Indications for sentinel lymph node biopsy in multifocal and multicentric breast cancer

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Background. *Multifocal and multicentric breast cancers have been regarded as relative contraindications for sentinel lymph node (SLN) biopsy, because initial validation studies noted an association with greater false-negative rates. The purpose of this study is to perform a meta-analysis of the literature evaluating the feasibility and accuracy of SLN biopsy in multifocal and multicentric breast cancer.*
Methods. *A PubMed search retrieved original articles published between 2000 and 2010 in which the authors evaluated the accuracy of SLN biopsy in multifocal and multicentric breast cancer. Sixteen original articles were included in our meta-analysis.*
Results. *Nine-hundred thirty-two patients with multifocal and multicentric breast cancer underwent SLN biopsy followed by axillary lymph node dissection. The overall accuracy rate and false-negative rate are 96% and 7.7%, respectively. Of the 37 false-negative biopsies, 7 patients had an additional relative contraindication for SLN biopsy. If we exclude these patients with additional known relative contraindication to SLN biopsy, the accuracy and false-negative rates are 96.7% and 6.3%, respectively.*
Conclusion. *When a multifocal or multicentric breast cancer has an additional relative contraindication to performing SLN biopsy, such as neoadjuvant chemotherapy or* $T > 5$ *cm, the false-negative rate increases. (Surgery 2012;152:389-96.)*

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Sentinel lymph node (SLN) biopsy has now replaced axillary lymph node dissection for the staging of primary operable breast cancer with clinically negative nodal disease because SLN biopsy can be performed with substantially less morbidity and with acceptable accuracy rates. SLN biopsy was introduced as a technique for staging breast cancer in 1993 by Krag using intraparenchymal injection of radioisotope,[1] followed in 1994 by Giuliano et al[2] using intraparenchymal blue dye injection. Veronesi et al[3] validated the use of SLN biopsy using both blue dye and radioisotope detection techniques in clinically node-negative patients with a tumor size equal to or less than 2 cm with an accuracy rate and false-negative rate of 96.9% and 8.8%, respectively. Large clinical trials now support the utility of SLN biopsy in the axillary staging of clinically node-negative primary operable breast carcinoma.[4,5]

The application of SLN biopsy to patients with clinically positive lymph nodes, locally advanced disease, history of previous breast or axillary surgery, previous chest wall radiation, neoadjuvant chemotherapy, and multifocal and muticentric breast cancer has been limited because of concerns of high false-negative rates.[6] Not only do multicentric and multifocal breast carcinomas have a greater incidence of lymph node metastasis,[7-9] but the authors of prevailing theories speculated that different quadrants of the breast might drain into separate SLNs.[10,11] A 2002 Consensus Conference Committee cautioned that multicentric and multifocal breast carcinoma represented a subcategory of breast cancer that seemed to have increased false-negative rates, and therefore, the known presence of multicentric/multifocal breast cancer should be a contraindication to performing SLN biopsy.[12]

In 2002, Kim et al[13] published a lymphatic drainage study on 5 patients with multicentric breast cancer, whereby radioisotope injection was performed at one site and peritumoral blue dye was injected at the second site of the breast. At least one axillary node was found to be both hot and blue,

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demonstrating that all quadrants of the breast drained into a common SLN. This study suggested that SLNs could be identified in patients with multicentric and multifocal breast cancer. The subareolar injection technique has been shown to communicate with the dermal lymphatics of the nipple areolar complex with intramammary lymphatics and drain ultimately to (a) common lymph node(s) regardless of tumor location.[14,15] Nevertheless, whether the false-negative rate for SLN is unacceptably high this population remains uncertain. Conflicting reports in the literature regarding SLN biopsy in multicentric and multifocal breast cancer continue, possibly because many studies represent single institution studies with relatively small sample sizes, as the incidence of known multifocal/multicentric breast cancer ranges only between 11.1% and 21%[16,17] of all primary operable breast cancers. The purpose of this report is to evaluate the SLN identification rate and the false-negative rate of SLN biopsy in multifocal and multicentric breast cancer with the use of a meta-analysis.

METHODS

A comprehensive PubMed literature search was performed to retrieve original articles published in English between 2000 and 2010 in which the authors evaluated the accuracy of SLN biopsy in multifocal and multicentric breast cancer. Search terms included "SLN biopsy," "multifocal breast cancer," "multicentric breast cancer," "accuracy," and "false-negative rates." Initially, 1,091 potentially relevant abstracts were identified in PubMed with the search phrase of "multifocal breast cancer or multicentric breast cancer." The abstracts were reviewed to determine whether the articles evaluated the utility of SLN biopsy in multifocal and multicentric breast cancer. Articles chosen for this meta-analysis were required to include patients with multifocal or multicentric breast cancer who underwent SLN biopsy followed by axillary lymph node dissection. Only original articles published in English were considered.

