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Lymphatic Mapping and Sentinel Node Biopsy of Operable Breast Cancer

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Abstract. The aim of this study was to evaluate the reliability and accuracy of sentinel node biopsy for invasive breast cancer and the predictability of axillary node status. Between January 1996 and June 1997 a total of 73 patients underwent patent blue dye lymphatic mapping and sentinel node biopsy followed by standard (level I and II) axillary node dissection (one bilateral procedure). The sentinel node was identified in 82.4% (61/74) of the cases and was predictive of axillary status in 96.7% (59/61). The false-negative rate of the procedure was 8.0% (2/25). The sentinel node was involved in 37.7% (23/61) and was the only one invaded in 30.4% (7/23). The sensitivity of the procedure was 92% ($CI_{95\%}$ 74–99%) and its specificity 100%. It is currently considered to be an attractive new procedure undergoing evaluation in prospective controlled trials. This study confirmed the reliability and reproducibility of intraoperative lymphatic mapping and sentinel node biopsy. This is the first step toward a new era of minimally invasive axillary surgery for breast cancer.

The development of breast-sparing procedures has led to a decrease in morphologic mammary sequelae. The same evolution should be expected in the prevention of functional axillary complications with the surgical concept of sentinel node biopsy [1].

Sentinel node biopsy was first described in 1977 by Cabanas [2] in patients with penile cancer and then investigated extensively in 1992 by Morton et al. [3, 4] in malignant cutaneous melanoma. The goal of the procedure is to identify the first lymph node draining the primary tumor that might be involved. At a time when some authors [5–13] have proposed sparing axillary clearance of small tumors [14], this technique offers the pathologist a selected nodal specimen for more accurate analysis [15] using serial sections and immunohistochemical or molecular biology techniques [reverse transcriptase-polymerase chain reaction (RT-PCR)]. Carried out in two French cancer institutions, the purpose of the present study was to assess (1) the reliability and the reproducibility of sentinel node biopsy for invasive, operable breast carcinomas, and (2) the predictive value of sentinel nodes for pathologic axillary status.

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Patients and Methods

Patients

Between January 1996 and June 1997 a total of 73 patients with invasive, operable (cT0, cT1, cT2 $<$ 3 cm) breast carcinoma (one synchronous bilateral cT0N0 and cT1N1), referred to the French Comprehensive Cancer Centers of Strasbourg (n = 41) and Lyon (n = 32) underwent intraoperative lymphatic mapping with patent blue dye (Guerbet, Aulnay-sous-Bois, France) and sentinel node biopsy followed by standard axillary (level I and II) clearance.

Exclusion criteria were pregnancy, large tumors (cT2 $>$ 3 cm, cT3, and cT4), multicentric tumors, and metastatic disease. Allergic patients were excluded as well to avoid any patent blue-induced anaphylactic reactions. Patients with previous breast tumor excision or axillary surgery, or who were treated by neoadjuvant chemotherapy or radiotherapy were also excluded from the study because of the potential modification or transection of the breast lymphatic vessels.

The mean age of patients was 59.5 years (range 39–80 years); 55 patients (74.3%) were postmenopausal. Tumor stage and clinical nodal status are outlined in Table 1. The breast tumor was clinically palpable in 61 patients (82.4%), and 70 patients (94.6%) were free of clinical axillary involvement. The primary tumor was situated in the outer quadrant in 44 cases (49.4%) and in the inner quadrant in 17 cases (23.0%). Altogether, 13 primary breast tumors had a center-line or retroareolar location. The average clinical tumor diameter was 1.45 cm (range 0–3 cm). Tumor malignancy had been documented preoperatively in all cases by fine-needle or core biopsy including those carried out for nonpalpable lesions. Histologic tumor size, hormone steroid receptors, and tumor grade are listed in Table 1.

Methods

As previously described [16–19], all patients underwent an intradermal 2 ml patent blue dye injection (Guerbet) in four peritumoral 0.5 ml aliquots at the palpable (cT1, cT2 $<$ 3 cm) tumors or the previously located (cT0) tumor site immediately before surgery. Nonpalpable lesions (cT0) were always localized preopera-

Table 1. Patient and tumor characteristics.

