathological factors in patients with one or two metastatic SNs.

		Patients n (%)	Non-SN metastases		*P*
			Positive 25 (19%)	Negative 107 (81%)	
pT	≦ 0, ≦ 2 cm	62 (47%)	8 (13%)	54 (87%)	0.06
	< 2, ≦ 5 cm	64 (48%)	14 (22%)	50 (78%)	
	< 5 cm	6 (5%)	3 (50%)	3 (50%)	
ER	+	111 (84%)	20 (18%)	91 (82%)	0.53
	-	21 (16%)	5 (24%)	16 (76%)	
PgR	+	105 (80%)	21 (20%)	84 (80%)	0.60
	-	27 (20%)	4 (15%)	23 (85%)	
HER2	+	12 (9%)	5 (42%)	7 (58%)	0.035
	-	120 (91%)	20 (17%)	100 (83%)	
ly	+	65 (49%)	15 (23%)	50 (77%)	0.23
	-	67 (51%)	10 (15%)	57 (85%)	
v	+	11 (8%)	2 (18%)	9 (82%)	0.95
	-	121 (92%)	23 (19%)	98 (81%)	

SN: Sentinel Lymph Node; pT: Pathological Tumor Diameter; ER: Estrogen Receptor; PgR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor-2; ly: Lymphatic Invasion; v: Venous Invasion.

approved by the Ethics Committee of the Jikei University School of Medicine, and patient consent was obtained.

Image evaluation

Axillary lymph nodes were evaluated by palpation, ultrasound, and contrast-enhanced MRI of the breast.

SNB procedure

Radioactive isotopes and pigments were used for SNB. $^{99m}T_c$-phytate colloid markers were intradermally or subdermally injected into the periphery of the tumors on the day of the operation (0.25 mL, 15 MBq) or on the day prior (0.5 mL, 30 MBq) to perform lymphoscintigraphy. Isosulfan blue (Lymphazurin; Covidien, Mansfield, MA) or indocyanine green (Diagnogreen; Daiichi Sankyo, Tokyo, Japan) pigments were subdermally injected into the periphery of the tumor or under the areola immediately before performing SNB.

Pathological evaluation

After slicing at 2-mm intervals, all SNs were evaluated by an intraoperative rapid diagnosis, and axillary lymph node dissection was performed when metastases of ≥ 2 mm were found. After fixing in formaldehyde, SNs were subsequently evaluated by immunostaining using anti-cytokeratin (CAM 5.2). The diameter of tumor invasion, Estrogen (ER) and Progesterone (PgR) receptors, Human Epidermal Growth Factor Receptor-2 (HER2), and lymphatic and venous invasions were evaluated. In terms of hormone sensitivity, ≥ 10% of invasive cells was considered positive. HER2 expression was examined following the HER2 test classification [9] as follows: Staining scores 3+ and 2+ and fluorescence *in situ* hybridization scores of ≥ 2 were considered positive.

Statistical analysis

Patients were assigned to the non-SN metastasis-positive and metastasis-negative groups, and correlations between their pathological factors and number of metastatic SNs, removed SNs, and non-SN metastases were evaluated using the Fisher's exact test. *P*-values ≤ 0.05 were considered significant. The analysis was performed using Stata analysis software (Stata SE 10; Stata Corp LP, College Station, TX).

Results

Patient background and correlations between non-SN metastases and pathological factors

As shown in Table 1, the pT, based on the pathological tumor diameter, was as follows: pT0,1: 62 (47%) patients; pT2: 64 (48%) patients; and pT3: 6 (5%) patients. The rates of ER and PgR positivity and HER2 over expression were 84%, 80%, and 9%, respectively. Non-SN metastasis was found in 25 (19%) patients. The median number of non-SN metastases was 5 (range, 1-20).

There were five (42%) patients in the non-SN metastasis-positive group among the 12 patients with HER2 over expressing tumors, whereas there were 20 (17%) patients in the non-SN metastasis-positive group among the 120 patients with low HER2-expressing tumors. The rate of non-SN metastasis positivity was significantly higher in patients who had tumors over expressing HER2 ($P = 0.035$). Non-SN metastases were observed in 13%, 22%, and 50% of pT1, pT2, and pT3 patients, respectively. Moreover, we found that the rate of non-SN metastasis positivity increased as the tumor diameter increased ($P = 0.06$). No correlations were noted with ER, PgR, or lymphatic and venous invasion.