Nineteen articles were initially considered; 3 were eliminated, however, because of insufficient data to perform validity calculations (Fig 1). We accepted articles with variable definitions of multifocal and multicentric breast cancer to include 2 or more ipsilateral invasive breast cancers. In addition, several techniques for performing the SLN biopsy were used. Many patients with additional relative contraindications to SLN biopsy were included in several of the articles selected. These relative contraindications included neoadjuvant chemotherapy, clinically positive nodes, previous breast or axillary surgery, and locally advanced disease.

The SLN identification (ID) rates were calculated as the number of patients whose nodes were mapped/total number of patients in the study. Patients with unsuccessful lymph node mapping were excluded from any analysis regarding SLN accuracy because the false-negative rate could not be calculated. Primary outcomes included the SLN ID, the number of patients with positive and negative SLN biopsies, accuracy rate, sensitivity, negative predictive value, and false-negative rates. The following formulas were used for validity calculations: Accuracy rate = (true-positive + true-negative)/total successful SLN biopsies. Sensitivity = true-positive/(true-positive + false-negative). Negative predictive value = true-negative/(true-negative + false-negative). False-negative rate = false-negative/(false-negative + true-positive). The Meta-DiSc software was used to perform a meta-analysis to evaluate the use of SLN as diagnostic test in mutifocal/multicentric breast cancers.[18]

RESULTS

Sixteen original articles evaluating the accuracy of SLN biopsy in multifocal and multicentric breast cancer were included in our meta-analysis (Fig 1). Seven were retrospective, and 9 were prospective studies. The overall SLN identification rate was 95.4% in 949 patients (Table I).[19-33] A total of 932 patients with multifocal and multicentric breast cancer who underwent successful SLN biopsy followed by axillary lymph node dissection were considered for our meta-analysis. All of the articles except 1[19] included patients with at least one additional relative contraindication to SLN biopsy. These relative contraindications included locally advanced disease, palpable axillary lymph nodes, previous breast or axillary surgery, neoadjuvant chemotherapy, and previous radiation therapy. Four-hundred forty-four patients had a positive SLN biopsy, and 487 patients had a negative SLN biopsy (Table I). The mean number of SLNs recovered was 2.11. A total of 37 false-negative SLN biopsies (Table II) were identified. Seven of 37 patients with false-negative biopsies had known relative contraindications for SLN biopsy, including locally advanced disease, palpable axillary lymph nodes, prior breast surgery, and neoadjuvant chemotherapy. One patient of the 7 had 2 additional known relative contraindications. No information was available regarding the characteristics for the remaining 30 patients with false-negative results. The overall false-negative rate was 7.7% (range, 0%–40%; Fig 2, *A*). The overall accuracy

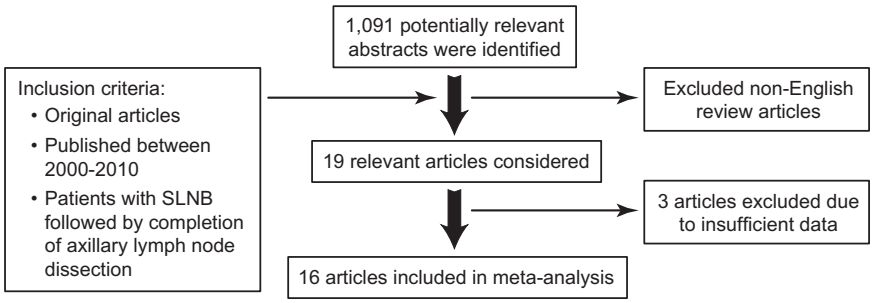

Fig 1. Flow diagram of study inclusion and exclusion criteria.

rate, sensitivity, and negative predictive value are 96% (77.8%–100%), 92.3% (60%–100%), and 92.4% (66.7%–100%), respectively. If the 7 of 37 patients with false-negative results associated with other relative contraindications to SLN biopsy are excluded; the false-negative rate improved to 6.3% (Fig 2, *B*) and the accuracy rate, sensitivity, and negative predictive values were similar at 96.7%, 93.7%, and 93.5%, respectively.