Parameters	No.	%
cT0	13/74	17.6
cT1	47/74	63.5
cT2 < 3 cm	14/74	18.9
cN0	70/74	94.6
pT1a	5/74	6.7
pT1b	13/74	17.5
pT1c	34/74	45.9
pT2	22/74	29.7
pN^-	47/74	63.5
SBR 1	37/74	50
SBR 2	27/74	36.5
SBR 3	8/74	10.8
ER^+	56/71	78.9
PR^+	54/71	76.0

cT: clinical tumor stage; pT: histopathologic tumor stage; cN0: no clinical axillary palpable node; cN1: clinical axillary palpable node; pN^-: no histologic node invasion; SBR: Scarff Bloom Richardson histopathologic grade; ER: estrogen steroid receptors; PR: progesterone steroid receptors.

tively by needle puncture with intramammary wire setting or by skin reference marks. Gentle circular motions of the breast were performed to improve vital blue dye axillary diffusion. A minimal 10 minute rest period was observed before starting tumor excision. For all patients, the sequence of the surgical procedure was tumor excision (conservative or radical) followed by the sentinel lymph node procedure, with completion of standard axillary (levels I and II) clearance (en bloc for modified radical mastectomy). In patients treated by the breast-sparing procedure, a separate transverse axillary incision was performed just below the hair-bearing area. Care was always taken to follow the stained lymphatic tracts until identification of the blue-stained sentinel lymph node.

Harvested sentinel and nonsentinel nodes were submitted separately to the pathologist. Frozen sections of the sentinel node were not used routinely. Each sentinel lymph node was grossly cut into sections of 2 to 3 mm thickness and embedded in paraffin. Both sentinel and nonsentinel nodes were stained with hematoxylin-eosin. Multiple microscopic step sections were used in sentinel nodes free of metastasis.

Data Analysis

The main parameter of interest is the sensitivity of the method. The sensitivity was calculated as the number of cases in which the sentinel nodes were positive, divided by the total number of cases with axillary node involvement. The false-negative rate, equal to 1 − sensitivity, was the proportion of cases with negative sentinel nodes among all cases with axillary node involvement. The 95% confidence intervals ($CI_{95\%}$) were computed according to the binomial law.

Results

All patients of this study were operated on by four senior surgeons (J.F.R. and J.C.J. in the Strasbourg Cancer Center, H.M. and A.B. in the Lyon Cancer Center). Altogether, 60 patients (81.1%) underwent breast conservation surgery, and 14 patients were treated by modified radical mastectomy. Invasive ductal (83.8%) and lobular (10.8%) carcinomas predominated. No allergic patent blue dye-induced reactions were observed in this series. The blue-stained axillary sentinel node was identified in 82.4% (61/74) of the axillary nodal basins mapped. The average number of sentinel nodes mapped was 1.41 (range 1–5). In 53 patients (87.1%) the sentinel nodes were situated at Berg level 1, in 7 patients (11.3%) at level 2, and in only 1 patient (1.6%) at level III. The mean number of nonsentinel nodes removed was 13.8 (range 4–28).

Table 2. Results of sentinel node biopsy.

Parameter	Identification rate (%)	No.
cT0	76.9	10/13
cT1	83.0	39/47
cT2	85.7	12/14
cN0	82.8	58/70
cN1	100	4/4
pN^-	78.7	37/47
pN^+	88.8	24/27
Outer quadrant tumor location	85.4	41/48
Center-line or retroareolar tumor location	84.6	11/13
Inner quadrant tumor location	69.2	9/13

Results of the sentinel node procedure according to clinical tumor stage, clinical and histopathologic axillary nodal status, and primary tumor location are given in Table 2. The sentinel node was predictive of axillary node status in 59 of 61 cases (96.7%). The sentinel node was falsely negative in two cases, and the false-negative rate for the procedure was 8% (2/25). Characteristics of these false-negative cases are outlined in Table 3. Histologic sentinel node spread was identified in 37.7% (23/61) of the patients. The blue-stained sentinel node alone was involved in 30.4% (7/23) of the patients. These premenopausal patients were treated by adjuvant chemotherapy. Lymph node metastasis were detected by routine hematoxylin-eosin staining and by multiple serial sections in three patients. The overall sensitivity of intraoperative lymphatic mapping and sentinel node biopsy was 92% ($CI_{95\%}$ 74–99%) and its specificity 100%. Applied to 36 cases, frozen sections were falsely negative in 5 cases (13.6%). The sensitivity of the sentinel node frozen section procedure was 86% ($CI_{95\%}$ 71–95%). The results from both cancer institutions are given in Table 4. The main characteristics of the patients with an unsuccessful sentinel node procedure are presented in Table 5.

Discussion

Because of the low accuracy of clinical examination and the high prognostic value of the axillary node status, axillary lymph node dissection has remained the standard for invasive breast cancer for a long time. Moreover, significant, even underestimated, postoperative morbidity has been reported [20]. Sentinel lymphadenectomy has recently been advocated [21–27] as a highly sensitive technique for identifying axillary metastasis, especially with small tumors associated with low rates of nodal spread [7, 8, 10, 13]. Using vital blue dyes, mainly isosulfan blue and patent blue V, sentinel node localizing rates ranged from 65.6% to 93.5% in the literature [1, 27, 28].