Correlation between the number of metastatic SNs and non-SN metastases

The number of patients with metastatic SN and non-SN metastasis status is shown in Table 2. We found non-SN metastasis in 18 (17%) of the 107 patients with one SN metastasis and in seven (28%) of the 25 patients with two metastatic SNs. No significant correlation was found between the number of metastatic SNs and non-SN metastasis ($P = 0.20$).

Table 2: Non-SN metastasis status and number of SN metastases in patients with one or two SN metastases.

Number of SN metastases	n (%)	Non-SN metastases		*P*
		Positive (n)	Negative (n)	
1	107 (81%)	18 (17%)	89 (83%)	0.20
2	25 (19%)	7 (28%)	18 (72%)	

SN: Sentinel Lymph Node.

Table 3: Number of removed SNs and non-SN metastases in patients with one or two SN metastases.

Number of removed SNs	Non-SN metastases		*P*
	Positive n (%)	Negative (n) n (%)	
1	7 (35%)	13 (65%)	0.11
2	11 (18%)	51 (82%)	
3	6 (20%)	24 (80%)	
≧ 4	1 (5%)	19 (95%)	

SN: Sentinel Lymph Node.

Table 4: Number of removed SNs and SN metastases in patients with one or two metastases.

		Number of removed SNs	Non-SN metastases		*P*
			Positive n (%)	Negative n (%)	
Total with 1 or 2 SN metastases		=	13 (35%)	24 (65%)	0.003
		≤	12 (13%)	83 (87%)	
SN metastases	1	1	7 (35%)	13 (65%)	0.19
		≥ 2	11 (20%)	43 (80%)	
	2	2	6 (35%)	11 (65%)	0.0005
		≥ 3	1 (2%)	40 (98%)	

SN: Sentinel Lymph Node.

Correlation between the number of removed SNs and non-SN metastases

The median number of removed SNs was two (range, 1-4). As shown in Table 3, there was no correlation between the number of removed SNs and non-SN metastasis positivity. When we compared whether the number of removed SNs was larger than or equal to the number of metastatic SNs, we found that the frequency of non-SN metastasis was significantly lower in the group for which the number of removed SNs was higher than the number of metastatic SNs, as shown in Table 4 ($P = 0.003$). In particular, in the group with two metastatic SNs, we found a significant and extremely strong correlation with non-SN metastasis (six patients, 35%) when the number of removed SNs was two compared with when the number of removed SNs was ≥ three (one patient, 2%) ($P = 0.0005$).

Discussion

The status of axillary lymph node metastasis is a prognostic factor of breast cancer and it is important in determining radiotherapy or pharmacotherapy regimens. While the removal of metastatic nodes by axillary lymph node dissection is the best method for preventing axillary recurrence, clinical trials involving early-stage breast cancer patients have reported that axillary lymph node dissection does not contribute to the overall survival rate [10]. Furthermore, dissection is often associated with complications, including edema in the upper limbs, pain, perceptual dysfunction, and restriction of the shoulder girdle [11,12]. To prevent these complications, SNB is now widely used for axillary evaluation in clinically axillary node-negative patients [1-3].

Previously, axillary lymph node dissection was the standard treatment to evaluate axillary nodes in SN-positive patients; however, approximately 40%-60% patients are non-SN-negative [13]. To prevent unnecessary dissections, predictive factors of non-SN metastasis have been analyzed in multiple studies, and tumor diameter, nuclear grade, lymphatic and venous invasion, and size of the SN metastasis were found to be predictive factors of non-SN metastasis [14-17]. The effectiveness of nomograms using these parameters has also been reported [18]. In addition, we have reported that the presence of stem cells in the SN was a predictive factor of non-SN metastasis [19].

