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Timing of Determining Axillary Lymph Node Status When Neoadjuvant Chemotherapy is Used

Eleftherios P. Mamounas^{1,2,3}

¹MD Anderson Cancer Center Orlando, 1400 S. Orange Avenue, MP700, Orlando, FL 32806, USA

²University of Central Florida College of Medicine, Orlando, FL, USA

³Florida State University College of Medicine, Tallahassee, FL, USA

Abstract

Neoadjuvant chemotherapy is the standard of care for patients with locally advanced breast cancer and is a reasonable alternative to adjuvant chemotherapy for those with large operable disease. Potential clinical advantages of neoadjuvant chemotherapy include the conversion of some patients requiring mastectomy to candidates for breast-conserving surgery, the potential for downstaging axillary nodes and thus reducing the extent of axillary surgery, and the ability to correlate clinical and pathologic response to neoadjuvant chemotherapy with improved long-term outcomes. An important and controversial locoregional therapy issue in patients who are candidates for neoadjuvant chemotherapy relates to the timing of sentinel lymph node biopsy – i.e., either before or after neoadjuvant chemotherapy. This review will focus on the performance characteristics of sentinel lymph node biopsy before vs. after neoadjuvant chemotherapy and on the pros and cons of each approach.

Keywords

Breast cancer; Neoadjuvant chemotherapy (NC); Sentinel lymph node biopsy before or after neoadjuvant chemotherapy; Axillary lymph node status; Adjuvant chemotherapy

Introduction

Neoadjuvant (preoperative) chemotherapy (NC) was first utilized in patients with locally advanced breast cancer in order to successfully render them operable candidates. When lumpectomy became an acceptable surgical procedure for patients with early-stage breast cancer [1–4], and when the efficacy of adjuvant chemotherapy was demonstrated in patients with negative axillary nodes [5, 6], the clinical rationale for neoadjuvant chemotherapy expanded to include patients with large operable disease in order to convert patients requiring mastectomy to candidates for breast-conserving surgery.

Compliance with Ethics Guidelines

Conflict of Interest - Eleftherios P. Mamounas declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent - This article does not contain any studies with human or animal subjects performed by any of the authors.

When compared to adjuvant chemotherapy, NC produces equivalent results in prolonging disease-free and overall survival [7–9]. In addition, NC offers several potential advantages. Compared to patients treated with upfront surgery, those receiving NC are able to achieve higher rates of breast-conserving surgery without significant increase in local recurrence rates [7–9]. NC significantly downstages involved axillary lymph nodes (in up to 40 % of patients when anthracycline- and taxane-containing regimens are employed) [7, 8, 10, 11, 19]. This observation was of limited importance when axillary lymph node dissection was the only surgical option for staging the axilla. However, the establishment of sentinel lymph node biopsy (SLNB) as the gold standard for axillary staging in patients with early-stage breast cancer provided an additional advantage for NC: the potential for decreasing the extent and morbidity of axillary surgery by downstaging involved axillary nodes. This approach is predicated on the premise that SLNB is feasible and accurate in patients who receive NC. Finally, a consistent observation in trials of NC is the strong correlation between the achievement of pathologic complete response (pCR) in the breast and axillary nodes with improved outcomes, leading to the hypothesis that pathologic tumor response can be used as an intermediate marker of chemotherapy efficacy and as a guide for tailoring locoregional and systemic therapy.

There are several unique locoregional therapy issues in patients who are candidates for NC. This review will focus on the accurate assessment and surgical management of axillary lymph nodes in patients receiving NC. More specifically, it will address the performance characteristics of SLNB before vs. after NC and the pros and cons of each approach.

Assessing the Status of Axillary Nodes in Neoadjuvant Chemotherapy Candidates

One of the potential concerns with using NC is the lack of knowledge of the baseline pathologic axillary nodal status at the time of diagnosis. Therefore it is important to assess the axilla with noninvasive or minimally invasive methods prior to NC. This assessment is usually performed with axillary ultrasound and fine-needle aspiration (FNA) of radiologically enlarged nodes or with SLNB.

