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Axillary Node Management in Patients Receiving Neoadjuvant Chemotherapy

Leopoldo J. Fernandez · Harry D. Bear

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Abstract Neoadjuvant chemotherapy (NAC) has increasingly been used to allow breast conservation, without compromising survival or local control. NAC can also downstage nodal status in about 40 % of women with positive nodes (cN+). Concurrently, primary surgical management of the axilla has transitioned towards sentinel lymph node biopsy (SLNB) as the preferred alternative to axillary lymph node dissection (ALND) for clinically node-negative patients. Although some still support SLNB prior to NAC for node-negative breast cancer, the use of SLNB after NAC has become an increasingly accepted practice. SLNB after NAC for node-positive breast cancer has remained more controversial. Recent trials show that the false-negative rates for SLNB after NAC for women presenting with positive nodes are approximately 10 % when two tracers are used for mapping and two or more SLNs are examined. This review summarizes the available evidence and rationale regarding management of regional nodes in women receiving NAC.

Keywords Sentinel lymph node · Sentinel lymph node biopsy · False negative rate · Axillary lymph node dissection · Neoadjuvant chemotherapy · Preoperative chemotherapy · Breast cancer

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L. J. Fernandez · H. D. Bear (✉)
Division of Surgical Oncology, Virginia Commonwealth University and Massey Cancer Center, West Hospital 7-422, 1200 East Broad Street, PO Box 980011, Richmond, VA 23298, USA
e-mail: hdbear@vcu.edu

L. J. Fernandez
e-mail: lfernandez@mcvh-vcu.edu

Introduction

Although initially used exclusively for locally advanced inoperable breast cancers, neoadjuvant chemotherapy (NAC) has increasingly been used for women with operable breast cancer [1]. Several trials, including the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial and the ECTO trial in Europe established that NAC resulted in equal long-term outcomes and increased the feasibility of breast conservation therapy (BCT) without a harmful increase in local recurrences [2–4].

Over the same two decades during which NAC has become more common, the surgical management of the axilla has become less invasive, with a gradual transition to sentinel lymph node biopsy (SLNB) instead of routine axillary lymph node dissection (ALND). This trend, of course, built on the recognition that removal of regional lymph nodes was more important as a staging procedure than as therapy. This has been recognized since the results of the NSABP B-04 trial showed clearly that removal of either negative or positive axillary nodes had little impact on overall survival [5]. The landmark NASBP B-32 trial demonstrated the accuracy of staging and the safety of SLNB [6]. Despite a false-negative rate of 9.8 % among those who underwent SLNB+ALND, there was no difference in locoregional control or survival between the group that had SLNB alone with negative SLN pathology and those that had ALND despite negative SLN pathology [6]. Today, in the USA, approximately 70 % of women with clinically negative axillary nodes undergo SLNB rather than initial full ALND, although the application of this less morbid approach is uneven [7]. SLNB has been shown to have lower short-term and long-term morbidity than ALND [8]. Furthermore, even patients who have positive SLNs may not benefit from completion ALND, as demonstrated by the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial [9].

Management of the Regional Lymph Nodes in Women Undergoing NAC

As both NAC and SLNB have become more common, it has occurred to some that NAC may not only increase the likelihood of BCT, but might also be used to allow less radical surgery for the axillary nodes. The B-18 trial comparing neoadjuvant to adjuvant chemotherapy with 4 cycles of doxorubicin+cyclophosphamide (AC) demonstrated clearly that NAC could downstage the axillary nodes in 30 % of patients with positive nodes. The B27 trial, in which one of the groups received 4 cycles of a taxane in addition to AC preoperatively demonstrated a further 13 % reduction of lymph node positivity at surgery. This led us to hypothesize that positive axillary nodes could be converted to negative nodes in roughly 40–45 % of patients with node-positive breast cancer. In fact, four subsequent trials involving women presenting with proven nodal involvement showed that NAC converted approximately 40 % of these women to node negative [10–12, 13•] and some series have reported nodal conversion rates above 70 % with the addition of trastuzumab to the NAC regimen for patients with HER2+ disease [14, 15] (see Table 1). These observations have led to considering that NAC could have the added benefit of allowing less morbid surgical management of the regional nodes in women with breast cancer. However, concern has been raised regarding failure to identify a SLN and potential for inaccurate staging by depending on SLN biopsy after NAC. This debate has also been fueled by the perceived need to add regional nodal irradiation to the treatment of women who have ever had a positive lymph node [16–19].

