

## Axillary Staging in the Neoadjuvant Setting

Alice Chung, MD and Armando Giuliano, MD

Department of Surgical Oncology, John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA

**ABSTRACT** Neoadjuvant chemotherapy (NAC) is increasingly being used in the treatment of locally advanced breast cancer as well as for early breast cancer. Axillary lymph node dissection has been the standard method of staging the axilla in the neoadjuvant setting. Since the sentinel lymph node biopsy was introduced in the early 1990s, less invasive approaches to axillary staging in patients undergoing neoadjuvant therapy have been proposed. In this review, we discuss the effects of NAC, the imaging modalities that have been used to evaluate the axillary lymph nodes, and the role and timing of sentinel lymph node biopsy in the neoadjuvant setting. Finally, we propose a treatment algorithm for patients undergoing NAC on the basis of the current data.

Neoadjuvant chemotherapy (NAC) was first introduced in patients with locally advanced or inflammatory breast cancer with the intention of transforming inoperable tumors into operable tumors. It is increasingly being offered to patients with early-stage breast cancer to improve their candidacy for breast conservation therapy. Current recommendations state that any patient who is expected to undergo postoperative chemotherapy may be eligible for preoperative chemotherapy.<sup>1</sup>

Axillary lymph node status remains one of the most important prognostic factors in breast cancer. Axillary lymph node dissection (ALND) has traditionally been the standard of care for staging patients undergoing NAC. With the advent of sentinel lymph node biopsy (SNB) and increased use of neoadjuvant therapy for early breast cancer, staging the axilla with ALND in the neoadjuvant setting has been challenged.

In this review, we present the issues surrounding axillary staging in patients undergoing NAC, discuss the various modalities available to evaluate the axillary lymph nodes, and propose a treatment algorithm on the basis of the current data.

### EFFECTS OF NAC

Our current understanding of the effects of NAC on breast cancer comes from a number of randomized NAC trials for patients with locally advanced breast tumors. In the earlier studies, patients were eligible for NAC if they presented with tumors >3 cm in size, clinically positive axillary lymph nodes, or inflammatory breast cancer. In these trials, preoperative chemotherapy was followed by surgical resection of the breast tumor and ALND. Primary end points included complete clinical response (cCR) and complete pathologic response (pCR) in the breast and axilla, and disease-free and overall survival. Clinical tumor response was defined as complete if there was no clinical evidence of palpable tumor in the breast and axillary lymph nodes at the time of surgery. The definition of pCR varied among studies, ranging from no or minimal residual cancer in the breast or axillary lymph nodes to ductal carcinoma-in situ only to no residual disease in the tumor but residual disease in the lymph nodes. From these studies, we have learned that the axillary lymph nodes are downstaged with NAC (Table 1).

The largest of the trials is the National Surgical Adjuvant Breast and Bowel Project (NSABP-B18) trial, which randomized >1500 women with operable breast cancer to four cycles of doxorubicin and cyclophosphamide either pre- or postoperatively.<sup>2</sup> Of these women, 185 had suspicious axillary lymph nodes at clinical examination. After NAC, 135 (73%) had a cCR in the axilla, and 29 (16%) had a partial clinical response. Patients with a cCR had a greater pCR and a greater decrease in positive nodes than those with partial clinical response. Overall, 59% of patients treated with NAC had no evidence of nodal metastases, whereas 43% of the patients treated with

**TABLE 1** Clinical trials of NAC demonstrating that the axillae are downstaged by NAC

Study	Patients	Axillary pCR
Milan (1998) <sup>53</sup>	536	13 (2%)
NSABP-B18 (1997) <sup>2</sup>	187	13 (7%)
MDA (1999) <sup>4</sup>	191	39 (20%)
NSABP-B27 (2003) <sup>3</sup>	350	39 (11%)

NAC neoadjuvant chemotherapy, NSABP National Surgical Adjuvant Breast and Bowel Project, MDA University of Texas M. D. Anderson Cancer Center, pCR complete pathologic response

postoperative chemotherapy were pathologically node negative ( $P < 0.001$ ). Thirty-six percent of the patients who received NAC and were judged before randomization to be clinically node positive were found to be pathologically node negative compared to 14% of those treated with postoperative chemotherapy ( $P < 0.001$ ).