Axillary ultrasound can identify radiologically enlarged or abnormal axillary lymph nodes, which then leads to biopsy of these lymph nodes by ultrasound-guided FNA or core needle biopsy [12, 13]. This is a simple, minimally invasive, and reliable technique for the initial evaluation of axillary lymph node status, and it has the advantage of providing direct evidence of chemosensitivity of axillary metastases to NC.

SLNB can also be used to assess axillary nodal status before NC [14–16]. The feasibility and accuracy of SLNB in patients with large operable breast cancer (typical candidates for NC) has been demonstrated in several single-institution series [14–18]. In addition, patients with large operable breast cancer have been included in most of the multicenter and randomized trials, and none of these trials has shown decreased feasibility or accuracy of SLNB according to tumor size [19–22]. However, as discussed in more detail below, there are advantages and disadvantages to performing SLNB before NC, and the timing of SLNB in patients receiving NC continues to be a subject of controversy.

Surgical Management of the Axillary Nodes after NC

It has been widely demonstrated that NC downstages involve axillary lymph nodes in a considerable proportion of patients (up to 40 % with anthracycline/taxane-containing regimens, and even higher rates in HER2/neu-positive patients treated with NC plus trastuzumab). Thus, if SLNB following NC is negative, patients who present with involved axillary nodes at diagnosis may potentially be spared from axillary dissection. However, this approach is predicated on the demonstration of feasibility and accuracy of SLNB after NC. There are reasons for questioning the performance characteristics of SLNB after NC. Does tumor response to NC cause tissue scarring that may affect the lymphatic drainage patterns? Does NC have the same effect on involved non-SLNs as it does on involved SLNs? Moreover, even if SLNB after NC is accurate and feasible, it is still unclear to what degree the initial extent of the tumor and its response to NC combine to determine risk of locoregional recurrence, in general, and axillary recurrence in particular, when previously involved axillary lymph nodes are not surgically removed.

Evidence for Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy

Single-Institution Studies of SLNB after NC

Several single-institution studies of SLNB after NC have reported significant variability in the SLN identification rate (70–100%) and false negative rate (FNR) (0–39 %), largely due to small sample size and the inclusion of patients with operable as well as locally advanced breast cancer. In general, SLN identification rates were somewhat lower in these studies compared to upfront SLNB, but the FNRs between the two approaches were comparable [22–25]. Similar findings were observed in more recently reported larger single institution studies, with considerable variability in SLN identification rate (71–100 %) and FNR (0–25 %). When these more recent studies are examined collectively, SLN identification rate is around 86 % (lower than in studies with upfront SLNB), and the FNR is around 10 % (comparable to studies with upfront SLNB) [22–25].

The largest single-institution experience with SLNB after NC was recently reported by Hunt et al. from MD Anderson Cancer Center [26]. The study also compared the accuracy of SLNB after NC ($n=575$) to that of SLNB before any systemic therapy ($n=3171$). SLN identification rates were 97.4 % in the NC group and 98.7 % in the surgery-first group ($P=0.017$). FNRs were similar between groups (5.9 % in NC vs. 4.1 % in the surgery first group, $P=0.39$). Based on these findings, the authors concluded that SLNB after NC is as accurate for axillary staging as SLNB prior to chemotherapy, and that SLNB after NC results in fewer positive SLNs and decreases unnecessary axillary dissections.

Multicenter Studies of Sentinel Node Biopsy after NC

The largest report to date comes from the NSABP B-27 trial [27] and includes 428 patients treated with NC followed by SLNB and axillary node dissection. The SLN identification rate was 85 % and was significantly higher when radiocolloid (with or without lymphazurin) was used for lymphatic mapping (88–89 %) vs. when lymphazurin alone was used (78 %). FNR

was 11 %, lower when radiocolloid was used for lymphatic mapping (8 %) vs. when lymphazurin alone was used (14 %). There were no significant differences in the FNRs of patients who presented with clinically negative vs. clinically positive axillary nodes (12.4 % vs. 7.0 %, respectively, $p=0.51$).

