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A comparison of sentinel node biopsy before and after neoadjuvant chemotherapy: timing is important

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Abstract

Background: Because neoadjuvant chemotherapy is being used more frequently, the optimal timing of sentinel node biopsy (SNB) remains controversial. We previously evaluated the predictive value of SNB before neoadjuvant chemotherapy in clinically node-negative breast cancer. Our identification rate of the sentinel node among 52 patients before chemotherapy with a mean tumor size of 4 cm was 100%. In this study, we compared the identification rates of SNB before and after neoadjuvant chemotherapy and evaluated the false-negative rate of SNB after chemotherapy.

Methods: A retrospective institutional database review identified 36 women who underwent SNB after neoadjuvant chemotherapy for breast cancer from 1999 to 2004. The initial clinical tumor size and lymph node status, SNB pathology, axillary lymph node dissection pathology, and residual pathologic tumor size were reviewed.

Results: Sixteen of 36 patients had a clinically negative axilla before neoadjuvant therapy. SNB after neoadjuvant therapy was successful in 29 patients (80.6%), although 7 patients did not map (19.4%). Six of the 7 patients who failed to map had a clinically positive axilla initially. Axillary disease was found in 6 of 7 of these patients at dissection (85.7%). Of the 29 patients who mapped successfully, 13 (45%) were SNB negative, and 16 (55%) were SNB positive. Of the 13 SNB-negative patients, 2 had a positive axillary lymph node dissection, yielding a false-negative rate of 11%. Thirteen patients who mapped had a clinically positive axilla before therapy (45%). Of the 11 patients with true-negative SNBs, 7 (64%) were clinically node negative at presentation. The initial tumor sizes on examination ranged from 2 to 9 cm (mean, 5.0 cm), and residual pathologic tumor sizes ranged from 0 to 6 cm (mean, 1.8 cm). Failure to map correlated with a clinically positive axilla at presentation (100% vs 45%) but did not correlate with initial tumor size.

Conclusions: Sentinel node identification rates are significantly better when mapping is performed before neoadjuvant chemotherapy (100% vs 80.6%), with failure to map correlated with clinically positive nodal disease at presentation and residual disease at axillary lymph node dissection. Among patients who map successfully after chemotherapy, the false-negative rate is high (11%). Given these findings, we currently recommend SNB before neoadjuvant chemotherapy for clinically node-negative patients, and raise concerns about the use of SNB after neoadjuvant therapy in patients with an initially clinically positive axilla.

Keywords: Breast cancer; Sentinel lymph node biopsy; Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is being used with increasing frequency for the treatment of breast cancer, beyond its initial indications for locally advanced disease. Treatment with chemotherapy before surgery permits the observation of clinical and molecular responses to treatment, providing prognostic information [1] and a valuable tool in the development of new therapies. Neoadjuvant chemotherapy also is used increasingly to downstage tumors that, although not locally advanced, otherwise would require a mastectomy [2–7]. Thus, an increasing number of clinically node-negative patients are candidates for neoadjuvant therapy.

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Table 1
Sentinel lymph node mapping success: preneoadjuvant versus postneoadjuvant therapy

	Sentinel node mapping	
	Success	Failure
SNB preneoadjuvant cN0 (n = 52)	52 (100%)	0
SNB postneoadjuvant cN0 (n = 17)	16 (94%)	1 (6%)
SNB postneoadjuvant cN1 (n = 19)	13 (68%)	6 (32%)

The appropriate use and optimal timing of sentinel node biopsy (SNB) in the setting of neoadjuvant chemotherapy remains controversial. In clinically node-negative patients, an SNB before neoadjuvant chemotherapy allows accurate nodal staging, avoiding the possibility of lymphatic scarring or uneven tumor response in the axillary nodes. On the other hand, clinically node-positive patients may have a significant rate of axillary clearance after chemotherapy [8], and staging after chemotherapy may provide those patients who become clinically node negative (N0) with options for less-invasive axillary therapy.

We previously showed a 100% identification rate when SNB was performed before neoadjuvant chemotherapy in clinically node-negative patients [9]. We sought to evaluate our experience with SNB after neoadjuvant chemotherapy and to compare it with our findings when performed before chemotherapy.

