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Original Article

Dye-Guided Sentinel Lymphadenectomy in Clinically Node-Negative and Node-Positive Breast Cancer Patients

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Background: Sentinel lymphadenectomy has been used to assess the axillary nodal status in patients with breast cancer in an attempt to avoid unnecessary axillary dissection. Most studies have examined the utility of this procedure in clinically node-negative patients. However, the clinical evaluation of axillary nodes is often inaccurate for both clinically node-negative and clinically node-positive patients.

Methods: We performed dye-guided sentinel lymphadenectomy in both clinically node-negative and clinically node-positive patients with breast cancer. All patients also underwent a formal axillary dissection. The results of imprint cytology, frozen sections, and permanent sections of the sentinel lymph node (SLN) were compared with each other and with histologic findings of the nonsentinel nodes.

Results: The SLN was identified in 30 (79%) of 38 patients with clinically negative nodes, and in 11 (92%) of 12 patients with clinically positive nodes. For clinically node-negative patients, SLN evaluation yielded a diagnostic accuracy of 90%, a sensitivitiy of 72%, and a specificity of 100%. For clinically node-positive patients, these values were 100%, 100% and 100%, respectively. These values were not significantly different for the two groups of patients.

Conclusions: Sentinel lymphadenectomy may be useful in assessing the axillary nodal status of both clinically node-positive and clinically node-negative breast cancer patients.

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Key words: Breast cancer, Sentinel lymph node

The axillary lymph nodes constitute the major regional drainage site for breast cancer. In the past, a complete axillary dissection has been an integral part of the surgical management of breast cancer. However, several randomized trials have demonstrated that axillary dissection in conjunction with mastectomy does not alter the incidence of systemic recurrence or affect survival in patients with breast cancer[1-3], while other studies have suggested that axillary dissection may be associated with improved long-term survival[4,5]. At present, axillary dissection is commonly regarded as a reliable method of assessing nodal status and treating regional disease[6-8]. However, routine axillary dissection has exposed a large number of patients, particularly those with node-negative breast cancer, to unnecessary perioperative risk and increased long-term morbidity[9]. This raises the question of whether axillary dissection should be performed routinely[10-15]. Accurate assessment of axillary status either before or during surgery could avoid unnecessary axillary dissection in clinically node-negative patients[16,17]. Even if axillary lymph node dissection is therapeutic, it is only therapeutic in patients with positive nodes[30].

Sentinel lymphadenectomy has been developed to assess the axillary lymph nodes accurately without removing most of the axillary contents[18]. Several studies have demonstrated that sentinel lymphadenectomy is a useful way to assess the axilla in breast cancer patients[19-24]. In these studies, sentinel lymphadenectomy has been investigated predominantly in patients with clinically negative nodes. However, it is well known that the clinical evaluation of axillary nodes is consistently inaccurate in both clinically node-negative and node-positive patients[16]. In this study, therefore, we examined whether sentinel lymphadenectomy

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Abbreviations:
SLN, Sentinel lymph node; IHC, Immunohistochemistry; H&E, Hematoxylin-eosin

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is useful for assessing the axillary lymph nodes not only in patients with clinically negative nodes, but also in those with clinically positive nodes.

Patients and Methods

Patients and Operation

After informed consent was obtained, 50 patients with operable breast cancer were scheduled to undergo sentinel lymphadenectomy at the Second Department of Surgery, Kanazawa University Hospital between February, 1996 and February, 1998. The average age of the patients was 55 years (range 28-82). Thirty patients were premenopausal and 20 were postmenopausal. There was 1 patient with T0, 24 with T1, 21 with T2, and 4 with T3 or T4 primary lesions. There were 38 patients with clinically negative nodes (N0, N1a) and 12 with clinically positive nodes (N1b, N2). After dye-guided sentinel lymphadenectomy, a complete axillary dissection (level Ⅰ-Ⅲ) was performed along with management of the primary lesion. Operative methods included modified radical mastectomy in 33 patients, and wide excision with axillary dissection in 17 patients.