More recently, Classe et al. [28] reported results of a prospective multicenter study designed to determine the identification rate, FNR, and accuracy of SLNB after NC in 195 patients with T0-3 N0-1 breast cancer. Lymphatic mapping was performed with a combination of blue dye and radiocolloid. The identification rate was 90 %, and the FNR was 11.5 %. Patients with clinically N0 disease before NC had higher identification rate compared to those with N1 disease (94.6 % vs. 81.5 %; $P=.008$), but the FNR was not significantly different by clinical nodal status before NC (9.4 % vs. 15 %; $P=.66$).

When these two large multicenter studies are examined in combination, the overall identification rate is 86.5 % and the overall FNR is 10.9 %, similar to those observed in the collective experience from recent single-institution studies, as discussed above.

Meta-Analyses of Studies Evaluating SLNB after NC

In 2006, Xing et al. [29] reported a meta-analysis of 1,273 patients from 21 studies of SLNB after NC. Eligible studies evaluated patients with operable breast cancer who had undergone SLNB after NC, followed by axillary dissection. The reported identification rates ranged from 72 % to 100 %, with a pooled estimate of 90 %. The FNR ranged from 0 to 33%, with a pooled estimate of 12 %. Based on their results, the authors concluded that SLNB is a reliable tool for planning treatment after NC.

More recently, Kelly et al. [30•] reported a systematic review and meta-analysis of 24 studies (1,799 patients) of SLNB after NC that were published between 2000 and 2007. The summary successful identification rate was 89.6 %, with moderate heterogeneity, and the summary FNR was 8.4 %, with no significant heterogeneity. Based on these results, the authors concluded that SLNB is a reliable tool for planning treatment in this population as an alternative to completion axillary lymph node dissection.

When one compares the identification rates and false negative rates of SLNB after NC observed in multicenter studies and in meta-analyses to those from other multicenter and randomized trials of upfront SLNB, the identification rates are lower after NC, but the FNRs are similar, with considerable overlap in the confidence intervals [19, 20, 22, 31].

SLNB after NC in Patients with Known Axillary Involvement at Diagnosis

Although, based on the above data, most surgeons have become comfortable performing SLNB after NC for patients who present with clinically N0 disease, there is still debate regarding the accuracy of SLNB in patients who present with documented involvement of the axilla. Several retrospective studies have addressed the performance characteristics of SLNB in this setting, with conflicting results.

Shen et al. [32•] reported on 69 patients with clinical T1-4/N1-3 disease and cytologic documentation of axillary nodal involvement who underwent SLNB following NC on

prospective institutional protocols at MD Anderson Cancer Center between 1994 and 2002. The SLN identification rate was 92.8 %, and in the 56 patients in whom a SLN was identified and an axillary dissection was performed, the FNR was 25 %. Based on these results, the authors concluded that SLNB is feasible after NC, even in patients who initially presented with cytologically involved axillary nodes, but that the FNR is much higher in this group of patients than that observed in clinically node-negative patients. However, the relatively small number of patients with positive nodes after NC and the inclusion of patients with locally advanced disease (T4 and N2-3) cause the results of this study to be less representative of the general population of patients with N1 disease for whom SLNB after NC should be considered.

A more recent update of the MD Anderson experience with SLNB after NC in patients presenting with documented axillary node involvement (between 1994 and 2010), [33•] included 150 patients with biopsy-proven axillary metastasis who underwent SLNB after NC, from which 121 also underwent axillary lymph node dissection (ALND). The SLN identification rate was 93 %, and the FNR was 20.8 %. Interestingly, in 52 patients with normalized nodes on ultra-sound, the FNR decreased to 16.1 %. Multivariate analysis revealed that smaller initial tumor size and fewer SLNs removed (<2) were associated with a false-negative SLN. Based on these findings, the authors concluded that SLNB in this group of patients is associated with a substantial FNR, and that normalization of the involved axillary nodes by ultrasound, as well as removing 2 or more SLNs, decreases the FNR.