The NSABP-B27 trial compared preoperative doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan) (AC) with preoperative AC plus docetaxel and preoperative AC plus postoperative docetaxel in 2411 women.<sup>3</sup> In this trial, 15.5% of patients with a pCR in the breast had tumor-involved nodes by histopathology; 35.4% of those with a complete clinical response in the breast had tumor-involved nodes. The authors concluded that nodal status correlated with pathologic response of the breast to NAC in all groups combined. Similar findings were reported by Kuerer and colleagues, who studied 191 patients with cytologically involved axillary lymph nodes in two prospective trials of NAC with 5-fluorouracil, doxorubicin, and cyclophosphamide.<sup>4</sup> They compared tumor characteristics in patients with a complete axillary response to those with partial axillary response and found that axillary pCR was more likely to occur in patients with smaller tumors and less advanced initial tumor stage. Furthermore, patients with a complete axillary response were more likely to have a pCR in the breast tumor than patients with an incomplete response in the axilla (59% vs. 6%,  $P < 0.001$ ). However, 41% of patients with a pCR in the breast still had positive axillary lymph nodes, indicating that nodal metastases may be more resistant to NAC than the primary breast tumor. Clearly NAC results in downstaging; however, the efficacy of treatment on axillary lymph node metastases may be lower than on the primary tumor.

### DOES THE POST-NAC STAGE REFLECT PROGNOSIS?

The American Joint Committee on Cancer (AJCC) staging system has incorporated a designation for post-treatment staging to acknowledge that patients have undergone NAC, radiotherapy, or both, indicated by the

prefix “y.” This designation indicates the extent of the tumor actually present at the time of that examination, rather than an estimate of tumor size before initiation of neoadjuvant therapy.<sup>5</sup> Several investigations provide evidence that the posttreatment stage accurately reflects the patient’s prognosis.

Carey and colleagues assessed the pathologic stage of residual tumor in 132 patients who underwent NAC followed by surgical resection.<sup>6</sup> At a median follow-up of 5 years, the pathologic stage in the surgical specimens after NAC according to the revised AJCC tumor, node, metastasis system was strongly associated with distant disease-free and overall survival. Patients with a complete pathologic response had a 5-year distant disease-free survival of 95%. Those whose residual tumors were stage I had a distant disease-free survival of 84%; those whose residual tumors were stage IIA, IIB, and IIIA had distant disease-free survival rates of 75%, 65%, and 68%, respectively. Those with residual tumors that were stage IIIC had distant disease-free survival of 18%. The differences in distant disease-free and overall survival were significant across all pathologic stages ( $P < 0.001$ ). Cox regression analysis found that posttreatment stage in this group of patients may be more closely associated with the number of involved lymph nodes than with the extent of residual tumor in the breast.

Kuerer et al. examined the disease-free and overall survival of 372 patients who underwent four cycles of preoperative doxorubicin-containing chemotherapy, followed by surgical resection, followed by postoperative chemotherapy and radiotherapy.<sup>7</sup> Median follow-up was 58 months (range, 8–99 months). They found that the 5-year overall and disease-free survival rates were far higher in the group that had a pathologic complete response than in the group that had less than a pathologic complete response (89%, 87%, respectively, vs. 64%, 58%, respectively). The authors concluded that pathologic response to NAC may serve as a marker for breast cancer relapse and survival.

In summary, complete clinical response does not always translate into complete pathologic response. Response in the primary tumor may be greater than the response in the axillary lymph nodes. Finally, response to NAC reflects prognosis.

### PREOPERATIVE AXILLARY STAGING

Since the advent of SNB, the question arises whether ALND is required in patients whose axillae are downstaged with NAC. Furthermore, with increasing use of NAC in clinically node-negative patients, patients are eligible for SNB as a means of staging the axillary lymph nodes. In

**TABLE 2** Studies comparing clinical axillary examination to final histopathology

Study	Patients	PPV (%)	NPV (%)	Accuracy (%)
Cutler (1970) <sup>54</sup>	1210	65	58	65
Fisher (1981) <sup>55</sup>	641	73	61	66
Sacre (1986) <sup>56</sup>	196	78	55	61
de Freitas (1991) <sup>57</sup>	115	82	50	68
Vaidya (1996) <sup>58</sup>	200	76	58	66

PPV positive predictive value, NPV negative predictive value

such cases, preoperative assessment of the axillary lymph nodes by physical examination and imaging becomes important to screen patients for SNB versus ALND. If patients can be identified as candidates for SNB before surgical intervention, they could potentially be spared the morbidity of an unnecessary ALND.