Methods

An institutional review board–approved retrospective study identified 36 women treated with neoadjuvant chemotherapy who subsequently underwent an SNB and completion axillary dissection at the time of definitive surgery between 1999 and 2003. All patients were treated on 1 of 2 neoadjuvant protocols, and received either sequential single-agent doxycycline (4 cycles, q 2 weeks) and paclitaxel (weekly for 9 cycles), or 12 weeks of trastuzumab (weekly) and paclitaxel (q 3 weeks), followed by adjuvant doxycycline and cyclophosphamide (4 cycles). All patients received adjuvant radiation.

For SNBs performed before neoadjuvant chemotherapy, data were obtained in an institutional review board–approved retrospective review of patients receiving neoadjuvant chemotherapy during the same time period [9]. In this setting, patients with negative sentinel nodes did not undergo a completion axillary dissection unless they progressed during chemotherapy (1 patient). Patients with a positive sentinel node were dissected at the discretion of the treating physician.

Sentinel node mapping techniques were chosen according to surgeon preference. Histologic evaluation of the sentinel nodes differed by institution. All patients had hematoxylin and eosin evaluation of 3 levels of the sentinel node. At Massachusetts General Hospital, immunohistochemical staining was performed if the hematoxylin and eosin stains were negative. Three cytokeratin sections per block were evaluated at approximately 200-μm intervals. Immunohistochemistry was not performed at Brigham and Women's Hospital.

Results

Sentinel node after neoadjuvant chemotherapy

Thirty-six women with T2–4, N0-1 invasive breast cancer underwent an SNB at the time of definitive surgery after neoadjuvant chemotherapy (without any prior axillary surgery). Nineteen patients (53%) had clinically involved axillary nodes at presentation. Eight of these patients had nodal involvement confirmed by fine-needle aspiration cytology before neoadjuvant chemotherapy. Overall, 86% of patients responded to neoadjuvant chemotherapy: 33% had a clinical complete response, 53% had a clinical partial response. Eight percent of patients had stable disease (6% unknown). The pathologic complete response rate was 16.7% (including patients with residual ductal carcinoma in situ only).

SNB was successful in 29 patients (81%) (Table 1). Mapping failed to identify a sentinel node in 7 patients (19%). All of these 7 patients had mapping with both technetium and blue dye. Six of the 7 patients who failed to map had a clinically positive axilla initially, and 6 of the 7 patients had residual disease at axillary dissection (Table 2). Among the 29 patients who were mapped successfully, 16 (55%) were SNB positive, and 13 (45%) were SNB negative. Two patients with a negative SNB had residual axillary disease, for a false-negative rate of 11% (2 of 18). Immunohistochemistry was used in only 7 patients (24%); it was not used for the 2 patients with false-negative sentinel nodes.

Among 19 patients with a clinically positive axilla before therapy, 13 mapped successfully. Seven patients had a positive sentinel node, and all of these 7 patients had additional axillary disease at dissection. Six patients had a negative sentinel node. Five of these patients had no additional disease (true negatives); 1 patient had 5 positive axillary nodes, all containing macrometastatic tumor foci (false negative).

Table 2
SNB examination and axillary pathology after neoadjuvant chemotherapy by clinical lymph node status

	cN0 (n = 17)		cN1 (N = 19)	
	ALND−	ALND+	ALND−	ALND+
SNB negative	6	1	5	1
SNB positive	6	3	0	7
SNB failed	0	1	1	5

ALND = axillary lymph node dissection.

The false-negative rate among patients with palpable nodes at presentation was 13% (1 of 8). Of the 6 patients in whom mapping failed to identify a sentinel node, 5 had positive nodes at axillary dissection.

Seventeen patients had clinically negative nodes at presentation, and sentinel nodes were identified in 16 patients. Seven patients had negative sentinel nodes; in 1 of these patients additional axillary disease was identified at dissection (false negative). The volume of disease in the patient with the false-negative sentinel node was quite small: 1 of 11 nodes contained a micrometastatic focus of tumor. Nine patients had positive sentinel nodes, and 3 of these patients had additional axillary disease, all with at least 1 focus of tumor greater than .2 cm. The false-negative rate among this group of clinically node-negative patients was 10% (1 of 10).

After neoadjuvant therapy, 26% of patients with initially palpable nodes had pathologically negative axillae. Among the 8 patients whose initial nodal involvement was confirmed with fine-needle aspiration before neoadjuvant therapy, 2 had complete axillary sterilization and no residual axillary disease at surgery (25%).

