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Role of Axillary Lymph Node Dissection After Tumor Downstaging With Induction Chemotherapy for Locally Advanced Breast Cancer

Henry M. Kuerer, MD, PhD, Lisa A. Newman, MD, Bruno D. Fornage, MD, Kapil Dhingra, MD, Kelly K. Hunt, MD, Aman U. Buzdar, MD, Fred C. Ames, MD, Merrick I. Ross, MD, Barry W. Feig, MD, Gabriel N. Hortobagyi, MD, and S. Eva Singletary, MD

Background: Induction chemotherapy has become the standard of care for patients with locally advanced breast cancer (LABC) and currently is being evaluated in prospective clinical trials in patients with earlier-stage disease. To better gauge the role of axillary lymph node dissection in patients with LABC this study was performed to assess initial axillary status on physical and ultrasound examination, axillary tumor downstaging following induction chemotherapy, and the accuracy of physical examination compared with axillary sonography in predicting which patients will have axillary lymph node metastases found on pathologic examination.

Methods: Between 1992 and 1996, 147 consecutive patients with LABC were registered in a prospective trial of induction chemotherapy using 5-fluorouracil, doxorubicin, and cyclophosphamide. Physical and ultrasound examinations of the axilla were performed at diagnosis and after induction chemotherapy. Segmental resection with axillary lymph node dissection or modified radical mastectomy was performed, followed by postoperative chemotherapy and irradiation of the breast or chest wall and regional lymphatics.

Results: Following induction chemotherapy, 43 (32%) of the 133 patients with clinically positive lymph nodes on initial examination had axillary tumor downstaging as assessed by physical and ultrasound examination. The sensitivity of axillary sonography in identifying axillary metastases was significantly higher than that of physical examination (62% vs. 45%, $P = .012$). The specificity of physical examination (84%) was higher than that of sonography (70%), but the difference did not reach statistical significance. Among the 55 patients in whom the findings of both physical and ultrasound examination of the axilla were negative following induction chemotherapy, 29 patients (53%) were found to have axillary lymph node metastases on pathologic examination of the axillary contents. However, 28 (97%) of these patients had either 1 to 3 positive lymph nodes or only micrometastases 2 to 5 mm in diameter.

Conclusions: Preoperative clinical assessment of the axilla by physical examination combined with ultrasound examination is not completely accurate in predicting metastases in patients with LABC following tumor downstaging. However, patients with negative findings on both physical and ultrasound examinations of the axilla may be potential candidates for omission of axillary dissection if the axilla will be irradiated because minimal axillary disease remains. Patients who have positive findings on preoperative physical or ultrasound examinations should receive axillary dissection to ensure local control. A prospective randomized trial of axillary dissection versus axillary radiotherapy in patients with a clinically negative axilla following induction chemotherapy is currently underway.

Key Words: Axillary lymph node dissection—Neoadjuvant chemotherapy—Axillary ultrasonography—Locally advanced and large primary breast cancer.

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From the Departments of Surgical Oncology (HMK, LAN, KKH, FCA, MIR, BWF, SES), Diagnostic Radiology (BDF), and Breast Medical Oncology (KD, AUB, GNH), The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

Dr. Kuerer is currently affiliated with the Department of Surgery, University of California San Francisco, UCSF Cancer Center, 2356 Sutter St., San Francisco, CA, 94115.

Dr. Dhingra is currently affiliated with Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285.

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Address correspondence and reprint requests to: S. Eva Singletary, MD, Dept. of Surgical Oncology, Box 106, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030.

Despite increased public awareness of the importance of early detection of breast cancer and the widespread use of screening mammography, the diagnosis of locally advanced breast cancer (LABC) is made in a significant number of women each year. It is estimated that between 10% and 15% of women diagnosed with breast cancer in the United States during 1997 (18,000 to 27,000 patients) will present with locoregionally advanced disease, and in developing countries this percentage may be as high as 30%.[1,2] Induction chemotherapy has become the standard of care for patients with LABC. However, information on the clinical and pathologic axillary lymph node response to induction chemotherapy is limited.[3–8]

The need for axillary dissection in patients with LABC has been questioned for the following reasons: (1) induction chemotherapy in patients with LABC and operable breast cancer has been shown to downstage positive axillary lymph nodes to negative pathologic lymph nodes in 25% to 44% of patients[9–12]; (2) in most treatment protocols, patients with LABC routinely receive additional postoperative chemotherapy and radiotherapy regardless of the findings at axillary dissection; and (3) some LABC series have reported equivalent axillary control rates after induction chemotherapy followed by axillary dissection alone, axillary irradiation alone, or a combination of both treatment modalities.[8,13,14] These results suggest that treatment of the axilla might be effectively restricted to irradiation of draining lymph nodes in selected patients with LABC.