Lee et al. [34] reported on 238 patients with positive axillary nodes at presentation who underwent SLNB and axillary dissection following NC. Axillary nodal positivity in the study was defined as lymph nodes that were palpable and had an SUV greater than 2.5 on PET scan. The identification rate was significantly lower in patients who received NC compared to those who did not (77.6 % vs. 97.0 %, respectively, $p < 0.001$) but the FNR was similar between the two approaches (5.6 % vs. 7.4 %, respectively, $p = \text{NS}$). Based on these results, the authors concluded that for patients who present with involved axillary nodes and who achieve complete clinical axillary response with NC, SLNB could replace axillary node dissection.

Finally, Newman et al. [35] from the University of Michigan reported their experience with a comprehensive approach to the management of the axilla in node-positive-patients receiving NC. Between 2001 and 2005, 54 consecutive breast cancer patients with biopsy-proven (SLNB or FNA) axillary nodal metastases at diagnosis underwent SLNB and axillary lymph node dissection after NC. The SLN identification rate was 98 % (100 % in patients who did not also undergo SLNB before NC), and the FNR was 10.7 % among 28 patients with positive nodes after NC and no prior SLNB. Based on their results, the authors concluded that SLNB after NC in patients with documented axillary nodal involvement at presentation accurately identifies cases that were downstaged. They further commented that this approach can potentially spare this subset of patients (32 %) the morbidity of an axillary dissection.

From the above, it is evident that the accuracy and utility of SLNB in patients who present with axillary node involvement and undergo NC remains controversial. The performance characteristics of SLNB after NC in patients with documented axillary nodal involvement

was addressed in two recently reported prospective clinical trials [36••, 37]. The first study (ACOSOG Z0171) [36••] was a single-arm prospective trial of women with clinical T0-4/N1-2/M0 breast cancer receiving NC. At the time of surgery, all patients were to undergo SLNB, followed by axillary lymph node dissection. The primary endpoint was FNR in women with cN1 disease with 2 or more SLNs reviewed. The protocol encouraged dual-tracer technique. A total of 756 patients were enrolled from July 2009 to July 2011. In patients with SLNB and ALND, the SLN identification rate was 92.5 % (92.7 % in cN1, 90 % in cN2). For patients with cN1 disease and > 2 SLNs identified, the FNR was 12.8 %. In patients with dual-tracer technique, the FNR was 11.1 %. Based on these results, the authors concluded that SLN surgery after NAC in node-positive breast cancer patients correctly identified nodal status in 84 % of all patients and was associated with a FNR of 12.8 %. This FNR was higher than the pre-specified study endpoint of 10 %, and thus the authors suggested that further analysis of factors associated with FNR should be performed prior to widespread use of SLN in these patients.

The second recently reported prospective trial was the German SENTINA (SENTinel NeoAdjuvant) trial [37, 38••], a 4-arm prospective multicenter cohort study designed to 1) evaluate a specific algorithm for the timing of SLNB in patients who undergo NC, and 2) provide reliable data for the detection rate and FNR in different settings. Patients were categorized into four treatment arms according to the clinical axillary staging before and after NC. Patients with a cN0 status underwent SLNB prior to NC (arms A and B). If the SLN was histologically negative, no further axillary surgery was performed after NC (arm A), whereas if the SLN was positive, a second SLNB and axillary dissection was performed after NC (arm B). Patients with a cN1 status before NC did not undergo axillary surgery prior to NC and were stratified as arms C and D. If patients converted to cN0 after NC, SLNB plus axillary dissection were performed (arm C), but those who remained cN1 after NC underwent axillary dissection (arm D). A total of 1,737 eligible patients were accrued. The detection rate for SLNB was 99.1 % before NC (arms A and B), 80.1 % in arm C (after NC), and 60.8 % in arm B (after NC and prior SLNB) ($p < 0.001$). In arm C, the FNR was 14.2 %. However, in the multivariate regression analysis, the number of removed SLNs was a significant predictor of the FNR (odds ratio for >1 vs. 1 SLN removed = .505, $p = .008$). Thus, the false negative rate was 24.3 % when one SLN was removed, 18.5 % when two SLNs were removed, and only 5 % when more than two SLNs were removed. The SLNB FNR was 51.6 % in arm B, indicating that SLNB before NC significantly impairs the detection rate and accuracy of SLNB after NC. Based on these findings, the authors concluded that in patients who convert from a positive to a negative clinical nodal stage during NC, the SLNB detection rate is significantly lower compared to upfront SLNB. The FNR was less favorable after NC compared to primary SLNB, but the FNR improved with removal of more than one SLN in this setting.

