Nonvisualization of Axillary Sentinel Node During Lymphoscintigraphy: Is There a Pathologic Significance in Breast Cancer?

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The aim of this study was to define the factors associated with nonvisualization of a sentinel node (SN) in the axilla area during preoperative lymphoscintigraphy. **Methods:** We retrospectively studied 332 women with T0, T1, or T2 <3-cm, N0 invasive breast cancer who underwent a sentinel lymph node biopsy procedure. All patients had intradermal and intraparenchymal injection of 37 MBq ^{99m}Tc-sulfur colloid in a total volume of 4 × 0.1 mL, above and around the tumor. Anterior and lateral static views were obtained a few minutes and 2–4 h after injection. Surgery was performed the next day. The SNs were localized intraoperatively with the aid of patent blue dye and using a hand-held γ-probe. SNs were analyzed by serial sections stained with hematoxylin–eosin, with the adjacent section stained with anticytokeratin antibodies. Different parameters, such as the number of positive lymph nodes, presence of lymphovascular invasion, tumor size, tumor grade, histology (invasive vs. in situ), prior excisional biopsy, and patient age were analyzed to determine whether they had any significant correlation with nonvisualization of SNs in the axillary area. **Results:** An axillary SN was successfully visualized on the preoperative lymphoscintigraphy in 302 of 332 patients (90.7%). No axillary drainage was found in 30 patients on the delayed images, even after a second injection of radiocolloid, and 5 of 30 patients showed uptake outside the axillary area. Positive nodes were identified in 86 of 302 patients (28.5%) with successful axillary drainage and in 19 of 30 patients (63.3%) with unsuccessful axillary drainage. More than 4 invaded axillary nodes ($P < 0.0001$) and the presence of lymphovascular invasion in the breast tumor ($P = 0.004$) were the only significant variables on univariate analysis, although multivariate analysis showed that only the increased number of invaded nodes was statistically significant. **Conclusion:** Patients with unsuccessful axillary mapping have an increased risk for axillary involvement.

Key Words: sentinel lymph node; breast cancer; lymphoscintigraphy

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Axillary lymph nodes represent the main basin for lymphatic drainage from the breast, and the ipsilateral axillary lymph nodes are the most common site of metastasis in breast carcinoma. Direct drainage from the breast to the axilla seems to be the rule. After injection of ^{99m}Tc-labeled nanocolloid into the breast carcinoma, there is generally a lymphatic channel leading directly from the tumor to the axilla (*1–5*). The cells detach from the primary tumor and reach the first node, or sentinel node (SN), which receives the lymph from the involved breast area. The axillary SN can be identified, and its status remains one of the most important prognostic indicators. At our institute, sentinel lymph node biopsy is a routine procedure. Lymphoscintigraphy mapping is systematically performed before surgery. In this study, patients without uptake in the axillary area were analyzed: for either failure of lymphatic mapping or an indirect drainage into the subclavicular area without uptake in the axillary lymph nodes. Our objective was to retrospectively define the relationship between the nonvisualization of a SN in the axillary area during preoperative lymphoscintigraphy and the histologic status of nodes.

MATERIALS AND METHODS

Patient Population

From March 1999 to December 2001, 332 consecutive women with an invasive breast cancer or a high-grade ductal carcinoma in situ (T0–T2 <30 mm, N0) were included in this study. Preoperative diagnosis was obtained by physical examination, mammography, and ultrasonography, followed by needle aspiration cytology or excisional biopsy. Informed consent was obtained from all patients, and lymphoscintigraphy was routinely performed. Exclusion criteria were clinical evidence of axillary lymph node metastasis, multicentric tumor, and adjuvant systemic treatment before surgery. Patient age at diagnosis was stratified as <70 or >70 y old. The tumor location was classified as inner, central, or outer in the upper quadrant or in the lower quadrant of the breast. Among them, 262 women underwent breast-conserving surgery and 70 received a modified radical mastectomy; most of the women received radiation therapy. Women with axillary lymph node involvement underwent chemotherapy and those with negative nodes, but with one or more risk factors (age, <40 y old; tumor >15 mm, grade 3; vascular invasion; negative hormonal receptors), received chemotherapy. Patients with positive hormonal receptors received tamoxifen for 5 y.