Even in SN metastasis-negative patients, 9%-10% of false-positive results occur; however, axillary recurrence in the non-dissected group remains extremely low, at 0.4%-0.7%, and the rates of intra-breast recurrence and distance metastasis are equal between the SNB negative, SNB-alone, and axillary lymph node dissection groups [20,21]. Based on these factors and the hypothesis that even if lesions remained in non-SNs, they can be cured and controlled by appropriate postoperative radiotherapy or pharmacotherapy, prospective studies examining the omission of axillary lymph node dissection in SN-positive patients was commenced. In the Z0011 trial, the American College of Surgeons Oncology Group (ACOSOG) found that the 5-year axillary recurrence rate in the axillary lymph node dissection omission group was 0.9% when partial mastectomy, postoperative radiotherapy, and appropriate pharmacotherapy were performed, even if micrometastases or one to two macrometastases were identified in the SNs, which was not significantly different from the axillary lymph node dissection group [4]. The 10-year axillary recurrence rate in an updated recent report was 1.5% in the SN-only group and 0.5% in the axillary lymph node dissection group, which was not significantly different [5]. Dissection was omitted in patients with micrometastases in the International Breast Cancer Study Group (IBCSG) 23-01, which found the 5-year regional recurrence rate to be 1% [6]. EORTC 10981-22023AMAROS study compared two groups that underwent axillary lymph node dissection and axillary radiotherapy; how-

ever, no significant difference in the 5-year axillary recurrence rate was found between the two groups [7]. Given the results of the ACOSOG Z0011 [4,5], the American Society of Clinical Oncology (ASCO) [21] and National Comprehensive Cancer Network (NCCN) guidelines [22] recommend the omission of axillary lymph node dissection for SN metastasis-positive patients who meet the following conditions: tumor diameter, ≤ 5 cm; number of metastases, ≤ 2; no preoperative chemotherapy; and undergoing a partial resection and postoperative radiotherapy.

These clinical trials have several shortcomings, including an insufficient number of enrolled patients and events, thereby leaving room for debate. First, the tumors that were studied were small, and tumors with diameters of ≤ 2 cm accounted for 71%, 69%, and 78% in the Z0011, 23-01, and AMAROS studies, respectively. Furthermore, the rate of micrometastasis was 45%, 98%, and 29% in the Z0011, 23-01, and AMAROS, respectively; thus the tumor load in the SN was low. Non-SN metastasis accounted for 27%, 33%, and 13% in the Z0011, AMAROS, and IBCSG 23-01, respectively, but given the low tumor load in non-SN patients, it is possible that recurrence was controlled by radiotherapy or pharmacotherapy.

There is only a limited number of reports on metastasis status or predictive factors of non-SN in patients with one or two lymphatic metastases. In one of these studies, Toshikawa, et al. has reported that among 54 patients with one or two SN metastases, 38.6% are non-SN metastasis, and the predictive factors are tumor diameter and lymphatic invasion [23]. In this study, we identified non-SN metastasis in 19% of the patients, which was associated with HER2 over expression and tumor diameter.

Ultrasound is reportedly effective for a detailed evaluation of axillary lymph nodes. Abnormal findings in an axillary ultrasound include the complete disappearance of the hilum and partial thickening or swelling of the skin [24]. We also preoperatively evaluated these factors in our study and it was difficult to predict non-SN metastases. Furthermore, although we found no significant association between the number of removed SNs and non-SN metastases, the incidence of non-SN metastasis increased when the number of metastatic SN and removed SNs were equal, particularly when there were two metastatic SNs.

The method of SN evaluation is also important. In the IBCSG 23-01 trial, the SNs were rigorously measured from 50-200 μm slices to assess micrometastases; however, this method is predictably difficult to perform in several practical clinical environments, thereby posing limitations. Indeed, the SNB registry trial in the Netherlands omitted SN micrometastasis dissection and found that the 5-year axillary recurrence rate was 5.6% [25]. Moreover, an Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis on randomized trials that enlarged and reduced the extent of local treatment before the concept of SNB was introduced reported an association between the 5-year local recurrence rate and the 15-year breast cancer mortality rate [26-28]. This suggests that breast cancer mortality increased because of locally identified persistent tumors.

The extent to which non-SN metastases can be controlled by postoperative radiotherapy and pharmacotherapy remains unknown. However, the node positive HER2 over-expressing patients will receive targeted therapy which is very effective, they will greatly benefit from systemic therapy.

Conclusions

The omission of lymph node dissection in patients with tumors exhibiting diameters of > 2 cm, HER2-over-expressing tumor and an equal number of SN metastases and removed SNs should be carefully considered. In the future, there may be an increase in the number of patients allowed to omit lymph node dissection; however, it is important to note that appropriate radiotherapy and adjuvant chemotherapy should be provided if it is omitted.

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