Giuliano et al. first emphasized the need for meticulous technique and adequate training with a significant technical learning curve [1, 14, 23–26]. At the beginning of the development of the technique in 1991, they encountered several critical technical

Table 3. Pathologic characteristics of falsely negative cases.

Patient	Histopathologic tumor status	SBR grade	No. of SLNs identified and pathologically negative	Histopathologic status of non-SLNs
1	pT1b	1	1	$1N^+/17$
2	pT1c	1	1	$2N^+/9$

SLNs: sentinel lymph nodes.

Table 4. Results from both institutions.

Parameter	Strasbourg Cancer Center	Lyon Cancer Center
Procedures (*n*)	42	32
SLN identification rate	85.7	78.1
Sensitivity	92	92
SLN and non-SLN in agreement	98	97
Falsely negative SLN	8	8

Unless indicated otherwise, numbers are percents.

Table 5. Characteristics of patients with a negative sentinel node procedure.

No. of patients	13
Median age (years)	58
Postmenopausal rate (%)	69.2
Clinical tumor stage (no. of cases)	
cT0	3
cT1	8
cT2	2
Tumor location (no. of cases)	
Outer quadrants	9
Inner quadrants	4
Pathologic tumor stage (no. of cases)	
pT1a	1
pT1b	3
pT1c	6
pT2	3
Histopathologic grade (no. of cases)	
SBR1	3
SBR2	8
SBR3	2
Histopathologic axillary involvement rate	23.07% (3/13)
Median no. of axillary nodes harvested	13.8

problems, such as the correct site and volume of the injection and difficulty identifying the lymphatics. In their initial report [1], the sentinel axillary lymph node identification rate increased from 58.6% to 78.0% (average 65.6%). Concurrently, the false-negative rates decreased from 5.7% to 0% (average 2.8%). More recently, in a study of 107 cases, Giuliano et al. reported sentinel node identification and false-negative rates of 93.5% and 0%, respectively [27].

In the present study, the sentinel node was identified in 82.4% (61/74) and, respectively, in 76.9%, 83.0%, and 85.7% of cT0, cT1, and cT2 lesions. Concerning our learning curve, the sentinel node was identified in 78.4% (29/37) and 86.5% (32/37) of the patients belonging to the first and second parts of the study, respectively. False-negative cases (3.28%) were observed twice [pT1b by the Scarff Bloom Richardson index (SBRI), pT1c SBRI] and occurred during the first half of the study. The main causes of failure of the sentinel node biopsy with intraoperative lymphatic mapping were identified [1, 3, 4, 17, 21–27] as inadequate amount of blue dye injection (3–5 ml for isusulfan blue depending on the tumor quadrant location, 2 ml for patent blue V), inappropriate timing for starting breast tumor excision or axillary clearance, and atypical lymph drainage (internal mammary, supra- or infraclavicular).

Modalities of blue dye injection vary in the literature: peritumorally below the subcutaneous fat by Giuliano et al. [1, 26, 27], intratumorally by Nieweg et al. [28], and intradermally in our study. In a 33-case pilot study, Borgstein et al. [29] recently demonstrated that the lymphatics of the overlying skin drain to the same axillary sentinel node as the underlying glandular breast tissue. Using this new approach, the technique for localizing the sentinel node is simplified, although some locally persistent blue staining of the skin ("skin tattoos") has been reported [16–18]. In our series of 73 operable tumors, the axillary sentinel lymph node was involved in 37.7% (23/61) and was the only one invaded in 30.4% (7/23). The values reported by Giuliano et al. in their last report [27] were, respectively, 42% and 67%.

As in several previous studies [1, 26–28], sentinel node biopsy was followed here by routine axillary clearance, allowing assessment of nodal status predictability of the axilla. This parameter is approximately 95% in all studies using blue dye only, although it was 100% for the Giuliano et al. [27] series of 107 patients operated on by a single, skilled breast surgeon. To increase detection of the sentinel node, Albertini et al. [21] advocated combining blue dye and radioisotopes, suggesting that these procedures were complementary. In a preliminary report on 62 invasive breast carcinomas, the authors [21] observed 93.5% sentinel node detection with blue dye and radioisotopes versus 73.0% with blue dye only.