Axillary Management for Women with Clinically Negative Nodes Receiving NAC

The optimal timing of axillary nodal staging for women whose nodes are clinically negative (including the increasingly common use of magnetic resonance imaging [MRI] and ultrasound [US] to examine the axilla) has been hotly debated in meetings and tumor boards. Staging the axilla with a SLNB prior to NAC has been advocated by some with the argument that only the "real" pretreatment nodal status has important prognostic implications and impacts treatment decisions, especially whether to give chemotherapy and regional nodal and chest wall irradiation. The counterargument is that post-treatment nodal status is at least as important as pre-treatment nodal status for prognosis. The impact of nodal status after NAC has been demonstrated repeatedly in a number of clinical trials and a recent meta-analysis [2, 20, 21, 22•]. This reflects the combined impact of the original nodal pathology as well as the response of cancer in the nodes to the systemic therapy. Moreover, it is possible that SLNB performed prior to NAC could remove the only positive LNs, thus depriving clinicians of even more powerful prognostic information provided by the response to treatment [23•]. Whether the nodes are negative because they were negative at presentation or because NAC has "sterilized" the cancer initially present is really not important, since the prognosis is good in either case [20, 21, 22•] (see Fig. 1). Moreover, decisions about systemic chemotherapy are increasingly based more on the molecular characterization of the tumor than on the anatomic staging based on tumor size and nodal status.

Clearly, if SLNs are removed prior to NAC and are negative, then no further axillary surgery is warranted unless additional nodes become clinically positive during treatment (a very uncommon event). On the other hand, if the SLNB is positive before NAC, then the question arises as to what should be done after NAC. Options are to perform a repeat SLNB after NAC, to perform ALND on every patient regardless of response to NAC, or to recommend no further axillary surgery. One small series from the University of Michigan suggested that a second SLNB after NAC could be performed [24], but the larger prospective SENTINA trial [25•] reported a high failure-to-map rate (60.8 %) as well an unacceptably high false-negative rate (FNR) (51.6 %) in patients who presented with clinically negative LNs, underwent staging SLNB prior to NAC which was positive and then underwent repeat SLNB after NAC (arm B of the study).

As noted above, ALND for every patient presenting with positive nodes would lead to potentially unnecessary ALND for 30–40 % of those patients with a pathologic complete response (pCR) in the axillary LNs. ALND would also not be beneficial to women whose only residual disease was in the SLN that were removed.

No further axillary surgery after a positive pre-treatment SLNB may also be supported on the basis of no improved benefit of completion ALND (cALND) after a positive SLN for selected patients included in the ACOSOG Z11 trial [9], especially in patients presenting with clinically negative nodes. Preliminary results from the AMAROS trial reported comparable oncologic results and less morbidity when

Table 1 Conversion rate of positive to negative nodes with neoadjuvant chemotherapy

Study	Number[a]	Percent of pCR in nodes[b]
Koolen [10]	80	40
Park [11]	178	40.8
Hieken [12]	272	38.5
Boughey [13•]	649	41

[a] Number of patients that received NAC

[b] Percent of patients that presented with positive nodes that converted to node-negative after NAC