Since the widespread adaptation of SLN biopsy as the diagnostic standard for staging primary operable breast cancers, SLN-negative patients have been shown to have extremely low incidence of axillary recurrence, further validating the low FNR of the SLN procedure. In a systematic literature review combining 48 studies, the median, overall weighted axillary recurrence rate at a median of 34 months was shown to be 0.3% (67/14,959) among SLN-negative breast cancer patients.[34] The axillary recurrence rates of published studies for patients with multifocal and multicentric breast cancers range from 0–2.4% over a follow-up period ranging between 17.9 and 60 months (Table III).[35-37]

DISCUSSION

The status of the axillary lymph nodes is the most important indicator of prognosis in patients with breast carcinoma and guides treatment plans. Therefore, accurate staging of the axilla is crucial. The use of SLN biopsy for staging in multifocal and multicentric breast carcinoma remains controversial. Conflicting evidence regarding the accuracy in the literature exist, suggesting that SLN biopsy may be considered a relative contraindication in multifocal, multicentric breast cancer. Our meta-analysis of 16 original articles evaluating the accuracy of SLN biopsy in patients with multifocal and multicentric breast cancer demonstrates an overall accuracy rate of 96% and a false-negative rate of 7.7% in 932 patients. These rates are comparable with that of unifocal breast cancers and suggest that the use SLN biopsy in multifocal and multicentric breast cancer is safe and accurate. The limitations of this study include the variability in the inclusion and exclusion criteria between the original articles and the variability of the SLN mapping techniques used. It should be noted that the data on false-negative rates for both unifocal and multifocal/multicentric breast cancers included in this report were obtained early in the collective experience of surgeons performing SLN biopsy for breast cancer and that false-negative rates significantly decrease with increased surgeon experience.[38,39] When we exclude 7 of 37 patients with false-negative results who were known to have at least one other known relative contraindication to SLN biopsy (in addition to having multifocal, multicentric breast cancer), the false-negative rate dropped slightly to 6.3%. The possibility exists that an analysis inclusive of the additional 30 patients, who may have other relative contraindications to SLN biopsy, may reveal a further decrease in the false-negative rate.

Very few data are available on patients with multifocal/multicentric breast cancers who have also undergone neoadjuvant therapy. Meta-analyses on the feasibility and accuracy of patients undergoing SLN biopsy after neoadjuvant therapy do not specifically address the inclusion or exclusion of multicentric/multifocal cancers.[40,41] The largest review,[24] which includes 27 studies, showed a pooled ID rate of 90.9% and a FNR of 10.5%. Only Canavese et al[42] reported that 37.5% of 64 patients had multicentric cancers and were included in this single institutional study of SLN biopsy after neoadjuvant chemotherapy. Inclusion criteria for this study were noninflammatory breast cancers >2 cm and clinically positive nodes. Overall, the SLN ID rate was 93.8% and the FNR was 5.1% (2 patients), demonstrating acceptable results. Because of the low incidence of false-negative results, however, they did not conclude on whether any specific clinical characteristic(s) contributed to a greater risk for a FNR.

Table I. Meta-analysis of the accuracy of SLN biopsy in patients with multifocal and multicentric breast cancer

Study	*No. patients*	*Identification rate*	*Positive SLN biopsy*	*Negative SLN biopsy*	*False negative*	*Mean no. SLN*	*Accuracy, %*	*Sensitivity, %*	*NPV, %*	*False-negative rate, %*
Ozmen et al[9]	18	85.7% (18/21)	6	12	4	2	77.80	60	66.70	40
Cipolla et al[19]	34	100% (34/34)	18	16	0	1.8	100	100	100	0
Fearmonti et al[21]	23	100% (23/23)	11	12	2		91.30	84.60	83.30	15.40
Kumar et al[22]	45	85% (45/53)	19	26	0		100	100	100	0
Knauer et al[23]	125	91.5% (130*/142)	79	46	3	1.67	97.60	96.30	93.50	3.70
Tousimis et al[24]	70	100% (70/70)	38	32	3	2.7	95.70	92.70	90.60	7.30
Goyal et al[25]	71	94.7% (71/75)	31	40	3	2.4	95.80	91.20	92.50	8.80
Ferrari et al[26]	31	100% (31/31)	13	18	1	2.1	96.80	92.90	94.40	7.10
D' Eredita et al[27]	30	100% (30/30)	15	15	1	1.93	96.70	93.80	93.30	6.30
Kim et al[28]	127	97.8% (131†/134)	36	91	3	2.68	97.60%	92.30	96.70	7.70
Holwitt et al[29]	41	100% (41/41)	26	15	2		95.10%	92.90	86.70	7.10
Lo et al[30]	23	100% (23/23)	7	16	0	1.13	100%	100	100	0
Layeeque et al[31]	40	100% (40/40)	25	15	0	2.3	100	100	100	0
Giard et al[32]	197	93.4% (197/211)	89	108	14	2.2	92.90	86.40	87	13.60
Behm et al[20]	38	Not listed	22	16	1	2.86	97.40	95.70	93.80	4.30
Schrenk et al[33]	19	100% (19/19)	10	9	0	1.7	100	100	100	0
Total	932	95.4% (903/947)	445	487	37	2.11	95.92	92.3	92.41	7.7
Overall with exclusion of 7 pts with contraindications	925		445	464	30		96.70	93.7	93.5	6.3