In addition, O'Hea et al. [30] identified the sentinel node by lymphoscintigraphy in 75% (42/56), by blue dye in 75% (44/59), by radioisotope in 88% (52/59), and by a combination of blue dye and isotopes in 93% (55/59). In French comprehensive cancer centers, an ongoing prospective multicentric trial is evaluating the results of combined detection procedures. Recent reports from Krag's group [31, 32], Veronesi et al. [33, 34], Borgstein et al. [35], and Roumen et al. [36] have focused on lymphoscintigraphy and gamma-probe detection mainly in T1N0 breast tumors. If the results of these studies look promising, the advantages of radioguided localization with a hand-held gamma probe are numerous [37–42]. The gamma probe precisely and rapidly locates the sentinel lymph node, allows selective axillary incision, and guides the surgical dissection; it detects any additional or atypical (internal mammary, supraclavicular, or contralateral) sentinel node. Finally, radiolabeling avoids residual blue dye-induced skin tattoos on the patient's breast [30, 35, 36] after conservative surgery, and the learning curve is usually reported to be less problematic.

The main challenge of the sentinel node procedure is to in-

crease the accuracy of the pathologic staging when sending a limited nodal specimen for examination by conventional techniques (H-E staining) as well as by costly, time-consuming special investigations (serial sectioning, immunohistochemical staining, molecular biology techniques such as RT-PCR) [18, 19, 31]. In 1997 Turner et al. [15] reported the use of cytokeratin immunohistochemical staining of sentinel and nonsentinel lymph nodes in a series of 103 cases. Of the 70 patients found to be tumor-free by H-E staining, 10 (14.3%) were sentinel node-positive, and the immunohistochemically stained lymph node conversion rate from sentinel node-negative to sentinel node-positive was 6.4%. For these authors [15], the probability of nonsentinel node involvement is less than 0.1% if the sentinel node is tumor-free, seen by both H-E and immunohistochemical staining.

Nevertheless, the reliability and accuracy of frozen-section examination appear to be limiting factors for proposing a one-time operation to a patient. Veronesi et al. [34] and Galimberti et al. [43] focused on, respectively, concordance of sentinel node intraoperative results and the final histologic examination in 83.2% and 87.2% of cases. These results agree with our rate of 86% and with the 13.6% (5/36) falsely negative rate from sentinel node frozen sections.

To improve the reliability of the intraoperative diagnosis, especially of micrometastatic foci, a technique for rapid immunostaining with a cytokeratin marker was reported by Chilosi et al. [44]. More recently, Rubio et al. [45] pointed out an interest in touch preparations (imprint cytology) on the sentinel node with a sensitivity of 95.7%. In ongoing selective sentinel node procedures, which are currently not followed by standard axillary clearance, the patient should be fully informed of the problem of intraoperative false-negative results, which could require further lymphadenectomy [34, 43]. Furthermore, as recently indicated by Veronesi et al. [34] and Galimberti et al. [43], the current low risk of false negatives may be reduced by excluding multicentric and multifocal lesions.

It is currently impossible to assert that sentinel node biopsy is a new, outstanding advance that avoids routine axillary dissection in pathologically negative sentinel node patients because data (axillary recurrences, 5-year disease-free and overall survival) from randomized trials on the safety of the procedure are not yet available [46]. However, Haddad et al. [47] recently outlined some guidelines and pointed out a persistent need for routine axillary lymphadenectomy. In fact, standard procedure should be considered not only for multifocal or large tumors and palpable axillary node metastasis but also for failures or contraindications to lymphatic mapping. The accuracy of sentinel node biopsy in patients treated by a previous axillary or breast operation (excision or plastic surgery) remains under clinical evaluation but does not constitute, according to Borgstein et al. [35], an exclusion criterion for the procedure.

The final goal is, especially for small tumors, to avoid standard axillary lymph node dissection in those women free of sentinel node metastasis, decreasing the cost and morbidity of the procedure, reducing the duration of hospital stay, and improving the detection rate of micrometastases using special histologic techniques on harvested axillary sentinel nodes.

As recently stressed by McMasters et al. [48] and Lopchinsky and Tartter [49], it is mandatory to determine the real false-negative rate for the procedure (ratio of the number of patients with a negative sentinel node biopsy but positive nonsentinel nodes and the number of patients with axillary lymph node metastases) and the specific characteristics of these patients. Until standardization of the surgical, nuclear medicine, and pathologic aspects of sentinel node biopsy in breast cancer can be achieved [46], this new diagnostic test cannot be accepted as the worldwide standard of care [48, 50].

Conclusions

Lymphatic mapping appears to be relatively simple in concept but remains technically challenging in practice. Standardization of the surgical and radiopharmaceutical methods to identify the sentinel node in patients with breast cancer are currently of critical importance. The future of this attractive concept is also strictly dependent on the quality of training and teaching and a reliable evaluation. Nothing could prejudice this exciting technique more than poor reasoning and hasty generalizations.