Preoperative axillary staging in the earlier randomized NAC trials was achieved by physical examination. Before the introduction of neoadjuvant therapy, a number of authors examined the accuracy of clinical axillary examination relative to the final pathology (Table 2). The positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of physical examination ranged from 65% to 82%, 50% to 61%, and 61% to 68%, respectively, demonstrating that axillary staging by physical examination alone is unreliable. Since this time period, a number of modalities have been investigated for their potential efficacy in the preoperative assessment of the axillary lymph nodes.

Vassallo and colleagues examined the use of in vivo ultrasound (US) to detect metastases in lymph nodes.<sup>8</sup> The most common sonographic signs of metastatic involvement included lymph node enlargement, variation in shape, and loss of the hyperechoic hilum. Feu et al. studied the US characteristics of 158 excised axillary lymph nodes of 40 patients surgically treated for breast cancer.<sup>9</sup> In their study, absence of the hilum was the most specific sonographic feature for detecting metastases.

Klauber-Demore et al. looked at the ability of high-resolution axillary US to predict pathologic lymph node status specifically in patients with locally advanced breast tumors undergoing NAC.<sup>10</sup> In this study, 53 patients underwent physical examination and axillary US after NAC before surgical excision. A lymph node was defined as suspicious if there was asymmetry of the cortex, heterogeneity of the hilum, or loss or displacement of the normal fatty hilum of the lymph node. All patients had ALND followed by pathologic analysis with standard hematoxylin and eosin staining. Any metastasis identified by hematoxylin and eosin staining was considered positive; metastases detected by immunohistochemical staining only were considered negative. They found that the PPV of postchemotherapy axillary US compared to physical examination was 83% vs. 93%, and the NPV was 52% compared to 58%. These findings were similar to those of parallel studies as shown in Table 3.<sup>11-13</sup>

Krishnamurthy and colleagues studied the accuracy of US-guided fine-needle aspiration (FNA) for indeterminate and suspicious axillary lymph nodes in the initial staging of breast cancer.<sup>14</sup> They compared the cytology of 103 cases of US-guided FNA with the final histopathologic status of the entire axilla after ALND. The PPV, NPV, and diagnostic accuracy were 100%, 67%, and 79%, respectively. Of note, 65 (63%) of 103 received NAC before assessment by US-guided FNA. All cases with three or more positive lymph nodes and 93% of those with metastatic deposits measuring >0.5 cm in size were detected by US-guided FNA. The probability of detecting lymph nodes with metastatic deposits of <0.5 cm was 44%. Alkuwari and Auger examined the accuracy of US-guided FNA in 115 axillary lymph nodes which were subsequently removed by either SNB or ALND.<sup>15</sup> They found that the sensitivity of US-guided FNA was highly dependent on the size of the metastatic deposit. When the metastatic deposit was <0.25 mm, the sensitivity was 16%; if the metastasis was  $\geq 1.5$  cm, the sensitivity increased to 88%. Bonnema et al. conducted US-guided FNA in 148 breast cancer patients with nonpalpable axillary lymph nodes at physical examination.<sup>16</sup> The sensitivity and specificity were 36 and 95%,

**TABLE 3** Axillary ultrasound compared to final histopathology of axillary lymph node dissection

Study	Patients	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
Kuerer (1998) <sup>13</sup>	147	83	44	62	70
Vlastos (2000) <sup>12</sup>	172	67	49	51	65
Oruwari (2002) <sup>11*</sup>	26	—	—	100	100
Klauber-Demore (2004) <sup>10</sup>	53	83	52	59	79
Alkuwari (2008) <sup>15*</sup>	153	100	60	65	100

PPV positive predictive value, NPV negative predictive value

\* With fine-needle aspiration

respectively, but when metastatic size of  $>5$  mm was used to define a pathologically positive lymph node, the sensitivity increased to 87% with a decrease in specificity to 56%.

Koelliker et al. studied US-guided axillary FNA in 75 patients with primary tumor sizes ranging from 0.3 to 12 cm.<sup>17</sup> They found that the sensitivity of this procedure increased as the size of the primary tumor increased. For T1 tumors, the sensitivity was 56%; for T2 tumors, the sensitivity was 64%; T3 tumors, 82%; and T4 tumors, 100%. de Kanter conducted a multicenter study of US-guided FNA in 185 clinically node-negative breast cancer patients.<sup>18</sup> No lymph nodes were identified by US in 116 patients, but 85 had metastatic involvement on definitive histological examination; there were no false-positive cases. The authors attributed failure of the examination to problems learning the procedure, difficulty in puncturing small lymph nodes, and sampling error. They concluded that this procedure was most valuable in patients with larger breast cancers.