Pros and Cons of Sentinel Node Biopsy Before vs. NC

As mentioned earlier, the timing of SLNB in patients treated with NC has been the subject of considerable controversy, as there are several advantages as well as limitations in each approach (Table 1). The primary advantage with SLNB before NC is that it provides information on axillary nodal status without the potential confounding effects of NC. This

information can be used for selecting optimal candidates for NC and appropriate NC regimens and for deciding on appropriate subsequent locoregional management of the patient. In particular, if the SLN is negative, the patient is spared an axillary dissection and may not require local-regional XRT other than breast XRT after lumpectomy. On the other hand, the primary limitation of SLNB before NC is that it does not take advantage of the potential downstaging effect of NC on the axillary nodes, as patients with a positive SLN (typically 50–70 % of patients with large operable breast cancer) will generally require an axillary node dissection either before or after NC [19–22, 27, 29, 31]. In addition, SLNB before NC requires two surgical procedures for patient management regardless of whether the SLN is negative or positive.

Furthermore, although upfront knowledge of SLN status is useful in some low-risk patients who may not need chemotherapy if the SLN is negative, this is generally not the case for the majority of NC candidates, as little to nothing is gained for most of these patients by knowing the pathologic nodal status at presentation. Clinical tumor size and biomarkers from the primary tumor, such as ER/PR and HER2/neu, are usually sufficient to quantify risk of recurrence and benefit of chemotherapy. Recent results with genomic profiling indicate that patients with ER-positive, node-negative, or node-positive breast cancer and a low 21-gene recurrence score by Oncotype DX have good prognosis and receive minimal to no benefit from the addition of adjuvant chemotherapy to hormonal therapy [39–41]. These data lend additional support to the concept that chemosensitivity is based on inherent tumor biology and not axillary nodal status, thus further diminishing the importance of obtaining histologic status of axillary nodes before proceeding with NC. Lastly, when SLNB is performed before NC, the prognostic significance of negative axillary nodes after NC and prior positive SLNB is dubious, since pathologically negative axillary nodes in this situation may reflect axillary nodal downstaging from NC or just the removal of all positive nodes by the SLNB.

Perhaps the most important reason for performing SLNB before NC is that knowledge of axillary nodal status before NC can help identify optimal candidates for adjuvant XRT to the chest wall (after mastectomy) or to regional lymph nodes (irrespective of surgical procedure). This is because most of the available information on the rates and patterns of locoregional recurrence (LRR) that dictate the need for adjuvant XRT is based on the pathologic status of the axillary nodes at presentation (as determined at surgery). In contrast, little information exists on the rates and patterns of LRR in patients with operable breast cancer who have received prior NC, and the effect of clinical and pathologic tumor response on the rates and patterns of LRR has not been well studied.