Lymphatic Mapping and Sentinel Lymphadenectomy

The technique of lymphatic mapping and sentinel lymphadenectomy for breast cancer has been described in detail elsewhere[19]. The clinical use of patent blue dye (CI 42045, Wako Pure Chemical Industry, Osaka, Japan) has been permitted by the ethical committee of the School of Medicine at Kanazawa University. After induction of general anesthesia, 4 ml of 1% patent blue dye was injected with a 25-gauge needle into the peritumoral area. If the primary tumor had been previously excised, the wall of the biopsy cavity and surrounding tissue were injected. Approximately 5 min later, blunt dissection was performed through the mastectomy incision or an axillary incision until a lymphatic tract or blue-stained node was identified. The dye-filled tract was dissected to the first blue lymph node. If possible, the tract was followed proximally to the tail of the breast to ensure that the identifed lymph node was the most proximal, and thus the sentinel lymph node (SLN). The SLN was excised and processed as a separate specimen. If there was no stained lymph node, but a blue lymphatic was seen going directly into the hilum of a non-blue lymph node, this lymph node was judged to be the SLN[25].

Histologic and Cytologic Examinations

1) Resected Breast Tissue

The resected breast tissue was fixed in 10% formalin and histologically examined on permanent section. Histologic type was determined according to the Histological Classification of Breast Cancer proposed by the Japanese Breast Cancer Society[26], a modification of the Histological Typing of the World Health Organization[27]. The tumors were classified histologically into three major types: noninvasive carcinoma, invasive ductal carcinoma, and other types of invasive carcinoma.

2) Sentinel Lymph Node

SLNs were bisected and the cut surfaces touched onto clean slides, which were dried and stained with May-Giemsa and cytokeratin (MAS 494; Harlan Sera-Lab, Loughborough, England). The SLN was then frozen and sections were cut and stained with hematoxylin and eosin (H&E) staining. Frozen tissue was fixed in 10% formalin and then processed routinely for permanent section with H&E staining. If no tumor was identified using H&E staining, cytokeratin immunohistochemical (IHC) staining was performed on one section. Thus, two sections of a tumor-free SLN were examined; one by H&E staining on permanent section, and one by IHC staining on permanent section.

3) Non-Sentinel Lymph Node

Non-sentinel axillary nodes were dissected fresh and processed by routine surgical pathology techniques for isolation of lymph nodes. The nodes were bisected, embedded in paraffin, sectioned, and examined by H&E staining. Further examination of nonsentinel specimens depended on the SLN histology. If the SLN had metastatis by H&E staining, cytokeratin-IHC staining was not performed on the corresponding nonsentinel nodes. If the SLN was metastasis-free by H&E staining, all corresponding nonsentinel axillary nodes were examined at two levels (total of four faces) using cytokeratin antibody.

Statistical Method

Comparisons of qualitative parameters were made using the chi-squared test.

Table 1. Clinicopathologic Charateristics in Clinically Node-Negative and Node-Positive Breast Cancer Patients

Clinicopathologic variables	Clinical nodal status		Total
	Node-negative (N0, N1a)	Node-positive (N1b, N2)	
No. of patients	38	12	50
Age (year)[a]	55±12	55±16	55±13
Menopausal status			
Pre-	22	8	30
Post-	16	4	20
Tumor size (mm)[a]	25±13	31±15	26±14
Histologic type of tumor			
Non-invasive ductal Ca	3	0	3
Invasive ductal Ca	34	11	45
Other invasive Ca	1	1	2
Axillary involvement			
Present	12	11	23
Absent	26	1	27

[a]All numbers expressed as mean±SD.
Ca, Carcinoma.