Lymphoscintigraphy

Lymphoscintigraphy was performed the day before surgery. All patients received a combination of intradermal and intraparenchymal injection of 37 MBq (1 mCi) ^{99m}Tc-sulfur colloid (Nanocis; Schering) in a total volume of 0.4 mL physiologic saline, given in 4 equal doses. The injections were administered above and around the tumor or biopsy site at a distance of <1 cm and usually around 5 mm. The purity of the tracer was controlled by chromatography for all patients. After injection of the radiocolloid, the area was massaged gently for approximately 5 min to improve the lymphatic drainage. Early planar views were obtained over 10 min to identify dominant lymphatic channels and delayed images were acquired 2–4 h after tracer injection: Static images were obtained during a 5-min period using a single-head gamma camera (SP6 Elscint; General Electric) with a low-energy, high-resolution collimator. Anterior views included the involved breast, the 2 axilla, and the clavicular regions. Lateral views required elevation of the ipsilateral arm. A second injection of radiocolloid was administered if no lymphatic node was visualized 2 h after the first injection. A skin marker was placed on the projection of the SN and the location was confirmed using of a hand-held γ-probe (Neoprobe 2000; MDS Nordion). A schema was drawn from the number and the location of the SNs. The topography of axillary nodes was approximately estimated as the Berg's level, and subclavicular and internal mammary nodes were noted.

SN Biopsy

Intraoperatively, 2 mL patent blue dye (Bleu Patente Laboratoire Guerbet) were injected into the peritumoral or subareolar site <10 min before surgery. Breast surgery preceded the axillary dissection. The SN dissection was performed by combined intraoperative γ-probe detection and blue dye methods. All lymph nodes presenting either blue dye or radioactivity uptake (or both) were identified as SNs and removed. All SNs were sent individually for histologic evaluation with the information concerning blue dye uptake and radioactivity count.

Complete Axillary Dissection

Axillary lymph node dissection including levels 1 and 2 was performed in patients whose breast tumor measured >3 cm, whose SNs were positive for metastasis, and in the event of nonidentification of the SN in the axillary area. Patients with negative axillary sentinel lymph nodes did not undergo further axillary surgery. The number, site, and counting rates of all removed lymph nodes were recorded and were compared with the preoperative scintigraphy. Palpation of the open axilla was systematically performed to detect enlarged non-SNs. These were excised and underwent histologic examination separately. No patient underwent clavicular or internal mammary node dissection.

Histology

Intraoperative imprint cytology of the SN was performed in all cases. If the node was macroscopically abnormal or >5 mm, frozen sections could be prepared. Patients with positive SNs underwent axillary surgery immediately. In the other cases, the SN was analyzed by serial sectioning of the whole node after formalin fixation and paraffin embedding. Every section of 150 μm (approximately 6) was stained with hematoxylin–eosin, with the adjacent section stained with anticytokeratin antibodies (KL1; Immunotech France) for the detection of micrometastasis (<2 mm and >0.1 mm in diameter). Standard hematoxylin–eosin staining was used to study the non-SNs.

Statistical Analysis

For each patient, age, primary tumor size, type of tumor (invasive carcinoma or in situ), number of positive nodes, presence of vascular invasion in the primary tumor, grade of tumor, and prior excisional biopsy were recorded. Univariate analysis was performed by the χ^2 test and the Student t test or by the Fisher exact test. Variables for which $P < 0.05$ in a univariate analysis were included in a stepwise logistic regression multivariate analysis. Relative risks are presented with their 95% confidence interval (CI). Analysis was performed using SPSS version 10.0.5 software (SPSS, Inc.).