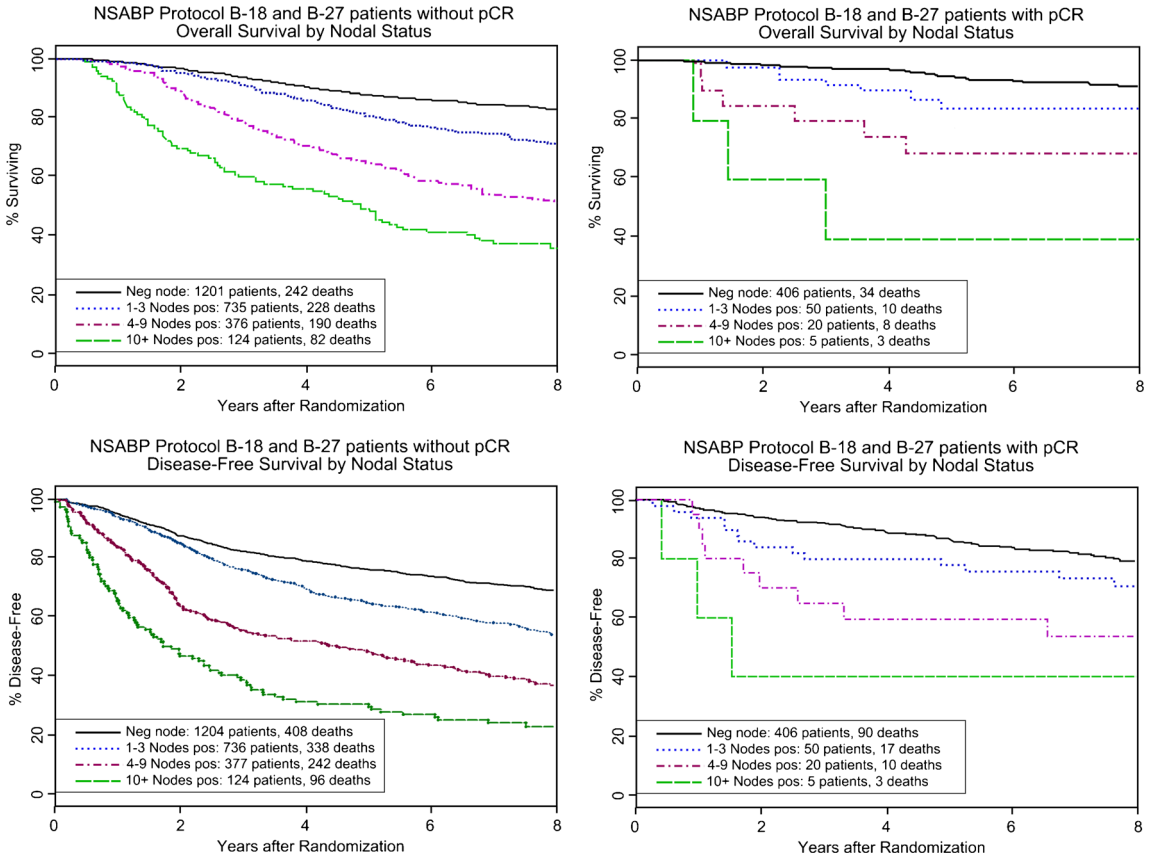

Fig. 1 Overall and disease-free survival by post-NAC nodal status of patients with or without pCR in the breast. The nodal status after NAC is an important marker of survival whether or not the patient had a pathologic complete response in the breast

comparing regional XRT to the axillary LNs versus ALND in patients with a positive SLNB [26]. However, neither of these trials included any patients treated with NAC, so their relevance to this setting is questionable at best, since residual disease following neoadjuvant chemotherapy is not analogous to the situation of a positive SLN where the patient then receives adjuvant chemotherapy.

SLNB before NAC doesn't seem to offer any particular clinical benefit, submits the patient to the need for two separate operations, and has the potential of reducing the number of patients who might benefit from down-staging of axillary LNs and thus avoiding ALND.