Table 2. Incidence of Sentinel Lymph Node (SLN) Detection according to the Surgeon's Experience

Period	% of SLN identification
Feb 1996-Jul 1997	72% (18/25)
Aug 1997-Feb 1998	92% (23/25)
Total	82% (41/50)

Table 3. Incidence of Sentinel Lymph Node (SLN) Detection according to Clinical Nodal Status

Clinical nodal status	% of SLN identification
N0, N1a	79% (30/38)
N1b, N2	92% (11/12)

Results

Tumor Histology and Axillary Lymph Node Metastases

Histologic types were identified as noninvasive ductal carcinoma in 3 patients, invasive ductal carcinoma in 45, and other types of invasive carcinoma in 2 (mucinous carcinoma in 1, and invasive lobular carcinoma in 1). The incidence of axillary metastases was 46% (23/50). When stratified by the clinical nodal status, 12 (32%) of 38 patients with clinically negative nodes had histologic evidence of axillary metastases, whereas 11 (92%) of the 12 patients with clinically positive nodes had histologically positive nodes (Table 1). The accuracy of physical examination for axillary metastases was 74%, with a sensitivity of 92% and a specificity of 68%.

Sentinel Lymph Node Identification

The SLN was identified in 41 (82%) of 50 patients by the dye-guided method. The number of SLNs removed ranged from 1 to 4 (mean, 1.5). Of the 41 patients in whom the SLN was identified, 36 (88%) had SLNs in level I, 3 (7%) had SLNs in level I and II, and 2 (5%) had SLNs in level II. The SLN was identified in 23 (92%) of the 25 most recent cases, and in 18 (72%) of the first 25 cases (Table 2). The difference was not statistically significant ($p=0.1383$). When stratified by the clinical axillary nodal status, the SLN was identified in 30 (79%) of 38 patients with clinically negative nodes, and in 11 (92%) of 12 cases with clinically positive nodes (Table 3). The incidence of SLN detection did not differ significantly based on clinical nodal status ($p=0.4251$). However, there was no stained lymph node in 2 (50%) of 4 patients with extensive axillary involvement. In one of them, a blue lymphatic entered directly into the hilum of a non-blue lymph node which was considered to be the SLN.

Postoperative Examinations of Sentinel Lymph Nodes

The SLNs on the permanent sections contain-

ed metastases in 18 (44%) of the 41 patients with identified SLNs. In 4 (22%) patients, the SLNs were the only metastatic nodes, whereas in the remaining 14 (78%) patients, other axillary nodes were positive. In 3 of 41 cases (7%), the SLN was falsely negative, ie no tumor was identified in the SLN, but at least one nonsentinel node harbored metastasis. Consequently, a diagnostic accuracy of 93%, a sensitivity of 86%, and a specificity of 100% were achieved in the diagnosis of axillary metastasis (Table 4). The predictive values of axillary lymph node metastasis achieved by H&E staining alone were not different from those achieved by H&E with IHC staining. In one patient in whom the SLN initially was interpreted as negative by H&E staining on the permanent sections, micrometastases were found by IHC staining; this finding was subsequently confirmed on one of the H&E stained permanent sections. When stratified by the clinical nodal status, the diagnostic accuracy of SLN evaluation was 90% in patients with clinically negative nodes and 100% in those with clinically positive nodes. This difference was not statistically significant ($p=0.5350$) (Table 5).

Intraoperative Examination of Sentinel Lymph Nodes

1) Frozen Sections

The reliability of SLN diagnosis by frozen section was examined in the 41 patients with identified SLNs. In 32 (78%) of these patients, the intraoperative diagnosis was confirmed by the final histologic examination. In 9 (22%) patients, however, the intraoperative diagnosis was falsely negative; they were positive on permanent sections from either the SLN or the nonsentinel nodes. Consequently, a diagnostic accuracy of 78%, a sensitivity of 57%, and a specificity of 100%

Table 4. Assessment of Axillary Lymph Node Metastasis by Sentinel Lymphadenectomy in Breast Cancer Patients