Résumé

Le but de cette étude a été d'évaluer la fiabilité et la précision de la biopsie ganglionnaire sentinelle dans le cancer invasif du sein et de déterminer sa valeur prédictive de l'envahissement des ganglions axillaires. Entre janvier 1996 et juin 1997, 73 patients ont eu une cartographie lymphatique par injection de bleu Patent et une biopsie ganglionnaire, suivies d'une lymphadénectomie axillaire standard (niveaux I et II) (une patiente a eu une intervention bilatérale). Le ganglion sentinelle a été identifié dans 82,4% (61/74) des cas et il était prédictif de l'état des lymphatiques de l'aisselle dans 96,7% (59/61) des cas. Le taux de faux négatifs du procédé a été de 8,0% (2/25). Le ganglion sentinelle était envahi dans 37,7% (23/61) et a été le seul ganglion envahi chez 30,4% (7/23). La sensibilité du procédé a été de 92% (CI 95%: 74%–99%) et sa spécificité, de 100%. Cette étude confirme la fiabilité et la reproductibilité de la cartographie lymphatique per-opératoire et de la biopsie lymphatique sentinelle, considérées dès à présent une méthode diagnostique intéressante, en cours d'évaluation par des études contrôlées prospectives. Cette méthode est le premier pas vers une nouvelle ère de chirurgie mini-invasive dans le cancer du sein.

Resumen

El propósito del presente estudio fue evaluar la confiabilidad y la certeza de la biopsia del ganglio centinela en pacientes con cáncer mamario invasor, así como la capacidad para predecir el estado ganglionar de la axila. Durante el periodo entre enero de 1996 y junio de 1997 se practicó mapeo linfático con el colorante Patent Blue seguido de biopsia del ganglio centinela y de disección ganglionar estándar de los niveles I y II (un procedimiento fue bilateral) en 73 pacientes. El ganglio centinela fue identificado en 82.4% (61/74) de los casos y predijo en forma correcta el estado axilar en 96.7% (59/61) de ellos. La tasa de negativo falso fue 8.0% (2/25). El ganglio centinela apareció afectado en 37.7% (23/61) y fue el único ganglio positivo en 30.4% (7/23). La sensibilidad del procedimiento fue 92% (CI 95% = [74%–99%]) y la especificidad 100%. Considerado como un procedimiento novedoso y atractivo que está siendo sometido a estudios prospectivos controlados, nuestro estudio confirma la confiabilidad y la factibilidad de realizar el mapeo linfático

intraoperatorio con la biopsia del ganglio centinela. Esto representa el primer paso hacia una neuva era de cirugá mínimamente invasora de la axila en pacientes con cáncer de seno.