On the other hand, advocates of axillary dissection in patients receiving primary chemotherapy assert that stratification of patients by the absolute number of involved lymph nodes may identify patients who might potentially benefit from high-dose chemotherapy or crossover to other chemotherapeutic regimens. However, high-dose chemotherapy cannot be recommended in the absence of prospective randomized data that show a survival advantage for high-dose chemotherapy over standard anthracycline-based chemotherapy in high-risk patients with LABC.[15] Phase II trials have demonstrated high activity of taxane-based chemotherapy (docetaxel and paclitaxel) in anthracycline-resistant breast cancer.[16,17] In this context, some patients with minimal response to anthracycline-based induction chemotherapy may be offered taxane-based regimens to increase survival rates in the adjuvant setting. However, decisions to cross patients over to a different chemotherapeutic agent on the basis of histologic assessment of the axilla may become less important if the trend in treatment is toward a sequential approach using anthracycline and taxane-based regimens prior to local therapy. To better gauge the role of axillary dissection in LABC, this study retrospectively analyzed 147 patients with respect to initial axillary status on physical and ultrasound examination, axillary tumor downstaging following four cycles of induction chemotherapy with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC), and the accuracy of physical examination compared with axillary ultrasonography in predicting which patients will have axillary lymph node metastases found on pathologic examination.

PATIENTS AND METHODS

Between 1992 and 1996, 147 consecutive patients with LABC treated at The University of Texas M. D. Anderson Cancer Center were registered in a prospective trial of neoadjuvant chemotherapy using FAC and had physical and ultrasound examination of the axilla at diagnosis and before surgery.[18] Locally advanced breast cancer was defined as breast cancer histologically or cytologically documented as stage IIA (with T at least 4 cm in size), IIB, IIIA, IIIB, or IV (with ipsilateral supraclavicular lymph node involvement only) using the 1992 American Joint Committee on Cancer classification system.[19] The diagnosis usually was established by fine-needle aspiration biopsy of the primary tumor and any involved axillary lymph nodes. A core-needle biopsy was performed to document invasion in patients without clinical adenopathy who were registered on the basis of having a large primary tumor. Patients with primary inflammatory carcinoma were excluded.

Each patient was examined by a multidisciplinary breast team consisting of surgical, medical, and radiation oncologists to confirm the diagnosis of LABC and to evaluate the clinical stage of disease at presentation and following four cycles of chemotherapy. The staging workup included a complete history and physical examination, complete blood count with differential and platelet count, blood chemistry analysis, chest radiograph, abdominal computed tomographic (CT) scan or ultrasonography of the abdomen, bone scan, and bilateral mammography. Each patient was entered prospectively into the protocol database and followed longitudinally. Complete medical records of all patients were available for review at the time of this analysis.

Treatment Protocol

Following four cycles of induction chemotherapy, patients who had at least 50% reduction in the product of the two largest perpendicular dimensions of the breast tumor and axillary adenopathy (140 patients) underwent either a segmental mastectomy with axillary lymph node dissection or modified radical mastectomy. Patients with

a clinically minor reduction or no change in tumor mass or with unresectable disease after induction chemotherapy (7 patients) underwent preoperative radiotherapy followed by modified radical mastectomy. For preoperative radiotherapy, a total dose of 50 to 60 Gy was delivered in 2-Gy fractions to the breast, internal mammary lymph nodes, and supraclavicular/high axillary lymph nodes.