*Only 125/135 patients had ALND.
†Only 127/131 patients had ALND.
ALND, Axillary lymph node dissection; *NPV*, negative predictive value; *SLN*, sentinel lymph node.

Table II. Breast cancer characteristics that increase the false-negative rate of SLN biopsies

Characteristics	*No. patients*
Intraoperative palpable lymph nodes	2[24,26]
Tumor >5 cm	3[24,27]
Tumor >5 cm and neoadjuvant chemotherapy	1[21]
Previous breast surgery	1[21]
Unknown	30

SLN, Sentinel lymph node.

Currently, the aim of a phase 2 American College of Surgeons Oncology Group (ACOSOG) clinical trial Z1071 is to evaluate the FNR of patients with node positive breast cancer (stage II-IIIB) after neoadjuvant chemotherapy. In practice, many surgeons have already adopted the use of SLN after neoadjuvant chemotherapy, arguing that the patient will have to undergo only 1 operation, and can be spared axillary lymph node dissection if they have no additional metastatic nodes by SLN after chemotherapy.[43] Current National Comprehensive Cancer Network guidelines, however, recommend a preference for definitive axillary staging with SLN biopsy if fine-needle aspiration is nondiagnostic before chemotherapy (www.nccn.org/; Breast cancer guidelines, version 1.2012), because this information may better guide subsequent adjuvant treatments. Furthermore, the clinical consequence of leaving behind lymph nodes that once harbored breast cancer deposits prior to chemotherapy is not known.

Multicentric and multifocal breast carcinomas been shown to have a greater frequency of lymph node metastasis.[7,8,44] When the AJCC T-staging classification is used, the largest diameter of a multifocal, multicentric breast cancer had a positive LN incidence of 48% and 67%, for T1 and T2 tumors, respectively, compared with unifocal T1 and T2 tumors, with 35% and 49% LN-positive cancers $P = .05$ and $P = .003$, respectively.[44] As with locally advanced tumors (T3, T4), where the risk of nodal metastasis has been shown to be as high as 75%,[45,46] the likelihood of a false-negative result increases when the prevalence of lymph node metastasis increases.[47,48] Thus, the risk of a false-negative SLN biopsy will be estimated to be greater for a T1 or T2 multifocal and multicentric compared with a unifocal T1 or T2 breast cancer. Because the pretest (SLN biopsy) probability of finding positive axillary node is greater in a multifocal and multicentric breast cancer, SLN biopsy should be approached cautiously with this fact in mind. The addition of an additional relative contraindication (greater

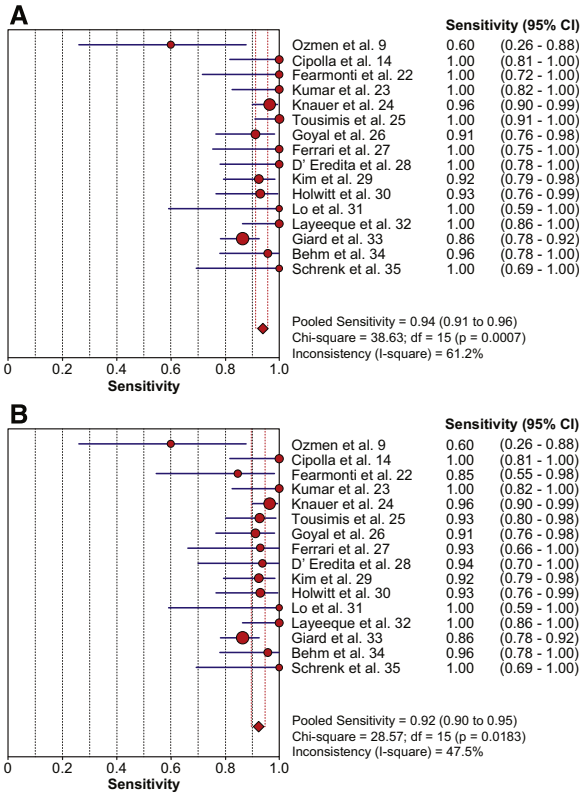

Fig 2. Forest plot of pooled sensitivity from 16 studies. (*A*) All patients, $N = 932$. (*B*) $N = 925$, excluding 7 patients with known false negative SLN biopsy with multifocal or multicentric breast cancer and also at least one other relative contraindication to SLN biopsy.

false-negative rates) such as locally advanced disease, palpable axillary lymph nodes, prior breast or axillary surgery, neoadjuvant chemotherapy, and previous radiation therapy, would be expected to further increase the false-negative rate.