RESULTS

Clinical Results

The mean patient age was 59 y (range, 30–88 y); among the 332 patients, 69 were >70 y old (20.8%) and 263 were <70 y old (79.2%). Patient characteristics are listed in Table 1. Diagnosis of breast carcinoma was made by pre-

TABLE 1
Patient Characteristics

Characteristic	No. of patients	%
Laterality		
Right	171	51.5
Left	161	48.5
Initial presentation		
Palpable mass	85	25.6
Nonpalpable mass	247	74.4
Invasive tumor size (cm)		
<2	140	42.2
2–5	133	40.1
>5	31	9.3
Tumor location		
Upper outer quadrant	185	55.7
Lower outer quadrant	44	13.3
Upper inner quadrant	50	15
Lower inner quadrant	32	9.7
Central	21	6.3
Tumor histology		
pTis	28	8.4
Invasive ductal	225	67.8
Invasive lobular	39	11.8
Other invasive	40	12
Grade*		
I	116	36
II	125	38.8
III	81	25.2
Vascular invasion		
Yes	71	21.4
No	261	78.6

*10 values missing.
pTis = pathologic stage was tumor in situ.

TABLE 2
Comparison Between Success and Failure of Axillary Mapping According to Patients and Tumor Characteristics

Characteristic	Axillary drainage: Successful (n = 302)	Failure (n = 30)
Age (y)		
>70	59 (85.5)	10 (14.5)
<70	243 (92.4)	20 (7.6)
Prior excisional biopsy	38 (86.3)	6 (13.6)
Tumor histology		
pTis	26 (92.8)	2 (7.2)
Invasive ductal	202 (89.7)	23 (10.3)
Invasive lobular	36 (92.3)	3 (7.7)
Other invasive	38 (95)	2 (5)
Invasive tumor size (cm)		
<2	132 (94.2)	8 (5.8)
2–5	119 (89.4)	14 (10.6)
>5	25 (80.6)	6 (19.4)
Tumor location		
Upper outer quadrant	171 (92.4)	14 (7.6)
Lower outer quadrant	39 (88.6)	5 (11.4)
Upper inner quadrant	46 (92)	4 (8)
Lower inner quadrant	28 (87.5)	4 (12.5)
Central	18 (85.7)	3 (14.3)

Values in parentheses are percentage.

vious excisional biopsy 2 wk before the lymphoscintigraphy in 44 patients (13.3%); all others underwent needle aspiration cytology or percutaneous biopsy diagnosis. The pathologic stage was tumor in situ (pTis) = 28 (8.4%) and invasive cancer = 304 (91.6%). The mean invasive tumor diameter, measured by the pathologist, was 20 mm (range, 0–170 mm); in 229 patients the diameter was <30 mm (75.1%) and in 76 patients it was >30 mm (24.9%). Positive SNs were identified in 105 patients: 1 with pTis (invasive breast tumor not found by histology, even after mastectomy) and 104 with invasive breast cancer. SNs were the only positive nodes in 59 of 105 patients (56%). In 38 of 105 patients (36.2%), nodes were only invaded by micrometastasis. Axillary lymphadenectomy was performed in 132 cases (39.7%) because of 105 invaded nodes, 22 histologic invasive tumor size of >30 mm, and 30 lymphatic mapping failures, or combined reasons. Seventy-one women had lymphatic or vascular invasion of the breast tumor and 47 of 71 had at least 1 positive axillary node (66.2%).

Lymphoscintigraphy successfully identified at least 1 SN in the axillary bed in 302 of 332 patients (91%). Table 2 summarizes the successful axillary mapping according to patients and tumor characteristics. Typical lymphoscintigraphy showed foci accumulation in the axillary area in the first 30 min after injection. Occasionally, a lymphatic pathway could be seen leading directly from the injection site to the first axillary node. The number of nodes varied from 1 to 8, but, in 88% of cases, 1–3 axillary nodes were seen that corresponded to Berg's level 1 and were confirmed by surgery. Lymph nodes were visualized both in the axillary and in the clavicular regions in 10 patients (3.3%); lymphatic drainage to both the axilla and the mammary chain was seen in 29 patients (8.7%). In these 302 patients with successful axillary uptake, SNs were positive in 86 patients (28.5%) and negative in 216 patients (71.5%). Complete axillary lymphadenectomy was performed in 107 patients in this group with well-visualized axillary nodes.