Patients with initially minor response or no change in disease received six cycles of methotrexate and vinblastine. The histologic response to induction chemotherapy was characterized as a complete pathologic response when there was no evidence of residual tumor. Patients received four additional cycles of FAC postoperatively or four more cycles of FAC followed by four cycles of methotrexate and vinblastine if four or more positive lymph nodes were found in the surgical specimen. Locoregional radiotherapy was instituted within 6 weeks of completion of chemotherapy. Postoperative radiotherapy was delivered to the chest wall or breast, internal mammary lymph nodes, and supraclavicular lymph nodes. A total dose of 50 Gy was delivered to these areas in 2-Gy daily fractions through abutting treatment fields. A posterior axillary field was used to supplement the dose to a total dose of 40 Gy at the mid-axilla in patients who presented with N2 disease. The chest wall was typically treated with a boost dose using electrons to achieve a total dose of 60 Gy.

Examination of the Axilla

Clinical evaluation of the ipsilateral axilla by physical examination and ultrasonography was performed at presentation and following four cycles of induction chemotherapy. Ultrasound examination of the axilla was performed by radiologists using a high-resolution 7-mHz transducer. Axillas without visible adenopathy and axillas that contained lymph nodes that were homogenous or echo-rich were considered negative for disease by ultrasonography. Axillas that contained lymph nodes that were inhomogenous or echo-poor and axillas containing lymph nodes larger than 5 mm that were not distinguishable by architectural criteria were considered positive for disease by ultrasonography.

Data Analysis and Statistical Methods

The accuracy of physical and ultrasound examination performed before surgery compared with that of histologic examination of the axillary contents was evaluated on the basis of sensitivity, specificity, positive predictive value, and negative predictive value determined using the matrix shown in Table 1.[20]

Data were analyzed using Statistica software (Statsoft, Inc., Tulsa, OK). Comparability of group outcomes was assessed by χ^2 analysis or Fisher's exact test. All comparisons were two-tailed. The statistical significance level (P) was taken as a measure of the strength of evidence against the null hypothesis, and $P \leq .05$ was considered statistically significant. The median follow-up for the entire group was 35 months (range, 9 to 64 months).

TABLE 1. *Physical and ultrasound findings vs. histologic findings**

	Findings on histologic examination of the axillary contents	
	Positive	Negative
Findings on physical or ultrasound examination of the axilla		
Positive	A	B
Negative	C	D

* Sensitivity is defined as A/(A + C); specificity as D/(B + D); positive predictive value as A/(A + B); negative predictive value as D/(C + D). Values were expressed with their 95% confidence intervals.

RESULTS

Table 2 summarizes the patient and tumor characteristics of the 147 evaluable women in this study. The median age was 46 years, and the majority of patients were 50 years of age or younger. Of the 97 patients (66%) who had initial tumor estrogen and progesterone receptor determinations, approximately half had tumors positive for one or both of these receptors. Seventy-two patients (49%) presented with anaplastic tumors (Black's nuclear grade 1). The median largest initial primary tumor diameter was 6 cm, with 98 patients (67%) presenting with T3 or T4 disease. One hundred forty patients (95%) had clinically locally advanced disease at presentation (stages IIB-IV [supraclavicular lymph node involvement]).

Initial Axillary Assessment

On initial assessment of the axilla, 14 of the 147 patients (10%) were assessed as having a disease-free axilla and 133 patients (90%) were assessed as having axillary metastases (Table 3). The results of physical and ultrasound examination of the axilla were concordant in 132 patients (90%) and discordant in 15 patients (10%) on initial evaluation (see Table 3). Of the 118 patients considered to have a positive axilla on both physical and ultrasound examination, 64 patients (54%) had N2 disease (see Tables 2 and 3). Axillary metastases were cytologically confirmed by fine-needle aspiration biopsy (FNA) in 72 (54%) of the 133 patients who presented with a positive axilla.

TABLE 2. *Patient and initial tumor characteristics of 147 evaluable breast cancer patients treated with induction chemotherapy*

Characteristic	No. (%)
Age*	
≤50 y	96 (65)
>50 y	51 (35)
Estrogen-receptor status at diagnosis	
Positive	47 (32)
Negative	50 (34)
Unknown	50 (34)
Progesterone receptor status at diagnosis	
Positive	43 (29)
Negative	51 (35)
Unknown	53 (36)
Black's nuclear grade at diagnosis	
1 (most anaplastic)	72 (49)
2	31 (21)
3	2 (1)
Unknown	42 (29)
Initial tumor size†	
TX (Prior excision)	3 (2)
T0	3 (2)
T1	8 (5)
T2	35 (24)
T3	41 (28)
T4	57 (39)
Initial clinical lymph node status	
N0	14 (10)
N1	54 (37)
N2	64 (43)
N3	5 (3)
M1 (supraclavicular)	10 (7)
Stage at diagnosis	
IIA	7 (5)
IIB	22 (15)
IIIA	52 (35)
IIIB	56 (38)
IV (supraclavicular M1)	10 (7)

* Median age was 46 years.
† Median initial tumor size (largest diameter) was 6 cm.