Two NSABP neoadjuvant trials in patients with operable breast cancer (B-18 and B-27) provide an important dataset to address some of the above questions. In both trials, regional nodal XRT after lumpectomy or chest wall and regional nodal XRT after mastectomy were not allowed per protocol guidelines, thus avoiding the confounding effects of selective use of XRT in patients with positive nodes or other high-risk features. Data from a combined analysis of these two trials provide important information on rates and patterns of LRR in patients treated with NC [42••] and help identify independent predictors of LRR in this setting. The 10-year cumulative incidence of LRR was 12.3 % for mastectomy patients

(8.9% local, 3.4 % regional) and 10.3 % for lumpectomy plus breast XRT patients (8.1 % local, 2.2 % regional). Independent predictors of LRR in lumpectomy patients were age, clinical nodal status (before NC), and pathologic nodal status/pathologic breast tumor response. In mastectomy patients, independent predictors of LRR were clinical tumor size (before NC), clinical nodal status (before NC), and pathologic nodal status/pathologic breast tumor response. With the use of these independent predictors, groups at low, intermediate, and high risk of LRR could be identified, and this, in turn, could help determine whether chest wall and regional nodal XRT after mastectomy or the addition of regional nodal XRT after breast-conserving therapy were needed. These findings further support the rationale for performing SLNB after rather than before neoadjuvant chemotherapy.

Current and Future Directions in Local-Regional Management After NC

With the development of more active chemotherapy regimens and the increasing utilization of genomic profiling as a tool for predicting pCR in the breast and axillary nodes, future studies should attempt to further individualize the extent of—or even the need for—axillary surgery after NC. By identifying patients at high likelihood of having negative axillary nodes (based on molecular/genomic markers and/or the achievement of pCR in the breast), axillary surgery (including SLNB) may be avoided altogether. By identifying patients at high likelihood of having positive SLNs but negative non-SLNs, completion axillary dissection can be avoided in an additional subset of SLN-positive patients [43]. For those SLN-positive patients at high likelihood of having residual positive non-SLNs, the most appropriate therapeutic strategy (completion axillary dissection vs. axillary XRT) will need to be determined, and this question is currently being addressed by randomized clinical trials [44] and other clinical studies [45].

Conclusion

NC results in considerable downstaging of the primary breast tumor and involved axillary lymph nodes. In appropriately selected patients, up to 50 % of involved axillary nodes at presentation can be sterilized following NC. With the use of SLNB, patients who present with axillary node involvement can be downstaged with NC and potentially avoid the morbidity of an axillary dissection. The performance characteristics of SLNB after NC are similar to those with upfront SLNB, even in patients who present with axillary node involvement, provided that 2 or more SLNs are removed. The strategy of performing SLNB after neoadjuvant chemotherapy extends the paradigm of tailoring locoregional therapy based on chemotherapy response. Although a negative SLNB before NC can provide useful clinical information for patients presenting with clinically negative axillary nodes, the advantages of performing SLN after NC outweigh those of performing it before.

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Table 1

Comparison of pros and cons of SLNB before vs. after NC

	SNB Before NC	SNB After NC
Pros	• Stages the axilla without the confounding effects of NC • Helps when selecting optimal chemotherapy candidates and appropriate NC regimens • Helps with decisions on the appropriate loco-regional treatment with surgery and XRT	• Capitalizes on the down-staging effects of NC • Generally requires one surgical procedure for resection of the primary breast tumor and axillary nodal staging • Provides direct evidence of chemosensitivity if the axillary nodes were cytologically or histologically positive before NC and the SLNB is negative afterwards
Cons	• Eliminates the advantage of down-staging involved axillary nodes with NC and generally commits patients with positive SLN to axillary dissection or axillary XRT • Requires two surgical procedures whether the SLN is positive or negative • The prognostic significance of negative axillary nodes after NC and prior SLNB is uncertain (i.e. the only positive node may have been removed by SLNB before NC) • Knowledge of SLN status before NC has minimal impact in selecting appropriate candidates for NC and in deciding which NC or adjuvant chemotherapy regimens to use	• Less information regarding the performance characteristics of SLNB after NC compared to SLNB in the upfront setting • SLN identification rates are lower after NC when compared to the upfront setting • Minimal information on axillary recurrence rates with SLNB alone after NC • Complicates the decision on whether to use adjuvant XRT if the SLN is negative, particularly if the axillary nodes were clinically or cytologically positive before NC