Most of the studies of axillary US and FNA have not specified histologic type of the primary tumor. Boughey and colleagues investigated the use of US-guided FNA in 80 patients with invasive lobular carcinoma (ILC) and indeterminate or suspicious findings on axillary US.<sup>19</sup> The overall sensitivity and specificity were 39% and 96%, respectively, suggesting that this procedure has similar utility in patients with ILC compared to those with invasive ductal carcinoma. As demonstrated in other studies, the authors found that sensitivity in ILC cases also correlated with the size of the metastatic deposit and primary tumor size.

On the basis of these studies, US with FNA cytology is better than US alone and physical examination in evaluating the axilla. The specificity is high, and false-positive cases are rare. Furthermore, although a cytologically positive lymph node accurately determines axillary lymph node status, a cytologically negative lymph node does not.

The use of other imaging modalities in the preoperative staging of the axilla has been explored. Kvistad and colleagues performed preoperative magnetic resonance imaging (MRI) of the axilla in 65 patients with invasive breast carcinoma who underwent subsequent ALND.<sup>20</sup> They found that MRI identified axillary lymph node metastases with a sensitivity, specificity, and accuracy of 83%, 90%, and 88%, respectively. The threshold for malignancy in this series required that the signal intensity increase in the lymph nodes was  $>100\%$  during the first postcontrast image. The use of lymph node size and morphology did not improve their results. Luciani et al. investigated the use of combined bilateral breast MRI and high-resolution MRI of the axilla in 16 patients undergoing lymphadenectomy.<sup>21</sup> This enabled one MRI of the breast

and axilla to be performed rather than performing a separate MRI of the axilla. The most important features suggestive of malignancy included the presence of nodes with irregular borders, high signal intensity on T2-weighted images, marked gadolinium enhancement, and round hila with abnormal cortices. On the basis of these criteria, the false-positive rate was 12% and the false-negative (FN) rate was 13%. Memarsadeghi et al. compared preoperative noncontrast MRI to MRI by means of a lymph node-specific magnetic resonance contrast agent known as ultrasmall superparamagnetic iron oxide (USPIO) in 22 patients undergoing ALND.<sup>22</sup> They were able to obtain a correlation between the magnetic resonance finding and histopathology in 133 lymph nodes. Noncontrast MRI yielded sensitivity, specificity and accuracy of 71%, 84%, and 79%, respectively; the use of USPIO-enhanced MRI increased those values to 100%, 98%, and 98%, respectively. This technique is variable among institutions, and it is not easily accessible or cost-effective.

2-Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan is a more accessible, potentially less expensive imaging modality that has been shown to accurately detect breast primary tumors.<sup>23-25</sup> It has been adopted as a reliable means of staging the whole body in patients with various malignancies, and there has been growing interest in its use in predicting axillary lymph node status in patients with breast carcinoma. Greco and colleagues conducted a prospective, single-institution trial of 167 patients who had ALND for breast cancer.<sup>26</sup> FDG-PET predicted axillary node status with a sensitivity of 94%, a specificity of 86%, and an overall accuracy of 90%. When they analyzed results on the basis of tumor size, there was no difference in the diagnostic accuracy; however, the sensitivity was highest in T2 tumors and the specificity was highest in T1a-b tumors. The mean tumor size in this study population was 2.2 cm, and the prevalence of node positivity was 43%. Wahl et al. performed a prospective multicenter trial of 360 women with breast cancer who had FDG-PET as an initial staging procedure.<sup>27</sup> There were 308 patients who had axillary findings on FDG-PET scan that correlated with histopathologic findings. They found that if at least one axillary focus was considered positive, the sensitivity, specificity, PPV, and NPV were 61%, 80%, 62%, and 79%, respectively. They also found that the accuracy for detecting axillary metastases was improved with the presence of multiple positive lesions, intense lesions, smaller size of the patient, and larger size of the tumor. The authors concluded that FDG-PET is currently not a suitable substitute for ALND in the assessment of axillary lymph nodes in breast cancer patients.

In summary, there are a number of imaging modalities that can detect breast cancer and axillary metastases with

variable accuracy rates. All imaging modalities are limited by the inability to detect small metastases, resulting in high FN rates. False-positive results can be eliminated by the use of image-guided needle biopsy. However, there is currently no imaging modality that can replace surgical staging of the axilla.