Axillary Assessment Following Induction Chemotherapy

Following four cycles of induction chemotherapy, the axillas of each of the 147 patients were reevaluated by physical and ultrasound examination. Of the 133 patients with positive lymph nodes on initial physical or ultrasound examination, 43 patients (32%) had negative lymph nodes on physical and ultrasound examination of the axilla after induction chemotherapy (see Table 3). The concordance rate between physical and ultrasound examination of the axilla decreased significantly following induction chemotherapy ($P < .001$). The results of physical and ultrasound examination of the axilla performed after induction chemotherapy and before surgery were concordant in 93 patients (63%) and discordant in 54 patients (37%; see Table 3). The presence of axillary metastases was not confirmed cytologically by FNA following induction chemotherapy.

Pathological Axillary Assessment

One hundred three patients (70%) had positive axillary lymph nodes on histologic examination of the axillary contents (see Table 3). The distribution of those patients with respect to the number of positive lymph nodes found at axillary dissection was 49 patients (47%) with one to three positive lymph nodes, 38 patients (37%) with four to ten positive lymph nodes, and 16 patients (16%) with more than ten positive lymph nodes (see Table 3). In 45 patients (31%) the results of axillary assessment by physical or ultrasound examination, or both, before surgery were incorrect compared with the results of histologic examination. More specifically, of the 55 patients in whom the axilla was assessed as negative by both physical and ultrasound examination, 29 patients (53%) had positive lymph nodes on pathologic examination, with ten of them having more than four involved lymph nodes (see Table 3). Of the ten patients with more than four involved lymph nodes, nine (90%) had lymph nodes with only micrometastases between 2 and 5 mm in diameter on histologic measurement. One patient (10%) with more than four positive lymph nodes had a 1.2-cm focus of residual axillary disease.

The accuracy of clinical evaluation compared with histologic examination was highest when the results of both physical and ultrasound examination were positive before surgery. Ninety-five percent of patients in whom the results of both physical and ultrasound examination were positive were correctly determined to have axillary metastases on histologic examination (see Table 3). The sensitivity of ultrasound in identifying axillary metastases was significantly better than that of physical examination ($P = .012$, 62% vs. 45%, Table 4). The specificities of physical examination (84%) and ultrasound examination (70%) were not significantly different (see Table 4). Overall, physical and ultrasound examination had positive predictive values of 87% and 83%, respectively, for identification of axillary metastases (see Table 4). The corresponding negative predictive values of physical examination were 39% and 44%. The positive and negative predictive values did not differ significantly between the two modes of examination. With a median follow-up of 35 months, 36 patients (35%) with positive lymph nodes have either died of disease or have developed distant metastases, compared with only seven patients (16%) who had negative lymph nodes on pathologic examination ($P = .015$).

DISCUSSION

The results of our study suggest that in many patients induction chemotherapy can completely clear the axilla

TABLE 3. *Axillary tumor downstaging: assessment by initial physical and ultrasound examination before and after four cycles of induction chemotherapy compared with the findings at surgical staging*

Findings on physical and ultrasound examination			Findings on pathologic examination of surgical specimen				
Finding	Patient distribution		Lymph nodes				
					Number nodes positive (N)		
Physical examination/ ultrasound	Initial No. (%)	After induction chemotherapy No. (%)	Negative No. (%)	Positive No. (%)	1–3	4–10	>10
–PE/–US	14 (10)	55 (37)	26 (47)	29 (53)	19	7	3
–PE/+US	5 (3)	39 (27)	11 (28)	28 (72)	14	10	4
+PE/–US	10 (7)	15 (10)	5 (33)	10 (67)	6	3	1
+PE/+US	118 (80)	38 (26)	2 (5)	36 (95)	10	18	8

PE, physical examination; US, ultrasound.

