Review Article

Sentinel lymph node biopsy following neoadjuvant chemotherapy: an evidence-based review and recommendations for current practice

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Abstract: Sentinel lymph node biopsy (SLNB) at upfront surgery is the gold-standard surgical method for axillary lymph node staging in early stage breast cancer: the technique provides adequate information regarding axillary status, with similar oncological safety and lower morbidity compared to axillary dissection, despite the false negative rates. Neoadjuvant chemotherapy (NACT), traditionally used for locally advanced breast cancer, plays an important role in the treatment of early stage breast cancer, making downstaging possible in axillary lymph node and breast cancer, thus minimizing the impact of surgery and reducing morbidity, as well as enabling patients with residual disease to be selected for adjuvant treatment. In this respect, the role of SLNB has proved controversial, particularly in view of the lack of data from randomized clinical trials on this subject. Currently, the de-escalation of axillary surgery after NACT is mainly based on retrospectives studies and false negative rates. This paper reviews current evidence on the management of axillary surgery following NACT under different circumstances, with suggested recommendations in each scenario: clinically negative nodes at diagnosis and SLNB after NACT, clinically positive nodes at diagnosis and SLNB after NACT, positive SLNB following NACT and finally the possibility of omitting axillary surgery in good responders.

Keywords: Breast cancer; sentinel node biopsy; neoadjuvant chemotherapy (NACT); axillary dissection

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Introduction

Sentinel lymph node biopsy (SLNB) at upfront surgery is the gold-standard surgical method for axillary lymph node staging in early stage breast cancer. Survival and oncological outcomes are pivotal when validating a new treatment or procedure; however, with respect to the sentinel lymph node (SLN), early studies overlooked these parameters and considered the rate of false-negative findings as the principal endpoint. In those series, patients with early-stage tumors were submitted to SLNB followed by conventional axillary dissection. The ideal false-negative rate (FNR) was defined as ≤5%, a number arbitrarily established in consensuses of specialists (1-3). Subsequent randomized clinical trials assessing oncological outcomes such as overall survival, disease-free survival and local control showed oncological safety similar to that achieved with axillary dissection. The FNR in some analyses, however, exceeded the value considered ideal in previous studies (4.6–9.8%) (4-6). Nevertheless, the technique has the advantages of reducing surgical morbidity with no negative effect on prognosis (4-7).

Neoadjuvant chemotherapy (NACT) was developed to convert originally inoperable tumors into operable tumors and to evaluate response to treatment. The National Surgical Adjuvant Breast and Bowel Project studies, NSABP B-18 and NSABP B-27, showed that initiating treatment with chemotherapy or providing adjuvant chemotherapy did not change prognosis (8,9). In the NSABP B-18 study, the group that began treatment with NACT had a higher rate of breast preservation (69.8% *vs.* 59.8%) and a similar rate of local recurrence (HR =0.98; 95% CI: 0.83–1.15; P=0.78) (8). In addition, neoadjuvant therapy showed a non-significant trend towards a better prognosis in women under 50 years of age (9). Prognosis was better in the women who experienced pathologic complete response (10% of those in the doxorubicin + cyclophosphamide arm and 17% of those in the doxorubicin + cyclophosphamide + docetaxel arm) (9). This came to be seen as a means of identifying those patients who would respond well to the drugs, but resulted in no changes in treatment (8). Based on those studies, the indications for NACT became highly objective: locally advanced, inoperable tumors (T3, T4, N1-3) or tumors for which breast-conserving surgery was not possible. In cases of tumors that could be treated with breast-conserving surgery (T1/T2, N0), surgery was generally the first treatment option. However, as knowledge increased regarding tumor biology and new treatments were implemented, the indications for NACT changed to include cases of tumors that can be treated with breast-conserving surgery. In this new scenario, axillary downstaging in responding tumors leads us to consider SLNB after NACT to avoid morbidity from complete axillary dissection.

Progress made in SLNB after NACT has followed the same pathway as upfront SLNB in that no randomized studies on oncological safety have been conducted up to the present time, irrespective of initial axillary node status. In patients with initially negative axilla (cN0) who receive NACT, FNRs are generally acceptable (≤10%) (10-12), and, indeed, data from non-randomized studies have shown low rates of axillary recurrence (12-14). Conversely, patients with clinically positive axilla (cN1/2) prior to treatment and who experience clinical complete response represent a more challenging group. In addition to the lack of randomized studies assessing clinical outcomes, overall FNRs are considered high, possibly impacting on local control and important prognostic information (15-23). More recently, there has been an increasing tendency to omit axillary dissection in patients with a positive SLNB (ypN+) following NACT, as in cases of upfront surgery in circumstances similar to those of the Z11 study, even when the residual burden is high (24-29). Another line of investigation has evaluated the consequences of omitting any axillary surgery in patients who respond well to NACT (30-37). The objective of the present paper is to review current findings on SLNB following NACT in different clinical circumstances, based on the best available evidence.