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References

1. Giuliano, A.E., Kirgan, D.M., Guenther, M., Morton, D.L.: Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann. Surg. *220*:391, 1994
2. Cabanas, R.M.: An approach for the treatment of penile carcinoma. Cancer *39*:456, 1977
3. Morton, D.L., Wen, D.R., Cochran, A.J.: Management of early stage melanoma by intraoperative lymphatic mapping and selective lymphadenectomy. Surg. Oncol. Clin. North Am. *1*:247, 1992
4. Morton, D.L., Wen, D.R., Wong, J.H., Economou, J.S., Cagle, L.A., Storm, F.K., Foshag, L.J., Cochran, A.J.: Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch. Surg. *127*:392, 1992
5. Cady, B.: Use of primary breast carcinoma characteristics to predict lymph node metastases. Cancer *79*:1856, 1997
6. Silverstein, M.J., Barth, A.: Use of primary carcinoma characteristics to predict lymph node metastases: reply. Cancer *79*:1862, 1997
7. Barth, A., Craig, P.H., Silverstein, M.J.: Predictors of axillary lymph node metastases in patients with T1 breast carcinoma. Cancer *79*: 1918, 1997
8. Copeland, E.M.: Is axillary dissection necessary for T1 carcinoma of the breast? J. Am. Coll. Surg. *184*:397, 1997
9. Haffty, B.G., Ward, B., Pathare, P., Salem, R., Mc Khann, C., Beinfeld, M., Fischer, D., Reiss, M.: Reappraisal of the role of axillary lymph node dissection in the conservative treatment of breast cancer. J. Clin. Oncol. *15*:691, 1997
10. Pandelidis, S.M., Peters, K.L., Walusimbi, M.S., Casady, R.L., Laux, S.V., Cavanaugh, S.H., Bauer, T.L.: The role of axillary dissection in mammographically detected carcinoma. J. Am. Coll. Surg. *184*:341, 1997
11. Chontos, A.J., Maher, D.P., Ratzer, E.R., Fenoglio, M.E.: Axillary lymph node dissection: is it required in T1a breast cancer. J. Am. Coll. Surg. *184*:493, 1997
12. Theodossiou, C., Schwarzenberger, P., Espinoza-Delgado, I., Wynn, R.B., Schapira, D.V.: Early stage breast cancer: an approach to treatment. Oncol. Rep. *4*:1305, 1997
13. Bland, K.I.: Enhancing the accuracy for predictors of axillary nodal metastasis in T1 carcinoma of the breast: role of selective biopsy with lymphatic mapping. J. Am. Coll. Surg. *183*:262, 1996
14. Giuliano, A.E., Barth, A., Spivack, B., Beitsch, P.D., Evans, S.W.: Incidence and predictors of axillary metastasis in T1 carcinoma of the breast. J. Am. Coll. Surg. *183*:185, 1996
15. Turner, R.R., Ollila, D.W., Krasne, D.L., Giuliano, A.E.: Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma. Ann. Surg. *226*:271, 1997
16. Rodier, J.F., Janser, J.C., Barlier-Pagel, C., Ghnassia, J.P., Velten, M.: Sentinel axillary lymphadenectomy with intraoperative lymphatic mapping in breast cancer. Adv. Ther. *13*:347, 1996
17. Rodier, J.F., Janser, J.C.: Surgical technical details improving sentinel node identification in breast cancer. Oncol. Rep. *4*:281, 1997
18. Rodier, J.F., Routiot, T., Mignotte, H., Bremond, A., Janser, J.C., Barlier, C., Ghnassia, J.P., Treilleux, I., Chassagne, C., Velten, M.: Individualisation du ganglion axillaire sentinelle par colorant lymphotrope dans les cancers du sein: etude de faisabilité à propos de 128 cas. Chirurgie *123*:239, 1998
19. Rodier, J.F., Janser, J.F., David, E., Barlier-Pagel, C., Ghnassia, J.P., Velten, M.: Intraoperative lymphatic mapping and sentinel node biopsy in breast cancer. Int. J. Oncol. *11*:894, 1997
20. Ivens, D., Hoe, A.L., Podd, T.J., Hamilton, C.R., Taylor, I., Royle, G.T.: Assessment of morbidity from complete axillary dissection. Br. J. Surg. *66*:136, 1992
21. Albertini, J.J., Lyman, G.H., Cox, C., Ye Balducci, L., Ku, N., Shivers, S., Berman, C., Wells, K., Rappaport, D., Shons, A., Horton, J., Greenberg, H., Nicosia, S., Clark, R., Cantor, A., Reintgen, D.S.: Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. J.A.M.A. *276*:1818, 1996
22. Statman, R.C., Jones, R.C., Cabot, M.C., Giuliano, A.E.: Sentinel lymphadenectomy: a technique to eliminate axillary dissection in node-negative breast cancer. Proc. Am. Soc. Clin. Oncol. *167*:125, 1996
23. Giuliano, A.E.: Lymphatic mapping and sentinel node biopsy in breast cancer. J.A.M.A. *277*:791, 1997
24. Giuliano, A.E.: Sentinel lymphadenectomy: a new axillary staging procedure for primary breast carcinoma. Breast Dis. *7*:16, 1996
25. Giuliano, A.E.: Sentinel lymphadenectomy in primary breast carcinoma: an alternative to routine axillary dissection. J. Surg. Oncol. *62*:75, 1996
26. Giuliano, A.E., Dale, P.S., Turner, R.R., Morton, D.L., Evans, S.W., Krasne, D.L.: Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann. Surg. *222*:394, 1995
27. Giuliano, A.E., Jones, R.C., Brennan, M., Statman, R.: Sentinel lymphadenectomy in breast cancer. J. Clin. Oncol. *15*:2345, 1997
28. Nieweg, O.R., Kapteijn, B.A.E., Peterse, J.L., Rutgers, E.J.T., Van Dongen, J.A., Kroon, B.B.R.: Identificatie van de Schildwachtklier bij patienten met mammacarcinoom. Ned. Tijdschr. Geneeskd. *140*:2235, 1996
29. Borgstein, P.J., Meijer, S., Pijpers, R.: Intradermal blue dye to identify lymph node in breast cancer. Lancet *349*:1668, 1997
30. O'Hea, B.J., Hill, A.D.K., El-Shirbiny, A.M., Yeh, S.D., Rosen, P.P., Coit, D.G., Borgen, P.I., Cody, H.S.: Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. J. Am. Coll. Surg. *186*:423, 1998
31. Gulec, S.A., Moffat, F.L., Carroll, R.G., Serafini, A.N., Sfakianakis, G.N., Allen, L., Boggs, J., Escobedo, D., Pruett, C.S., Gupta, A., Livingstone, A.S., Krag, D.N.: Sentinel lymph node localization in early breast cancer. J. Nucl. Med. *39*:1388, 1998
32. Krag, D., Weaver, D., Ashikaga, T., Moffat, F., Klimberg, V.S., Schriver, S., Kusminsky, R., Gadd, M., Kuhn, J., Harlox, S., Beitsch, P.: The sentinel node biopsy in breast cancer: a multicenter validation study. N. Engl. J. Med. *339*:941, 1998
33. Veronesi, U.: Sentinel-node biopsy in breast cancer. Lancet *350*:808, 1997
34. Veronesi, U., Paganelli, G., Galimberti, V., Viale, G., Zurrida, S., Bedoni, M., Costa, A., De Cicco, C., Geraghty, J.G., Luini, A., Sacchini, V., Veronesi, P.: Sentinel node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph nodes. Lancet *349*:1864, 1997
35. Borgstein, P.J., Pijpers, R., Comans, E.F., Van Diest, P.J., Boom, R.P., Meijer, S.: Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. J. Am. Coll. Surg. *186*:275, 1998
36. Roumen, R.M.H., Valkenburg, J.G.M., Geuskens, L.M.: Lymphoscintigraphy and feasibility of sentinel node biopsy in 83 patients with primary breast-cancer. Eur. J. Surg. Oncol. *23*:495, 1997
37. Alex, J.C., Krag, D.N.: Gamma-probe guided localization of lymph nodes. Surg. Oncol. *2*:137, 1993
38. Collet, G.J., Pijpers, R., Hoekstra, O.S., Boom, R., Meijer, S.: Sentinel node biopsy in breast cancer using Tc 99m-colloidal albumin. Eur. J. Surg. Oncol. *22*:430, 1996
39. De Cicco, C., Cremonesi, M., Chinol, M., Bartolomei, M., Pizzamiglio, M., Leonardi, L., Fiorenza, M., Paganelli, G.: Optimization of axillary lymphoscintigraphy to detect the sentinel node in breast cancer. Tumori *83*:539, 1997
40. Perre, C.I., Rütter, J.E. Vos, P.A.F.M., Hooge, P.: Technetium-99m-sestamibi uptake in axillary lymph node metastases in breast cancer patients. Eur. J. Surg. Oncol. *23*:142, 1997
41. Pijpers, R., Meijer, S., Hoekstra, O., Collet, G., Comans, E.F.I., Boom, R.P.A., Van Diest, P.J., Teule, G.J.J.: Impact of lymphoscintigraphy on sentinel node identification with technetium-99m-colloidal albumin in breast cancer. J. Nucl. Med. *38*:366, 1997
42. Offodile, R., Hoh, C., Barsky, S.H., Nelson, S.D., Elashoff, R., Eilber,