Accuracy of Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy in Node-Negative Breast Cancer

Frequently cited arguments in favor of pretreatment SLNB and against depending on SLNB after NAC are the potential for failure to find a SLN after NAC and the possible inaccuracy of SLNB after NAC. This argument may be quite different for patients with clinically negative versus those presenting with biopsy-proven nodal metastases. The concern about failure to map and high false-negative rates is based on possible fibrosis of lymphatics or nodes during chemotherapy and the possibility that cancer in the sentinel nodes might undergo a complete response even while other nodes continue to harbor metastatic cancer cells.

Those opposed to SLNB after NAC based on the potential for failure to map will find no disagreement on this point from those who advocate post-NAC SLNB. They would agree that failure to map should result in proceeding with an ALND. So, failure to map is really a non-issue, except for potential wasted effort (time and cost) of injecting the mapping agents and attempting to find a sentinel node without success. The important question is: when the SLN are identified, how reliably does this reflect the residual axillary nodal status? This has been addressed in a number of reports of patients undergoing NAC followed by SLNB+ALND and three meta-analyses [27–31]. Some of these included a mix of clinically node-negative and node-positive patients. These studies, including a large series of mostly node-negative patients enrolled in the NSABP B-27 trial [32], showed that the false-negative rates (FNR) were in the range of 10–12 %, remarkably similar to the FNR observed in large trials of SLNB+ALND performed without prior treatment [6, 33–35] (see Table 2). A series from MD Anderson also demonstrated similar false-negative rates

Table 2 Comparison of SLNB false negative rate among primary surgery and post-neoadjuvant series

Study	*n*	cN0	cN+	FNR (%)
Primary surgery SLN				
Multicenter SB2 trial [33]	443	443	0	11.4
Italian randomized trial [34]	257	Not specified	Not specified	8.8
University of Louisville [35]	806	806	0	7.2
NSABP B-32 randomized trial [6]	2807	2807	0	9.8
Anne Arundel (without NAC) [27]	939	939	0	13
Post-NAC SLN				
Anne Arundel (with NAC) [27]	29	29	0	0
NSABP B-27 (after NAC) [32]	428	326	102	10.7
Meta-analysis (Xing [28])[a]	1273	594	276	12.0
Meta-analysis (Kelly [29])[a]	1799	873	691	8.4
Meta-analysis (van Deurzen [30])[a]	2148	1127	919	10.5

n number of patients analyzed, *cN0* number of patients with negative node status at presentation (before NAC), *cN+* number of patients with positive or abnormal nodes at presentation (before NAC), *FNR* false-negative rate

[a] 13/24 (Xing), 19/24 (Kelly), and 24/27 (van Deurzen) of the original manuscripts were available and contained nodal status at presentation

for SLNB between women with clinically and US-negative nodes receiving NAC and node-negative women operated on without prior treatment (5.9 vs. 4.1 %, respectively) [36]. This group went on to perform SLNB in a large series of node-negative women who had received NAC and only performed ALND for those with positive SLN pathology after treatment. This resulted in dramatic decreases in the incidence of ALND for women with T2 and T3 cancers compared to women with similar size tumors who underwent primary surgery (27.1 vs. 40.6 % for T2; 45.1 vs. 65.7 % for T3).

Axillary Management for Women With Clinically Positive Nodes Receiving NAC

A number of small retrospective series suggested that the FNR for women undergoing SLNB was quite high, in the range of 30 % [37, 38]. More recently, two large prospective trials have addressed this question. The ACOSOG Z1071 trial [13•] enrolled patients presenting with positive lymph nodes (cN+) documented by fine needle aspiration (FNA) or core biopsy prior to NAC. Patients with N1 or N2 disease were included, but prior axillary surgery was not allowed, including SLNB before NAC. After undergoing NAC, all patients underwent SLNB and ALND. The primary end point was defined as the FNR for women with clinical N1 disease in whom at least two SLNs were identified and removed. The SLN detection rate was 92.9 % for patients presenting with N1 disease and 89.5 % for those presenting with N2 disease. The FNR for all patients with two or more SLNs identified (study target) was 12.6 %, not reaching the prespecified threshold of 10 %. Several factors affected the accuracy of SLNB: when surgeons used both a blue dye and radiocolloid tracer, the FNR was 10.8 %, lower than the 20.3 % rate observed when only one agent was used. Identifying three or more SLNs was associated with a FNR of 9.1 % compared to 21.1 % when only two SLNs were examined.