No axillary drainage was found by lymphoscintigraphy in 30 patients (9%). Table 2 summarizes the failure of axillary mapping according to patients and tumor characteristics. In this group of complete lymphoscintigraphy failure, no uptake was seen either in the axilla or outside the axillary bed in 25 of 30 patients, even after a second injection of radiocolloid and massage after injection. The SN could not be identified with the γ-probe the next day during surgery. All of these patients had complete axillary lymph node dissection. Axillary nodes were positive in 14 of 25 and negative in 11 of 25 cases. We observed 4 of 30 patients who showed drainage directly to the subclavicular area with faint uptake in the mammary chain, but without axillary uptake; 1 of 30 patients showed axillary drainage in the contralateral axilla. All 5 women underwent ipsilateral axillary lymphadenectomy. Nodes were invaded in all of these cases (100%) of skipping to a higher level, and 4 patients had >4 positive nodes.

Statistical Results

An increased risk of unsuccessful axillary mapping was statistically associated with the number of positive axillary nodes; We observed 4.9% of unsuccessful lymphoscintigraphy in pN0 patients, 9.6% in patients with 1–3 positive nodes, and 50% if there were >4 invaded nodes ($P <$ 0.0001). These data are listed in Table 3. A similar conclusion was reached using the t test: The median number of invaded nodes was 0 with successful lymphoscintigraphy (SD = 2) but was 5 when lymphoscintigraphy failed (SD = 6) ($P < 0.0001$). An increased risk of unsuccessful mapping was also statistically associated with the presence of vascular invasion in the primary tumor. These data are listed in Table 4: There was 6.5% failure in the absence of vascular invasion but 18.3% with vascular invasion (P = 0.004). Table 5 summarizes the P value according to different

TABLE 3
Relationship Between Unsuccessful Axillary Mapping and Number of Invaded Axillary Nodes

Parameter	n = 0	n = 1–3	n > 4	Total	P
Success	216	75	11	302	
Failure	11 (4.9)	8 (9.6)	11 (50)	30	<0.0001
Total	227	83	22	332	

Values in parentheses are percentage.

parameters: Previous excisional surgery ($P = 0.26$), histology of the primary tumor, pTis versus invasive tumor ($P = 0.99$), tumor grade I versus grade II versus grade III ($P = 0.51$), and tumor location were not statistically associated with unsuccessful mapping. Two variables showed a statistical trend with lymphoscintigraphy failure: age <70 y old versus >70 y old ($P = 0.096$, Fisher exact test) and tumor size <20 mm versus >20 mm ($P = 0.059$, *t* test).

Vascular or lymphatic invasion and involved nodes were studied in logistic regression multivariate analysis. Only >4 invaded nodes were statistically associated with unsuccessful mapping, with relative risks of failure = 15.3 and 95% CI = 5.9–39.8. The presence of lymphatic vascular invasion was not an independent predictor of unsuccessful axillary mapping.

TABLE 5
Statistical Analysis in Unsuccessful Lymphatic Mapping According to Different Parameters Analyzed

Parameter	*P* (χ^2 test)	*P* (*t* test)	*P* (Fisher exact test)
Invaded nodes >4	<0.0001	<0.0001	
Vascular invasion			0.004
Age >70 y		0.41 (NS)	0.096
Tumor size < 20 mm		0.059	0.13 (NS)
Tumor grading	0.51 (NS)		
Prior excisional biopsy			0.26 (NS)
Tumor type (in situ, invasive)			0.99 (NS)

NS = no significance.