F.R., Economou, J.S., N'Guyen, M.: Minimally invasive breast carcinoma staging using lymphatic mapping with radiolabeled dextran. Cancer *82*:1704, 1998
43. Galimberti, V., Zurrida, S., Zucali, P., Luini, A.: Can sentinel node biopsy avoid axillary dissection in clinically node-negative breast cancer patients? Breast *7*:8, 1998
44. Chilosi, M., Lestani, M., Pedron, S.: A rapid immunostaining method for frozen sections. Biotech. Histochem. *69*:235, 1994
45. Rubio, I.T., Korourian, S., Conan, C., Krag, D.N., Colvert, M., Klimberg, S.: Sentinel lymph node biopsy for staging breast cancer. Am. J. Surg. *176*:532, 1998
46. Nieweg, D.E., Jansen, L., Valdes Olmos, R.A., Rutgers, Peterse, J.L., Hoefnagel, K.A., Kroon, B.B.R.: Lymphatic mapping and sentinel node biopsy in breast cancer. Eur. J. Nucl. Med. *26*:S11, 1999
47. Haddad, F.H., Cox, C., Reintgen, D.S.: Cancer du sein: une approche conservatrice de la région axillaire pour une meilleure évaluation pronostique. Ref. Gynecol. Obstet. *5*:265, 1997
48. McMasters, K.M., Giuliano, A.E., Ross, M.I., Reintgen, D.S., Hunt, K.K., Byrd, D.R., Klimberg, V.S., Whitworth, P.W., Tafra, L.C., Edwards, M.J.: Sentinel lymph node biopsy for breast cancer: not yet the standard of care. N. Engl. J. Med. *339*:990, 1998
49. Lopchinsky, R., Tartter, P.I.: Sentinel lymph node biopsy. J. Am. Coll. Surg. *187*:337, 1998
50. Rodier, J.F., Janser, J.C., Routiot, T.: Sentinel node biopsy: a valid selection criterion? Swiss Surg. *5*:212, 1999