Method	Histologic nodal status		Prediction of presence of axillary lymph node metastases	
	Positive	Negative		
H&E & IHC staining on permanent sections			Accuracy	93%
Positive	18	0	Sensitivity	86%
Negative	3	20	Specificity	100%
H&E staining on frozen sections			Accuracy	78%
Positive	12	0	Sensitivity	57%
Negative	9	20	Specificity	100%
May-Giemsa & IHC staining on imprint cytology			Accuracy	82%
Positive	7	0	Sensitivity	70%
Negative	3	7	Specificity	100%

H&E, Hematoxylin and eosin staining; IHC, Immunohistochemistry.

Table 5. Assessment of Axillary Lymph Node Metastases by Sentinel Lymphadenectomy according to the Clinical Nodal Status

Clinical nodal ststus	SLN status[a]	Histologic nodal status		Prediction of presence of axillary lymph node metastases	
		Positive	Negative		
N0, N1a	Positive	8	0	Accuracy	90%
	Negative	3	19	Sensitivity	72%
				Specificity	100%
N1b, N2	Positive	10	0	Accuracy	100%
	Negative	0	1	Sensitivity	100%
				Specificity	100%

H&E, Hematoxylin and eosin staining; IHC, Immunohistochemistry; SLN, Sentinel lymph node.
[a]SLN status was determined by H&E and IHC staining on permanent sections.

were achieved with H&E staining of frozen sections (Table 4).

2) Imprint Cytology

Imprint cytology of the SLNs was performed in the 17 recent sequential patients. In 14 (82%) of these patients, the cytologic diagnosis was confirmed by the final histologic examination from either the SLN or the nonsentinel nodes. In one patient in whom the SLN was negative on frozen section, it was positive on imprint cytology, and subsequent permanent section confirmed this positivity. Consequently, a diagnostic accuracy of 82%, a sensitivity of 70%, and a specificity of 100% were achieved with May-Giemsa and IHC staining on imprint cytology (Table 4). The diagnostic accuracy of imprint cytology of SLNs was equivalent to that of frozen sections ($p=1.000$).

Complications

There were no complications such as allergic shock or asthma during surgery. There were also no postoperative complications from the injection of blue dye into the breast parenchyma or from the surgical excision of the SLNs. A few patients had a faint blue haze in the area of injection, which persisted for several days, and most patients noted green urine for 12 to 24 hours. However, all patients had been advised of these side effects and no patients reported either as bothersome.

Discussion

For sentinel lymphadenectomy to be useful, the surgeon must be able to identify the SLN accurately and easily. Giuliano *et al*[19] have reported that the SLN was identified in 114 of 174 cases (66%) by the dye-guided method, while the identification rate of this method was reported to be 93% in the hands of more experienced surgeons[20]. Similarly in the present study, the SLN was identified in 23 (92%) of the 25 most recent cases, and in 18 (72%) of the first 25 cases. Thus, the technique has a "learning curve." The use of blue dye has an important drawback, in that axillary tissue must be dissected blindly until the blue node is located. The blue dye travels rapidly through the lymphatics, and may not remain in the nodes long enough for surgical identification and excision[28]. The surgeon may find it difficult to identify a blue-stained node in a sea of tissue[28]. A more reliable method for the identification of SLNs is required before sentinel lymphadenectomy is accepted as useful for assessing axillary nodal status. The success rate achieved with a combination of dye- and gamma probe–guided techniques[21] is clearly superior to results previously reported using the dye-guided technique alone[19].

In prior studies, SLNs have been examined histologically by H&E staining and/or IHC staining on multiple permanent sections[21,22,30]. Giuliano *et al*[30] have reported that the use of serial sections and IHC staining of SLN specimens significantly increased the detection of axillary micrometastasis. In their study, an overall accuracy of 96%, a sensitivity of 88%, and a specificity of 100% were achieved with H&E and/or IHC staining of permanent sections[19]. However, Veronesi *et al*[22] have reported an accuracy of 98%, a sensitivity of 95%, and a specificity of 100% with H&E staining alone. In the present study, a diagnostic accuracy of 93%, a sensitivity of 86%, and a specificity of 100% were achieved with H&E and/or IHC staining of permanent sections. The addition of IHC staining did not significantly improve the prediction of axillary lymph node metastases.