Sentinel node before neoadjuvant chemotherapy

Fifty-two women with T2–T4, N0 invasive breast cancer underwent an SNB before neoadjuvant chemotherapy [9]. SNB was successful in all 52 patients (Table 1). Twenty-two patients (42%) had a negative sentinel node. Only 1 patient with a negative sentinel node who progressed during chemotherapy had an axillary dissection, showing 8 of 18 positive nodes. Thirty patients (58%) had a positive SNB.

Among patients who had an SNB after chemotherapy, with a mean follow-up period of 46 months, there have been no local recurrences. All patients had a completion axillary dissection. Six patients have developed distant disease (17%), and there have been 3 deaths. Among those who had the sentinel node preceding chemotherapy, with an average follow-up of 10.7 months, there have been no local recurrences.

Comments

Sentinel node identification rates are significantly better when mapping is performed before neoadjuvant chemotherapy in clinically node-negative patients (100%) than after chemotherapy in a group of patients who were either clinically N0 or N1 at presentation (81%). Failure to map after chemotherapy is correlated with clinically positive nodal disease at presentation and residual disease at axillary lymph node dissection. Among patients who map successfully, the false-negative rate is high (11%). Interestingly, false-negative sentinel nodes occurred in patients with both initially clinically positive and initially clinically negative axillae. Thus, clinically positive nodal status before neoadjuvant chemotherapy is not the only cause of false-negative results in these patients.

Previous studies evaluating SNB after neoadjuvant chemotherapy have shown wide variability in identification and false-negative rates. The largest series to date consists of patients enrolled in National Surgical Adjuvant Breast and Bowel Project B-27, in which 428 patients received neoadjuvant chemotherapy followed by SNB and completion dissection [10]. In this multicenter trial, the identification rate was 85%, with a false-negative rate of 11%. Lang et al [11] recently evaluated the accuracy of SNB after neoadjuvant chemotherapy based on clinical nodal status at presentation. They reported decreased sensitivity and accuracy in SNBs performed after chemotherapy in patients with clinically palpable nodal disease at presentation, compared with patients who were clinically N0. They identified a sentinel node in 91% of clinically N1 patients, with a false-negative rate of 9%, versus an identification rate of 97% and a 0% false-negative rate in N0 patients. Our false-negative rate is remarkably similar to that in both of these trials, and quite a bit higher than the 5% acceptable rate published by the Consensus Conference on the Role of Sentinel Lymph Node Biopsy in Carcinoma of the Breast in 2002 [12].

The reasons for an increased false-negative rate after neoadjuvant chemotherapy are unclear. It may relate to either lymphatic occlusion with tumor emboli or lymphatic scarring caused by chemotherapy, with the subsequent creation of new drainage patterns. It also may be caused by an uneven effect of chemotherapy in patients with multiple positive nodes, so that the sentinel node is sterilized but residual disease persists in nonsentinel nodes. It is interesting that neither of the falsely negative sentinel nodes was processed with immunohistochemical techniques.

Given these findings, we currently recommend SNB before neoadjuvant chemotherapy for patients clinically node-negative at presentation. Our mapping success rate is 100%, with no axillary recurrences in short-term follow-up evaluation of patients who received no further axillary therapy for a negative sentinel node. In addition, accurate axillary staging allows potential optimization of chemotherapy regimens and appropriate planning of radiation therapy. For patients needing mastectomy, the knowledge of nodal status and the need for chest wall radiation may aid in reconstruction decisions. We currently recommend that completion dissection for a positive sentinel node be performed at the time of definitive surgery after neoadjuvant chemotherapy. From a practical standpoint, this avoids delays either in waiting for a frozen section for a patient having an SNB alone, or in bringing the patient back another day. Even more importantly, however, residual axillary disease after neoadjuvant chemotherapy is of significant prognostic value and may guide the use of additional adjuvant therapies [1].

Among patients presenting with palpable axillary nodes, the false-negative rates of SNB after neoadjuvant chemotherapy (13% in our series) may be too high to forego further axillary therapy at this time. It may be reasonable to

consider axillary radiation rather than dissection as a less morbid alternative for those patients initially clinically node positive whose sentinel node is negative after neoadjuvant chemotherapy. This would help avoid overtreatment in the form of more morbid surgery for the patients who have little or no axillary disease after neoadjuvant therapy. For those clinically node-negative patients who do not have a sentinel node before neoadjuvant therapy, we generally recommend an axillary dissection, although axillary radiation after a negative SNB may be considered in these patients as well. Ultimately, we hope to be able to identify reliably the patients whose axillae are sterilized during neoadjuvant chemotherapy, and forego an axillary dissection in these patients.

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