Invited Commentary

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The authors from the French Comprehensive Cancer Centers of Strasbourg and Lyon present a well designed study of the emerging technology of radio-guided surgery and sentinel lymph node (SLN) biopsy in women with invasive breast cancer. This technique has the potential of changing the standard of care for breast cancer patients and promises to stage the axilla more accurately when compared with a complete axillary node dissection, at the same time providing a less morbid operation for the patient. Criteria for a successful program include a high success rate of finding an axillary SLN and a low "skip" metastasis rate. A "skip" metastasis would be defined as a negative SLN, with higher nodes in the basin being positive for metastatic disease. Using a vital blue dye lymphatic mapping technique, the authors had an 82.4% success rate for finding an axillary SLN in their first 73 patients. The false-negative SLN biopsy rate was 8%. The authors were going through the "learning curve" with this technique, so every SLN harvest was followed by complete axillary node dissection. They should be applauded for this approach, as it is the responsible way to introduce a new technique into surgical practice. In this way, false-negative SLN biopsy rates may be ascertained immediately while all the patients eventually undergo the standard of care, that is, a level I and II axillary node dissection.

The paper describes some basic principles of lymphatic mapping procedures. The SLNs were not always located in level I of the axillary, with 13% of primary tumors showing direct drainage to level II and III nodes. Thus a blinded sampling of the level I lymph nodes of the axilla may provide inaccurate nodal staging 13% of the time. Routine histologic examination identified 87% of the patients with metastatic disease in their SLN, but serial sectioning was necessary to find low volume disease in the remainder. This is one of the advantages of lymphatic mapping and SLN. The surgeon has the ability to give the pathologist the one or two SLNs that are most likely to contain metastatic disease, and it is not too much to expect the pathologist to perform a more detailed examination on the SLNs. This more detailed examination may include more sections, immunohistochemical staining for metastatic breast cancer (cytokeratin staining), or even a molecular biology assay for occult metastases. The surgery becomes less morbid but the staging of the axilla more accurate.

The average number of SLNs harvested per patient was 1.4 in this study. At the Moffitt Cancer Center (MCC), we utilize preoperative lymphoscintigraphy and intraoperative lymphatic mapping with both a vital blue dye and a technetium 99-labeled sulfur colloid. With this combination method our success rate of finding an axillary SLN is 95%. We harvest, on average, 2.0 axillary SLNs per patient; and after a positive SLN biopsy the frequency of finding higher nodes positive with a CLND is only 33%. This suggests that lymphatic mapping using vital blue dye alone has a lower success rate and fails to identify all of the SLNs. Additionally, use of the radiocolloid aids in the identification of extraaxillary lymphatic drainage to the internal mammary nodes or supraclavicular lymph nodes, for example. This is not to discount the importance of using a vital blue dye. There is a subgroup of patients, mostly those with upper outer quadrant tumors, in whom significant "shine through" radioactivity prevents localization of lymph nodes in close proximity to the primary tumor. The SLN cannot be imaged by preoperative lymphoscintigraphy or be located with the hand-held gamma probe. In this situation, identifying a blue-stained afferent lymphatic or lymph node may be the only way to identify the SLN. Proper timing of the vital blue dye injection and SLN harvest is critical for this mapping technique to work. Armando Giuliano, from the John Wayne Cancer Institute, pioneered the blue dye lymphatic mapping method. He is a proponent of injecting the vital dye into the breast parenchyma around the primary tumor or excisional biopsy cavity (not into the skin above the tumor). This is followed by performing "heavy" massage on the breast to increase interstitial pressure that drives the mapping agents into the lymphatics. After 5 minutes of massage an incision is made in the axilla to harvest the SLN.

Using a combination mapping method, the SLN can be identified in the axilla 95% of the time. Adding radiocolloid mapping to the vital blue dye technique can lessen the learning curve of the technique and increase the success rate of the localization. It can result in harvesting an increased number of SLNs, some of which are clinically significant because they contain metastatic disease.

One of the greatest benefits of selective axillary lymph node dissection is the reduced number of specimens presented to pathology for evaluation. This allows rigorous examination of one or two SLNs instead of the 15 to 30 nodes typically removed during complete axillary node dissection. By utilizing techniques such as immunohistochemical staining and serial sectioning, the sensitivity of the SLN biopsy should be greatly enhanced. Additionally, submicroscopic disease may be identified using molecular biology techniques such as the RT-PCR. The authors of this study relied on routine H-E staining, occasional serial sectioning, and occasional frozen sections to identify the presence of metastatic disease. To take full advantage of the technique, a more detailed examination of the SLN should be performed.

In conclusion, using a combination mapping technique may reduce the technical difficulties associated with lymphatic mapping, lessen the learning curve, and increase the success rate of axillary SLN identification. Additionally, a more detailed examination of the SLN can lower the incidence of false-negative SLN biopsies and help to realize the full potential of the technique. The clinicians from the two French Cancer Centers outline a process to introduce responsibly a new surgical technique to treat women with invasive breast cancer.