### SNB IN THE NEOADJUVANT SETTING

SNB has replaced ALND and is now accepted as the standard of care for staging of early breast cancers. The sentinel node identification rate ranges from 95% to 98% and the accuracy of SNB is 95% to 98%.<sup>28</sup> With the increased use of NAC in earlier tumors, SNB has been introduced in the neoadjuvant setting. The use of SNB in patients undergoing NAC for locally advanced breast tumors has been discouraged for a number of reasons. The data on SNB for large tumors are limited. Because NAC is known to alter the nodal status, the timing of SNB becomes a question. In addition, NAC may cause obstruction of lymphatic pathways that is unpredictable. The response of lymph nodes to chemotherapy may occur in a nonuniform fashion. These factors may limit the reliability of the SNB procedure.

Chung and colleagues evaluated SNB in 41 patients with breast tumors >5 cm in size.<sup>29</sup> The accuracy of SNB was

98% with a FN rate of 3%. This study demonstrates that SNB can be used in patients with larger tumors. However, American Society of Clinical Oncology practice guidelines from 2005 state that there are insufficient data to recommend SNB in this population.<sup>30</sup> Despite this, most surgeons will perform SNB on patients with large tumors in attempt to spare some patients ALND if possible.

There have been a number of studies reporting on SNB after NAC (Table 4). Sample size ranged from 14 to 428, and clinical T stage of tumors ranged from T0 to T4. Failure to map the sentinel lymph node (SLN) occurred in 0% to 28% of cases, and the FN rate varied from 0% to 33%. All patients in these studies had clinically negative axillary lymph nodes before SNB, although in most studies, patients may have initially presented with palpable lymph nodes before NAC. Only three studies required clinically negative axillary lymph nodes at initial presentation.<sup>31–33</sup> Many of these trials were included in a meta-analysis published by Xing and colleagues on 21 published reports of SNB after NAC from 2000 to 2004 in >1270 patients.<sup>34</sup> All patients in these studies had SNB after NAC, and ALND was performed regardless of SLN status. The authors reported a pooled SLN identification rate of 90%, FN rate of 12%, and overall accuracy of 94% for SNB after NAC.

**TABLE 4** Studies of sentinel lymph node biopsy after neoadjuvant chemotherapy

Study	No. of patients	T stage	Mapping failure	FN rate (%)
Tafra (2001) <sup>33*</sup>	29	1, 2	2/29 (7%)	0
Miller (2002) <sup>59</sup>	35	1–3	5/35 (14%)	0
Haid (2001) <sup>60</sup>	33	1–3	4/33 (12%)	0
Julian (2002) <sup>61</sup>	34	1–3	3/34 (9%)	0
Brady (2002) <sup>62</sup>	14	1–3	1/14 (7%)	0
Tanaka (2006) <sup>63</sup>	70	1–3	7/70 (10%)	3
Hunt (2009) <sup>32*</sup>	575	1–3	15/575 (3%)	6
Balch (2003) <sup>64</sup>	26	2–4	1/26 (4%)	7
Yu (2007) <sup>65</sup>	127	3	11/127 (9%)	8
Tausch (2008) <sup>66</sup>	167	1–3	25/167 (15%)	8
Newman (2007) <sup>67</sup>	54	1–4	1/54 (2%)	9
Schwartz (2003) <sup>68</sup>	21	2–4	0/21 (0%)	9
Kang (2004) <sup>69</sup>	54	2–4	15/54 (28%)	11
Mamounas (2005) <sup>35</sup>	428	1–3	65/428 (15%)	11
Classe (2009) <sup>70</sup>	195	0–3	19/195 (10%)	12
Breslin (2000) <sup>71</sup>	51	2, 3	9/51 (18%)	12
Stearns (2002) <sup>72</sup>	34	3, 4	5/34 (15%)	14
Gimbergues (2008) <sup>73</sup>	129	1–3	8/129 (6%)	14
Lee (2007) <sup>74</sup>	219	2, 3	49/219 (22%)	16
Piato (2003) <sup>31*</sup>	42	1, 2	1/42 (2.4%)	17
Kinoshita (2006) <sup>75</sup>	77	1–3	5/77 (6.5%)	11
Fernandez (2001) <sup>76</sup>	40	1–4	4/40 (10%)	20
Nason (2000) <sup>77</sup>	15	2, 3	2/15 (13%)	33