Immediate and reliable intraoperative information on the SLN is vital to the technique's success, as the surgeon must decide whether or not to perform a total axillary dissection[20,22]. One current protocol includes the intraoperative staging of breast cancer using selective axillary dissection with intraoperative frozen-section analysis[31]. In a recent study, however, Veronesi *et al*[22] compared the intraoperative diagnosis of SLNs by frozen section with the final histologic results obtained via examination of permanent sections. In 89 of 107 cases (83%), the intraoperative diagnosis was confirmed by the final histologic examination. However, the intraoperative diagnosis was falsely negative in 18 of these cases (17%) because micrometastatic foci were later identified on permanent sections. Consequently, the overall accuracy was 83%, with a sensitivity of 64% and a specificity of 100%. Similarly in the present study, a diagnostic accuracy of 78%, a sensitivity of 56% and a specificity of 100% were achieved with frozen section. Thus, the accuracy of SLN diagnosis using frozen sections is questionable[22]. If sentinel lymphadenectomy can be done with local anesthesia on an outpatient basis[30], therefore, the SLN should be histologically examined on permanent sections. Nevertheless, it is important to de-

velop techniques to improve the intraoperative evaluation of SLNs. It has been reported that examination of cytologic imprints from lymph nodes is useful for intraoperatve assessment of axillary metastases in breast cancer[32,33]. Multiple cut surfaces can be examined quickly by imprint cytology. In the present study, however, the result of imprint cytology was equivalent to that of frozen section. Further study will be required since imprint cytology and frozen sections are complementary in the intraoperative diagnosis of metastasis to SLNs.

Clinical evaluation of axillary nodes consistently has been shown to be inaccurate[16]. From 22% to 33% of nodes thought to be diseased clinically (N1b, N2) have been found to be free of metastasis by histology. Conversely, from 22% to 45% of nodes that appeared disease-free on clinical examination (N0, N1a) have been found to be involved by tumor on histologic analysis. In the present study, the accuracy of physical examination for axillary metastases was 74%, with a sensitivity of 92% and a specificity of 68%. In several studies, however, sentinel lymphadenectomy has been investigated only in patients who are clinically node-negative[21,22,24]. Other studies have included a small number of patients with clinically positive nodes[19,23]. In clinically node-positive patients, it has been suggested that SLN staining diminishes as the proportion of tissue occupied by metastasis becomes greater. Gulec *et al*[34] suggested that effacement of regional nodes by gross tumor may adversely affect both the localization rate and predictive value of sentinel lymphadenectomy because of an altered pattern of lymph flow[35]. In the present study, however, the incidence of SLN detection and the predictive value of sentinel lymphadenectomy did not differ significantly according to clinical nodal status. Nevertheless, there were either no blue-stained lymph nodes, or only a blue lymphatic directly entering the hilum of a non-blue lymph node in some patients with extensive axillary involvement. In practice, moreover, sentinel lymphadenectomy is unnecessary for those patients. Therefore, sentinel lymphadenectomy is useful in both clinically node-negative and node-positive patients, when patients with extensive axillary metastases are excluded.

Current published experience with sentinel lymphadenectomy strongly suggests that this procedure may soon replace routine axillary dissection as the preferred staging operation for clinically node-negative breast cancer[22,25]. Before sentinel lymphadenectomy gains general acceptance for patients with primary breast cancer, however, further studies will be required to improve identification of the sentinel node and detection of metastasis in this node. We will continue to perform complete axillary dissection until sentinel lymphadenectomy has been mastered as a predictable, reproducible technique.

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