What is the clinical significance of a potentially greater false-negative rate? A review of available data from 5 studies (Table III) suggests a slightly greater local axillary recurrence rate of up to 2.5% after being staged as node negative by SLN biopsy. Among the 459 patients contributing to the pooled results, only 11 of 459 patients (2.4%) had neoadjuvant chemotherapy before SLN biopsy. The majority of the published studies specifically excluded patients who have had neoadjuvant chemotherapy.[20,35-37] Even if the incidence of local axillary recurrence is greater among multicentric, multifocal breast cancer patients, the benefit/utility of axillary dissections, particularly in the presence of low-volume disease in the SLN, have been questioned.[49] The ACOSOG Z011 trial demonstrated that among a select subgroup of patients with positive SLN who underwent partial mastectomy, adjuvant radiation, chemotherapy, and/or

Table III. Axillary recurrences in patients with mulifocal/multicentric breast cancer who were staged to be SLN negative and who did not undergo completion ALND

Author	N	*Median follow-up, mo*	*No. axillary recurrences,* n *(%)*	*Comments**
Gentilino[36] Multi-institutional	138	60	3 (2.2%)	One of the recurrences died of disease.
Carpenter[35] Single institution	108	44.3	0 (0%)	Two patients with Her-2 overexpressed cancers developed distant disease.
Behm[20] Single surgeon	38	17.9	0 (0%)	Compared patients with SLN and complete ALND (one false negative) and SLN only.
Howlitt[29]	52	57.6	0 (0%)	17% had neoadjuvant chemotherapy and 4% had neoadjuvant endocrine therapy. All patients underwent mastectomy.
Meretoja[37]	121	42	3 (2.4%) mean tumor size 16 mm	Two patients later developed distant disease after axillary clearance; 1 patient had concurrent breast recurrence. The authors compared axillary recurrence rates with patients with unifocal cancers: 7/1138 (0.6%); $P = .179$.
	2		0 (0%) mean tumor size 43 mm	

*Patients with neoadjuvant chemotherapy were excluded from these studies in all cases except Howlitt et al.[29]
ALND, Axillary lymph node dissection; *SLN*, sentinel lymph node.

hormonal therapy but no completion axillary lymph node dissection, the axillary recurrence rate at a median follow-up of 6.3 years was 0.9% (4/445 patients).

Currently, we have not extended these findings to spare SLN node-positive mastectomy patients a completion axillary dissection. Because a clinical trial will be unlikely ever to address specifically the axillary recurrence rate of SLN-negative patients with a multifocal/multicentric breast cancer who have already received neoadjuvant chemotherapy, the management of the axilla in this setting relies on weighing with the risk of underdiagnosing, and consequentially undertreatment, with the risk of overtreatment. The results of the Z011 trial have not only changed the surgical management of the axilla in a subset of selected patients, but this trial has generated additional questions regarding the extent to which the tangential fields used in whole breast radiation contribute to the low axillary recurrence rate in the trial. Although these factors are being evaluated, some radiation oncologists now advocate adding nodal radiation fields for patients at high risk for having additional positive lymph nodes, beyond the 1 or 2 resected SLN, who do not undergo completion axillary lymph node dissection, in order to ensure better locoregional control.[50] For example, patients with multifocal breast cancer who undergo partial mastectomy fall into this high-risk category. If it is shown that tangential fields in whole breast radiation do decrease the axillary recurrence rate, then a similar case could be made to treat patients with radiation after total mastectomy with low volume SLN metastasis. Because the vast majority of multicentric tumors require mastectomy, many clinical scenarios exist in which avoiding axillary lymph node dissection (eg, negative SLN after neoadjuvant chemotherapy) may be replaced by axillary radiation.

In conclusion, SLN biopsy predicts the lymph node status in patients with multifocal and multicentric breast cancer with an accuracy rate and a false-negative rate that is comparable with unifocal tumors, particularly in the absence of additional relative contraindications, as shown in the majority of the studies in this meta-analysis. Clinical trials, such as ACOSOG Z1071, which will evaluate the accuracy of SLN biopsy after neoadjuvant chemotherapy, may better address additional management issues in multifocal/multicentric breast cancers.

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