FN false negative

\* Included only patients who were clinically node negative at initial presentation

One of the largest of the trials was a subgroup of patients in the NSABP-B27 where SNB was performed with ALND on 428 patients after NAC with Adriamycin and Cytosan or Adriamycin, Cytosan, and docetaxel.<sup>35</sup> Lymphatic mapping was performed with radiocolloid alone in 15%, Lymphazurin alone in 30%, and a combination of radiocolloid and Lymphazurin in 55% of cases. The overall SLN identification rate was 85%. Mapping was more successful when both radioisotope and Lymphazurin were used compared to the use of Lymphazurin alone (89% vs. 78%,  $P = 0.03$ ). There was no marked difference in mapping failure on the basis of the clinical tumor size, nodal status, age, or year of random assignment. The FN rate of SNB was 11%, and there were no differences in FN rates on the basis of patient or tumor characteristics, method of lymphatic mapping, or breast tumor response to chemotherapy. The authors concluded from this study that SNB is applicable in patients with operable breast cancer who have received NAC. It is important to recognize that the reported mapping failure rate of 15% is comparable to that of the earliest studies of SNB, where the SLN identification rate ranged from 66% to 93% but not to contemporary results where mapping failure is reported in <5% of cases.<sup>36–49</sup>

A more recent study by Hunt and colleagues included the largest sample size of the trials ( $n = 575$ ) and found a much higher SLN identification rate of 97.4% and a lower FN rate of 6%.<sup>32</sup> These patients were clinically node negative at the time of presentation before initiation of NAC. In this study, the SLN identification rate was significantly improved with increased experience ( $P < 0.0001$ ), suggesting that higher mapping failure rates may be due to inexperience in the earlier studies and that a learning curve is required in the subset of patients undergoing SNB after NAC to achieve equivalent SLN identification and FN rates to those undergoing SNB before chemotherapy.

Some have proposed that patients undergoing NAC should have SNB performed before the initiation of chemotherapy. Proponents of this approach argue that performing the SNB before chemotherapy would avoid the potential confounding effects of NAC on the status of the axillary lymph nodes. Furthermore, SLN-negative patients could avoid ALND after NAC, whereas there is no convincing evidence that patients with a negative SLN after NAC can be spared ALND. Sabel and colleagues performed SNB on 25 patients with clinical N0 status before treatment.<sup>50</sup> They identified the SLN with a 100% success rate. Thirteen (52%) of the 25 patients were found to have a positive SLN. Twelve of these patients had ALND after NAC; five were found to have no residual nodal disease. Overall, SNB before NAC avoided ALND in 12 (48%) of 25 patients. Ollila et al. performed SNB before chemotherapy in 21 patients with T2 or T3 tumors who were

**TABLE 5** Studies of sentinel lymph node biopsy before neoadjuvant chemotherapy

Study	No. of patients	T stage	ID rate (%)	FN rate (%)
Sabel (2003) <sup>50</sup>	25	1–2	100	0*
Ollila (2005) <sup>51</sup>	21	2–3	100	0*
Cox (2006) <sup>78</sup>	47	3	98	0*
van Rijk (2006) <sup>79</sup>	25	2	100	0*
Schrenk (2008) <sup>80</sup>	25	1–4	100	0
Menard (2009) <sup>81</sup>	31	2–3	100	0

ID identification, FN false negative

\* Clinical FN rate

clinically node negative.<sup>51</sup> The median tumor size in this group was 5 cm. SLN identification rate was 100%. Nine patients (43%) had a positive SLN and underwent ALND after NAC; six had no residual nodal disease. With a median follow-up of 36 months, no axillary recurrences were identified. The authors conclude that SNB before NAC can be performed accurately in patients with larger breast tumors and may have prognostic and therapeutic implications. For patients with a positive SLN, ALND may be performed after chemotherapy. Table 5 lists the studies that have been published to date investigating SNB before NAC. Completion ALND was not performed in patients with negative SLNs identified before NAC, so the FN rate cannot be determined in some of these studies. However, a “clinical FN rate” was provided in some of the studies on the basis of clinical follow-up of axillary recurrences.