of microscopic axillary metastases as assessed by standard histologic lymph node examination. Of the 133 patients with axillary disease on initial examination, 43 patients (32%) were downstaged to a negative axilla as assessed by physical and ultrasound evaluation following induction chemotherapy. A pathologic complete axillary lymph node response was found in 30 patients (23%). Of the 72 patients with cytologically proven axillary metastases on initial evaluation, 15 patients (21%) were confirmed to have histologically negative axillary lymph nodes following induction chemotherapy. Although disappearance of cytologically proven axillary metastases following induction chemotherapy has not previously been reported, both McCready et al.[9] and Schwartz et al.[11] have reported conversion of clinically involved axillary disease to pathologically negative lymph node status in about 25% of patients following induction chemotherapy. In comparison to a group of women with less advanced disease at presentation, 71 of 185 patients (38%) in the induction chemotherapy arm of the National Surgical Adjuvant Breast and Bowel Project (NASBP) B-18 trial with initial clinical N1 axillary disease were found to have negative axillary lymph nodes on histologic examination following induction chemotherapy.[12]

Physical examination of the axilla has long been reported to be inaccurate in predicting lymph node metastases in breast cancer patients.[21] The presence of lymph node metastases remains the most accurate prognostic indicator in breast cancer. Over the last decade, the use of axillary ultrasonography in the preoperative assessment of breast cancer patients has been developed because of the desire to increase the accuracy of clinical staging.[22] At our institution, the size of the largest lymph node visualized on preoperative axillary ultrasonography has been shown to correlate well with the size of the largest lymph node found on pathologic examination.[23] If preoperative axillary staging were completely accurate, axillary dissection and the potential morbidity associated with it could be eliminated in a large proportion of breast cancer patients. The sensitivity of physical examination of the axilla has been reported to be between 32% and 68%, and the sensitivity of axillary ultrasonography has been reported to range from 56% to 73% in the detection of axillary metastases.[22,24–26] This is comparable to the results of the present study, which found a sensitivity of 42% for physical examination and 62% for axillary ultrasonography. The specificity of physical examination was higher (84%) than that of ultrasonography (70%) in correct identification of axillary metastases in our study, but this difference did not reach statistical significance. Recently, Bonnema et al. reported that both sensitivity and specificity can be increased to 80% to 100% in preoperative detection of axillary metastases by combining fine-needle aspiration biopsy with axillary ultrasonography.[27] We believe that the accuracy of ultrasonography in detecting axillary metastases in patients with LABC receiving induction chemotherapy could also be markedly improved with the concurrent use of fine-needle aspiration biopsy, although this conclusion can only be confirmed with a prospective randomized trial.

It is interesting that the concordance rate between physical and ultrasound examination of the axilla was 90% on initial evaluation but fell to 63% following induction chemotherapy. This finding is consistent with statistical theory that relates prevalence rates to the predictive value of any given clinical test.[20] The more uncommon a given abnormality becomes in a population at

TABLE 4. *Accuracy of physical examination and ultrasound evaluation of axillary lymph node metastases in breast cancer patients after induction chemotherapy*

	Physical examination	Ultrasonography	*P* value
Sensitivity (95% CI)	45% (35%–55%)	62% (52%–72%)	.012
Specificity (95% CI)	84% (70%–93%)	70% (55%–83%)	.127
Positive predictive value (95% CI)	87% (75%–95%)	83% (73%–91%)	.568
Negative predictive value (95% CI)	39% (29%–50%)	44% (32%–57%)	.527

risk, the less accurately a positive test result indicates an abnormality. This is the case with axillary tumor downstaging achieved with induction chemotherapy. In our study, the overall negative predictive values of physical and ultrasound examination of the axilla were only 39% and 44%, respectively.

Fifty-five patients were deemed to have a negative axilla by physical and ultrasound examination before surgery. Positive lymph nodes on histologic examination were found in 29 patients (53%). Nineteen of these patients (66%) had only one to three positive lymph nodes, and in nine of the patients (90%) with more than four positive lymph nodes, only micrometastases were present. Data from the NSABP-B04 trial, in which patients were randomly assigned to radical mastectomy or total mastectomy with or without axillary radiation, suggests that axillary irradiation in these patients might be effective in controlling residual microscopic disease in the 19 patients with less than three involved lymph nodes.[28] However, the patient population in the current analysis presented with disease of a much more advanced stage compared with patients analyzed in the NSABP-B04 trial. Whether complete elimination of microscopic disease with the use of axillary radiation and additional systemic chemotherapy is possible in the ten patients with more than four involved nodes treated in this manner is not known.