DISCUSSION

The SN concept is based on the orderly progression of tumor cells within the lymphatic system (*6*). Lymphatic mapping allows us to determine the number of lymph nodes that are on a direct drainage pathway and to locate the SNs. The tracers used are colloidal particles labeled with ^{99m}Tc, which accumulated in lymph nodes by active phagocytosis macrophages, independently from the presence or absence of metastatic involvement. The dermal and the parenchymal lymphatics of the breast drain to the same axillary nodes in most patients with a high level of concordance (*7–9*). However, subdermal injection may underestimate the visualization of lymph nodes outside the axilla, and the inner mammary chain was only seen after peritumoral injection (*9–13*). We preferred to use both techniques of injection, subdermally surrounding the tumor site and intraparenchymally around the tumor. Intraparenchymal injection seems to be the best choice to obtain secondary drainage of the breast and intradermal injection may improve axillary mapping (*7*). The addition of massage after injection significantly improves the uptake of tracer by the SNs, further increasing the sensitivity of the procedure (*14*). Many studies show that a radioactive node is generally visualized in 82%–98% of patients (*2,10,11,15–19*).

Lymphoscintigraphy also identifies the failed radiopharmaceutical migration. In some cases, nodes do not accumulate the tracer and remain undetected by imaging and even by further use of the γ-probe. In this study, there was no significant difference between patients with axillary positive SNs (82%) compared with negative SNs (95%), when the lymphatic mapping was successful. In fact, if the number of axillary invaded nodes was <3, we observed that 90.4% of the node-positive group achieved successful mapping. However, a 50% risk of lymphoscintigraphy failure was seen if the number of invaded nodes was >4; in this case, our data indicate that there was a statistically significant difference in the number of positive SNs (<4 vs. >4) between visualized and nonvisualized axillary nodes ($P < 0.0001$). As the involved nodes in the axilla increase, the success rate of SN mapping decreases. Lymphatics become progressively infiltrated with tumor cells and do not allow the passage of radionuclides (*20–25*). Cancerous involvement of the lymphatic system may influence the drainage pattern: Completely invaded nodes may lead to unsuccessful axillary node detection due to a lack of ability of tracer uptake in the leading node. Heuser et al. reported 5 cases in which no axillary SN could be detected and consecutive axillary surgery revealed a positive nodal status in 4 of these patients with unsuccessful mapping (*25*). Tanis et al. found similar results: A patient with a tumor-positive lymph node has an increased risk of nonvisualized lymph node (*15*). A multicenter trial of SNs in breast cancer reported a low identification rate of biopsy in patients with ≥5 involved axillary nodes (*5*). Our results indicate that the most suitable indication of lymphoscintigraphy is obtained in patients with <4 positive axillary nodes. In patients with nonvisualized SNs, palpation of the open axilla to detect enlarged non-SNs seems to be judicious (*26,27*).

Borgstein et al. reported significant correlation between mapping success and invasive tumor size of <5 cm (*10*), but other investigators found no correlation (*11,26,28*). In contrast, we found some relationship between unsuccessful axillary mapping and tumor size when >20 mm ($P = 0.059$, *t* test). The incidence of nodal involvement in carcinoma in situ is approximately 0%–1%. For invasive carcinoma, lymph node involvement increases for each size T category: from 3% to 17% for stage T1a and from 29% to 64% for

TABLE 4
Relationship Between Failure of Axillary Mapping and Vascular Invasion in Breast Tumor

Parameter	Vascular invasion: No	Vascular invasion: Yes	Total	*P*
Success	244	58	302	
Failure	17 (6.5)	13 (18.3)	30	0.004
Total	261	71	332	

Values in parentheses are percentage.

stage T3 (*27,29,30*). This could explain the connection between mapping failure, the number of involved axillary nodes, and the tumor size. Patients with small invasive tumors of <3 cm can benefit from lymphoscintigraphy because the probability of positive axillary lymph nodes is low and the risk of axillary mapping failure remains weak. In these cases, SN biopsy is a minimally invasive method for staging the axilla, avoiding an extensive and morbid surgical intervention. For patients with ductal carcinoma in situ (pT0), controversy exists regarding the role of SN biopsy (*31*). In our study, we reported 1 case of breast carcinoma in situ, with micrometastasis in the SN; no invasive cancer was found even after mastectomy. This example can be used as an argument to perform SN biopsy in the current treatment of carcinoma in situ.