The appropriate use and optimal timing of SNB in the neoadjuvant setting remain controversial. Advocates of pre-NAC SNB believe that determining the axillary status before chemotherapy provides more accurate staging, may more accurately determine radiation fields, and allows assessment of the response to chemotherapy. In addition, this approach seems to have a higher SLN identification rate and lower FN rate. Reasons for this are unclear but may be the result of mapping before lymphatic scarring has been induced by chemotherapy, leading to altered lymphatic drainage patterns, and by avoiding the effects of a nonuniform response to chemotherapy in the axilla. The disadvantages of this approach include potential delays in initiating chemotherapy, potential increase in ALND, the requirement of an additional operation, and the loss of nodal response to chemotherapy in the nodes removed as SLNs. Proponents of post-NAC SNB believe that this approach determines the post-NAC axillary status, which may be of better prognostic value, may decrease the incidence of ALND, and requires only one operation. Disadvantages of the post-NAC SNB include lower SLN

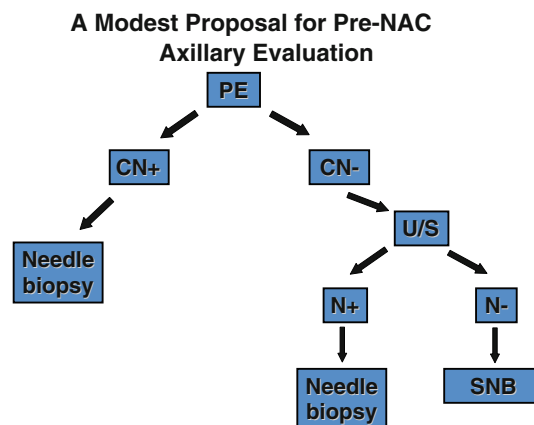
identification rates, higher FN rates, and the unknown effect of no axillary surgery in patients whose nodes were downstaged by NAC.

One of the first authors to address this controversy was Jones et al., who conducted a retrospective comparison of 52 patients with clinical T2–4, N0 breast cancer who had SNB before NAC and 36 patients who had SNB after NAC.<sup>52</sup> The SLN identification rate in the pre-NAC group was 100%, compared to 81% in the post-NAC group. Failure to map correlated with clinically positive axilla at presentation and residual nodal disease at ALND, but not to initial tumor size. The FN rate in the pre-NAC group was 2%, compared to 11% in the post-NAC group. The authors attribute this discrepancy to potential obstruction of lymphatic pathways caused by the tumor, sclerosis of the lymphatics caused by chemotherapy, or an uneven response of the tumor to NAC in the axilla. On the basis of these findings, they recommend SNB before NAC for patients who are clinically node negative at presentation. Patients who are SLN negative will be spared ALND after NAC. The authors recommend performing ALND after NAC on patients who are SLN positive. A much larger study has recently compared results for 575 patients who underwent SNB after NAC to 3171 patients who had SNB before chemotherapy.<sup>32</sup> All patients included in the study had clinically node-negative T1–T3 breast cancer. The SLN identification rate in the group who had SNB after NAC (97.4%) was significantly lower than the SLN identification rate in the group who had SNB before chemotherapy (98.7%), with a *P* value of 0.017. However, there was no significant difference between the two groups with respect to FN rate—5.9% in the SNB after NAC group versus 4.1% in the SNB before chemotherapy group (*P* = 0.39). Patients were more likely to have FN events when mapping was performed with blue dye alone or when fewer than two SLNs were removed. When analyzed by tumor size, there was a far lower incidence of metastatic SLNs in the SNB after NAC group compared with the SNB before chemotherapy group, resulting in fewer ALNDs being performed for those who had SNB after NAC. The authors concluded that SNB after NAC is as accurate as SNB before chemotherapy and that SNB after NAC results in fewer positive SNBs and may reduce unnecessary ALNDs. It is important to note that all patients underwent preoperative axillary US, with FNA if the US was suspicious. Patients found to have positive axillary nodes preoperatively were excluded from the study. Therefore, it is not possible to determine from this study whether patients with a positive axillary lymph node at presentation who became node negative after NAC can be spared ALND.