Similarly, the SENTINA trial [25•] aimed to answer multiple questions and included multiple arms: patients with cN0 disease underwent SLNB prior to NAC, and those with negative SLNs had no further axillary intervention after NAC (arm A); if the initial SLN was positive, repeat SLNB was attempted after NAC (arm B). For patients presenting with cN+disease and converted to clinically node negative after NAC (ycN0), SLNB and ALND was performed after NAC (arm C); those who presented with cN+ and remained ycN+ after NAC underwent ALND without SLNB (arm D). Arm C is the one of most interest and was comparable to the patients in the Z1071 trial.

The overall post-treatment SLN detection rate was 80.1 % in arm C. Similar to the Z1071 trial, detection was improved to 87.8 % in arm C when surgeons used both blue dye and radioactive colloid. As with detection rate, the number of SLNs identified increased when dual tracers (blue dye and radiocolloid) were used. Multivariate analysis demonstrated that the only factor improving detection rate in arm C was the use of two mapping agents. The overall FNR was 14.2 % in arm C, but when two mapping agents were used, the FNR rate was only 8.6 %. In agreement with the Z1071 trial, the FNR was lower with increasing number of SLNs identified, 24.3 % for 1 SLN, 18.5 % for 2 SLNs, and 7.3 % for 3 SLNs. For all patients with three or more SLNs, the FNR was 4.9 %.

The Canadian SN FNAC study [39] enrolled patients with biopsy-proven positive nodes (N1 and N2) after NAC, and all patients underwent SLNB followed by ALND; with a pCR rate of 34 %, the SLN identification rate was 87.2 %. The overall FNR was 9.9 % (19 % if only one SLN was removed and 6.6 % if two or more SLNs were removed).

Many have interpreted the Z1071 and SENTINA results as evidence that SLNB after NAC is not an appropriate management strategy for women presenting with clinically positive

nodes. However, an alternative interpretation is that these data support the use of SLNB in those patients who present with positive axillary nodes, as long as two mapping agents are used and at least two SLNs are identified. Clearly, if no SLN is identified, then ALND should be performed, whether the nodes were clinically positive or not at presentation. If only one SLN is identified, then ALND should also be considered. With these caveats, SLNB after NAC can be used to avoid non-therapeutic ALND and its associated morbidity in the 30 to 40 % of patients that present with positive LNs and are down-staged by NAC. As NAC (including the use of targeted agents) improves, the potential number of patients who could avoid ALND will certainly increase.

There are technical factors (i.e., modifiable by the surgeon) and non-technical factors that influence FNR. As described above, dual tracer with a radiolabelled colloid and a visible dye should be used; this will increase the SLN detection rate and the number of SLNs identified and decrease the FNR [13•, 25•].

What Are the Potential Consequences of Understaging the Axillary Nodes After NAC?

Although the data accumulated over the past four decades suggest that removing positive nodes has little therapeutic impact, this is in part a result of systemic therapies and irradiation. However, if residual cancer is present in regional nodes after adequate NAC, these cells are by definition chemoresistant and may have different consequences if left behind. Potential understaging of the axillary nodes after NAC would not generally impact adjuvant systemic treatment, since most centers give all of the chemotherapy up front and there is no evidence that additional systemic therapy (other than hormonal therapy for hormone receptor positive cancers) will improve outcomes, regardless of response to NAC. However, as new agents (especially targeted therapies) are developed, the presence of residual cancer in the breast or nodes may influence postoperative decisions related to additional therapy. This may also apply to the addition of regional and chest wall radiation after surgery, which may improve outcomes, especially for patients with less than a pCR in the nodes. Although the current standard is to give regional irradiation to women who present with positive nodes, regardless of response to NAC, this may change in the future, making accurate post-NAC staging of the axilla more important (see below).