Our data revealed 5 cases of nonaxillary drainage: 4 to the subclavicular area and internal mammary chain and 1 to the contralateral axillary basin. Each of these cases showed involved nodes in the ipsilateral axillary nodes. We found similar results in other studies: Haigh et al. (*32*) reported 3 cases in which dominant internal or clavicular drainage and metastasis were present in the axillary nodes; likewise, Uren et al. (*3*) described 1 case with only internal mammary and subclavian nodes uptake, which had axillary nodal metastasis. Lymphatic drainage appears predominantly to the lower axilla in 73%–93% of cases, sometimes both to the axillary and the internal mammary and to the clavicular regions (*3,17,26,33*). There are normal variations in lymphatic anatomy and flow patterns. However, it seems that drainage exclusively outside the axillary area with obvious skipping to higher levels, directly to infraclavicular nodes, means high risk of metastasis in axillary lymph nodes. Axillary lymph node involvement influences the drainage pattern to minor lymphatic pathways, and drainage exclusively to these areas increases with the number of positive axillary lymph nodes (*10*). The location of the primary neoplasm did not influence the site of the SN. In this study, 3 breast cancers were situated in the outer quadrant and 2 were in the inner quadrant. Uren et al. reported that 72% of inner-quadrant lesions show drainage to the axilla, and 40% of outer-quadrant lesions show drainage to internal mammary nodes, so 49% of lesions drain across the centerline of the breast; generally, lymph drainage includes the axilla in 93% of all lesions (*3*). We observed that patients with extraaxillary hot spots revealed on lymphoscintigraphy, without obvious uptake in the axilla, seemed to have a higher risk of positive axillary status.

Vascular invasion is another factor that influences the number of positive axillary lymph nodes. Different studies (*18,34–36*) found a relationship between lymphatic invasion in the primary tumor and spread of the disease beyond the SN. For Veronesi et al., it was the most important factor (*18*). The estimated probability of invaded axillary nodes varied from 12% to 36.8% according to the histologic size and from 23.9% to 47.8% according to the absence or presence of vascular invasion (*30*). Similar results are found by different authors who have demonstrated that nodal involvement is significantly related to a histologic size of >2 cm (pT2 and above) and to vascular or lymphatic invasion (*33–36*). In a univariate analysis, our data show a statistical association between unsuccessful mapping and the presence of vascular invasion in the primary tumor ($P = 0.004$) with 6.5% unsuccessful axillary mapping in the absence of vascular invasion and 18.6% in the presence. We found that 66.2% of cases with positive nodes have vascular invasion in the primary tumor. The relationship between vascular invasion and unsuccessful axillary mapping was certainly explained by the increased risk of invaded nodes in the presence of vascular invasion. For Gajdos et al., vascular invasion might be considered as the precursor of nodal involvement and probably all patients with nodal involvement could be assumed to have vascular invasion in the primary tumor, whether or not detected by the pathologist (*36*). Weiser et al. demonstrated that the presence of vascular invasion is highly correlated with the size of the primary tumor (*34*). In this study, patients with small breast cancer of <1 cm (T1a/b), absence of vascular invasion, and micrometastatic disease in the SN have a low risk of non-SN metastasis and may not require complete axillary dissection (*27,30,34*).

The other variables evaluated, such as patient age (<70 y or older), grade, type of primary tumor (invasive vs. in situ), and previous excisional biopsy, show no relation to unsuccessful lymphoscintigraphy. Successful mapping in women who had undergone prior excisional biopsy is similar to that reported by other investigators (*26*); patients who had prior surgical biopsy can benefit from this technique.

Some authors (*37*) have claimed that lymphoscintigraphy in addition to intraoperative γ-probe detection is unnecessary; our data show clearly that cancerous involvement influences the physiology of breast drainage. Lymphoscintigraphy before surgery provides important information for the surgeon who is thus aware of the number and the site of radioactive nodes. Knowledge of the lymphatic mapping may be a useful tool in planning surgery.

CONCLUSION

We observed that 2 factors showed a statistical association with unsuccessful axillary mapping: the high number of positive axillary lymph nodes and the presence of vascular and lymphatic invasion in the breast tumor. Patients with unsuccessful mapping or with skipping foci to higher levels have an increased risk of axillary involvement.

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