The rate of axillary recurrence in clinically node-negative stage I and II breast cancer patients who receive axillary nodal irradiation without axillary dissection has been reported to be between 1% and 3%.[29–32] The Early Breast Cancer Trialists' overview analysis of randomized trials comparing axillary surgical clearance versus radiotherapy found no difference in total mortality between groups regardless of the type of axillary treatment.[32] It is unclear whether the excellent results obtained in patients with earlier-stage breast cancer treated with axillary irradiation alone can be achieved in patients with LABC downstaged to similar disease with neoadjuvant chemotherapy. On the other hand, some LABC series have reported equivalent axillary control rates after induction chemotherapy followed by axillary dissection alone, axillary irradiation alone, or a combination of both treatment modalities.[8, 13,14] It is generally agreed that some form of treatment to the axilla should be offered to patients with LABC treated with induction chemotherapy. However, there is currently no evidence that suggests superiority of surgical clearance alone, axillary radiation alone, or a combination of both treatment modalities in this group of patients found to have a clinical negative axilla following induction chemotherapy.

With the prospect of reducing the need for axillary dissection, novel and alternative techniques have been developed to assess the axilla in breast cancer patients. Investigators at the Princess Margaret Hospital have studied axillary lymphoscintigraphy using a subcutaneously injected technetium colloid to determine the presence of metastases.[33] They found that the sensitivity and specificity of lymphoscintigraphy in predicting axillary involvement at subsequent surgery were 76% and 67%, respectively. The detection of axillary lymph node metastases using radiolabeled monoclonal anti–human breast cancer antibodies has also been investigated.[34] When this method was used in 40 patients, the overall sensitivity was 33%, and the specificity was 62%. Positron emission tomography (PET) also has been analyzed recently in the preoperative detection of axillary metastases.[35] Although the negative predictive value of this technique was reported to be 84%, this value was not significantly different from the negative predictive value of 70% of physical examination in their patient population. The evolving role of sentinel lymph node biopsy in breast cancer management may facilitate the transition from full axillary dissection for all LABC patients treated with induction chemotherapy to complete omission of axillary dissection in many of these patients.[36,37] However, sentinel lymph node biopsy in patients treated with induction chemotherapy will prove accurate only if metastatic deposits within each axillary lymph node respond identically to the effect of chemotherapy. Sentinel lymph node biopsy in patients with LABC treated with induction chemotherapy has not been studied. Currently, axillary ultrasonography, lymphoscintigraphy, monoclonal antibody technology, and, presumably, sentinel lymph node biopsy in patients treated with primary chemotherapy are not yet completely accurate in predicting breast cancer lymph node metastases.

In summary, 32% of patients in this study had downstaging of axillary lymph node metastases as assessed by physical and ultrasound examination following four cycles of induction chemotherapy with FAC. The sensitivity of axillary ultrasonography (62%) in identifying axillary metastases was significantly higher than that of physical examination (45%). The specificity of physical examination (84%) was higher than that of ultrasonography (70%), but the difference did not reach statistical significance. When both physical and ultrasound examination of the axilla were negative following induction chemotherapy, axillary lymph node metastases were still found in 53% of patients. However, 28 of these patients (97%) had either only 1 to 3 positive lymph nodes or micrometastases between 2 and 5 mm in diameter. Because all of these patients will routinely receive

radiation treatment and additional anthracycline-based systemic chemotherapy, we feel that they are the most acceptable potential candidates for omission of axillary dissection. Patients who have preoperative positive findings on physical or ultrasound examinations, or both, should continue to receive axillary dissection to ensure local control. We have begun to enroll patients with less advanced breast cancer treated with induction chemotherapy in a prospective randomized trial of axillary dissection versus axillary radiotherapy in patients whose disease has been clinically downstaged to T0-2, N0 in an effort to better gauge the necessity of axillary dissection. Taken together with the results of this present study, the data generated from our prospective study of patients with less advanced breast cancer may provide a rationale for a randomized trial to study the omission of axillary dissection in selected patients with LABC.

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