The Future of Management of Regional Lymph Nodes Based on Surgical Staging After NAC

It is becoming more common to add regional nodal irradiation and, for mastectomy patients, chest wall irradiation for women with any positive nodes. This is based on older trials, published in the late 1990s from Canada and Denmark as well as the MA20 trial and the recent overview meta-analysis showing a survival benefit for node-positive patients undergoing partial or total mastectomy and receiving systemic chemotherapy [16–19, 40]. Although all of these data are based on patients undergoing primary surgery, they drive a tendency to add more radical radiotherapy for women with positive nodes at presentation, even if they are converted to negative by NAC. This, in turn, raises more concern about false-negative SLNB results after NAC and understaging of the residual nodal disease. However, analysis of local-regional recurrence (LRR) rates in patients who received NAC in the B-18 and B-27 trials suggest that even for patients with clinically positive nodes prior to NAC, LRR may not be a serious concern if the nodes are pathologically negative after treatment [23•]. It is critical to understanding these results to realize that post-mastectomy irradiation and addition of regional nodal radiation after BCT was not allowed in these trials. Nevertheless, in women who were converted from clinically node positive to pathologically node negative (determined by ALND in all patients), the LRR rates were quite low. This has led to the hypothesis that the response to NAC can be used to "tailor" postoperative radiation to limit its use to women with residual positive nodes and avoid the morbidity of this added treatment (including compromising the results of reconstruction) in selected patients whose nodes become negative after NAC. This is being tested in a recently opened NRG Oncology trial randomizing women in this situation to receive or not to receive regional nodal irradiation after partial or total mastectomy and chest wall radiation after total mastectomy (NSABP B-51/RTOG 1304). Post-NAC nodal staging for this trial can be performed either by SLNB or ALND.

Conversely, despite data showing that ALND has little value for women with positive SLNs at primary surgery, it has been considered standard to perform ALND and to add regional irradiation for women presenting with positive nodes or to proceed with completion ALND plus regional irradiation for women with positive SLNB after NAC. This approach is also being challenged in a prospective randomized Alliance trial (A11202), in which women who present with biopsy-confirmed nodal metastases and who still have positive SLNs after NAC are randomized to completion ALND and regional nodal irradiation versus no additional surgery and regional nodal irradiation.

Conclusions

NAC is an established approach to treat inoperable breast cancer as well as to avoid the need for mastectomy in patients desiring BCT but who are not optimal candidates at presentation. By

down-staging the regional lymph nodes in approximately 40 % (or more for some subsets) of patients presenting with node-positive disease, NAC also has the potential to scale back the extent of axillary surgery. This approach seems to be quite accurate and acceptable for women who present with clinically negative nodes. The detection rate and FNR after NAC are better when both radioactive colloid and blue dye are used to identify the SLN. For women who present with clinically positive nodes, confirmed by biopsy, the acceptability of relying on SLNB after NAC has been more controversial. The use of two agents to identify SLNs in these patients also results in decreased FNRs, in the range of 10 % or less. Increasing the number of SLNs identified is associated with lower FNRs, consistently below 10 % when three or more SLNs are identified. The therapeutic significance of occult-positive disease left in other nodes after a false-negative SLNB is currently unknown, but at this time, the axillary LN stage after NAC doesn't usually change systemic management. Maturing and ongoing studies will further define the role of regional XRT as an adjunct to or in lieu of ALND for node-positive breast cancer, which converts to ypN0 after NAC. Likewise, ongoing trials will define the role of completion ALND for women with persistently positive axillary nodes after NAC.

Compliance with Ethics Guidelines

Conflict of Interest Leopoldo J Fernandez declares that he has no conflict of interest.

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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.

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