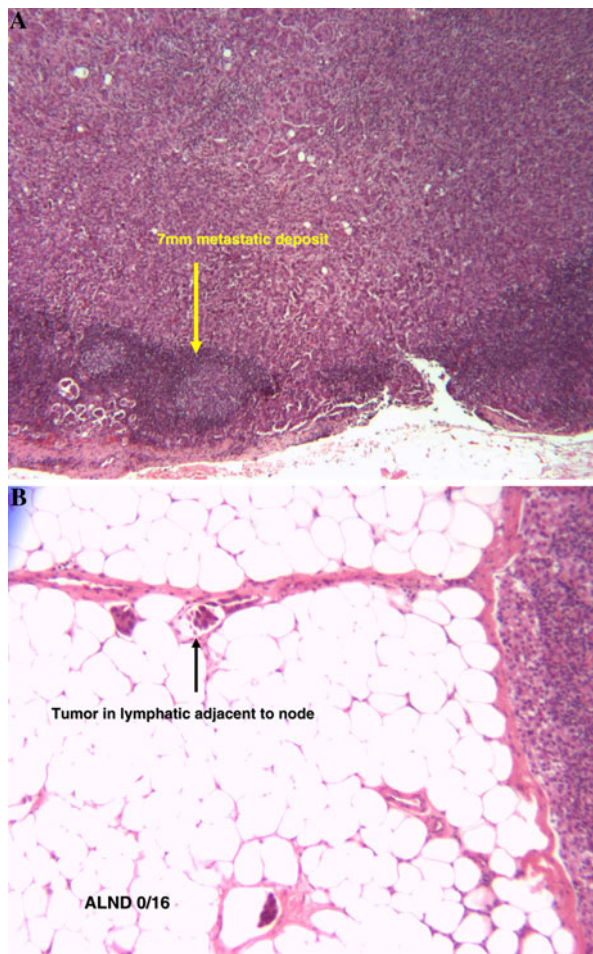
Despite the results reported in these various studies, controversy still exists on the appropriateness and optimal timing of SNB in the neoadjuvant setting. To date, there

has been no published randomized data to address this issue. We await the results of the American College of Surgeons Oncology Group (ACOSOG) clinical trial Z1071, which is currently accruing patients with T1–4, N1–2, M0 breast cancer who will undergo preoperative NAC followed by SNB and ALND to evaluate the role of SNB and ALND after NAC in women with node-positive breast cancer at initial diagnosis.

We propose an algorithm for staging the axilla for patients undergoing NAC on the basis of our interpretation of the data currently available (Fig. 1). Once a patient is determined to be eligible for NAC, the pretreatment axillary status is assessed by physical examination of the axillary lymph nodes. If the patient has clinically positive lymph nodes, needle biopsy is performed to obtain cytologic or histologic confirmation of the pretreatment status. If the patient is clinically node negative, we recommend axillary US with needle biopsy if any suspicious nodes are detected. If axillary US does not identify any suspicious axillary lymph node, SNB should be performed before the initiation of chemotherapy. We believe that management of the axillary lymph nodes after NAC should be based on the findings of pre-NAC SNB, although this remains an area of controversy among breast surgeons across the United States. We await findings of the ACOSOG Z1071 trial to answer this question. At this time, axillary findings after NAC in patients with involved lymph nodes before NAC are not well documented. Furthermore, it is not known whether patients who convert from node positive to node negative after NAC should be treated without ALND. Figure 2 shows axillary fat involvement after NAC in a patient who was sentinel node positive before NAC. Upon ALND after NAC, all lymph nodes were tumor-free. Had ALND not been performed in this patient who would have



**FIG. 1** Proposed algorithm for axillary staging in the neoadjuvant setting. PE, physical examination; CN+, clinically node positive; CN-, clinically node negative; U/S, ultrasound of the axilla; N+, suspicious nodes on axillary U/S; N-, normal nodes on axillary U/S; SNB, sentinel node biopsy



**FIG. 2** **a** Histopathology of sentinel lymph node from a patient with locally advanced breast cancer performed before neoadjuvant chemotherapy. **b** Representative section from the axillary dissection performed after chemotherapy, where 0 of 16 lymph nodes contained metastases. There was extensive tumor within the lymphatics adjacent to the lymph node. This figure demonstrates the nonuniform response that the axillary lymph nodes can have to chemotherapy

had a negative SNB, considerable tumor volume would have been left in the axilla.

## CONCLUSIONS

Axillary staging is necessary to establish prognosis and determine possible therapeutic options in breast cancer. Physical examination is inadequate, and no imaging modality can replace surgical staging to evaluate the axillary lymph nodes. Of the available imaging modalities, US with FNA is the most useful adjunct before NAC, but it cannot substitute for surgery in cases where the node is negative on US. Although the experience with SNB in the neoadjuvant setting is limited, SNB results seem to be improved when performed before NAC, and ALND may be avoided in patients with a negative SNB performed

before NAC. SNB may still be performed after NAC with acceptable identification and FN rates. However, the effect of leaving behind lymph nodes that were clinically involved with metastatic breast cancer before NAC is unknown.

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