Clinically negative nodes at diagnosis and SLNB after NACT

In patients with initially negative axilla (cN0), SLNB following NACT has been performed over the years, principally on the basis of FNRs similar to those found with upfront surgery. Some meta-analyses have reported overall FNRs of around 10% irrespective of the use of dual tracers or the number of lymph nodes removed (10-12). These rates are similar to that found in the NSABP B-32 study and are considered safe (*Table 1*). One of those reviews included 2,148 patients from studies conducted between 1993 and 2009. The analysis resulted in an SLN identification rate of 90.9% (88–93.1%), FNR of 10.5% (8.1–13.6%), accuracy of 94.4%, and negative predictive value of 89% (12). In another meta-analysis involving 24 studies conducted between 2000 and 2007 with a total of 1,799 patients, the SLN identification rate was 89.6% (86–92.3%), with a FNR of 8.4% (6.4–10.9%) (10). On the other hand, studies on

Table 1 Studies on false-negative rates in initially negative axilla (cN0) patients submitted to sentinel lymph node biopsy following neoadjuvant chemotherapy

Author	Number of patients	False-negative rate
Shirzadi *et al.* (11)	1,521	7% (5–9%)
Kelly *et al.* (10)	1,799	8.4% (6.4–10.9%)
van Deurzen *et al.* (12)	2,148	10.5% (8.1–13.6%)

clinical outcome are limited to data from non-randomized trials. A retrospective study conducted at the MD Anderson Cancer Center evaluated cN0, T1–T3 patients undergoing SLNB following NACT (n=575) or upfront surgery (n=3,171). Lymph node recurrence rate was 1.2% in the NACT group and there was no difference in terms of disease-free survival or overall survival (13). The GANEA-2 study was a prospective multi-institutional French cohort study aimed at assessing the accuracy and safety of SNLB after NACT in initially cN0 and pN1 patients. Of the 419 initially cN0 patients treated with SNLB alone, only one patient had lymph node recurrence after a mean follow-up time of 36 months, while patients allocated to the pN1 group underwent SLN dissection (SLND) and axillary dissection (FNR: 11.9%) (14).

Initially positive axilla (cN1/2) and negative SLNB following NACT

Traditionally, the FNRs for SLNB in patients with initially clinically positive axilla who achieved clinical/imaging complete response following NACT were considered unacceptable (>20%); therefore, all these women were submitted to axillary dissection despite the fact that a considerable number of patients had axillary pathologic complete response (11). The SENTINA, Z1071 and SN-FNAC studies changed this concept. The overall FNRs reported by those studies for patients submitted to NACT were 14.2%, 12.6% and 13.3%, respectively, rates that were higher than that of 10% previously specified as being safe but lower than other previously reported rates (15-17). Furthermore, analysis of subgroups revealed that the identification of more than three lymph nodes; SLN mapping using dual tracer imaging with the patent blue dye and radioisotope combination technique; clipping the affected lymph node prior to NACT; or even the use of immunohistochemistry reduced the FNR to <10% (15-17). A recent meta-analysis that included 1,921 patients with biopsy-proven node-positive breast cancer reported an identification rate of 90% and a FNR of 14%; however, when three or more lymph nodes were identified, the FNR fell to 4% (19).

Clipping the metastatic lymph node before neoadjuvant treatment and removing the clipped node at the time of surgery have been suggested as a means of reducing FNRs (18). In the Z1071 study, a FNR of 7.2% was found in a subgroup of patients in whom the metastatic lymph node was marked with a clip prior to NACT and then resected (16). The findings varied with the technique used to identify the clipped lymph node: the SLN was indeed the clipped lymph node in 78% of cases (101/130) when dual tracers were used and 50% when a single tracer was used (16). In a retrospective study conducted at the MD Anderson Cancer Center, of the 134 patients who underwent SLND, the clipped node was not identified as an SLN in 23% (31 of 134) of patients. The overall FNR was 10.1% for SLNB, 4.2% for clipped lymph nodes and 2% when the SLN was marked and located using iodine-125 seeds (I-125 seed), a procedure referred to as targeted axillary dissection (TAD). In TAD, patients with a clipped node (biopsy-confirmed nodal metastases) are marked with an I-125 seed. This is performed after undergoing NACT and receiving an injection of mapping agents (radioisotope and/or blue dye) prior to surgery. A gamma probe is then used to identify the seed and the radioisotope-containing nodes removed during surgery, including nodes containing blue dye alone or those found to be palpable (18). In another study, the identification rate was 77.8% (329/423) for cases of clipped lymph node and 86.9% (199/229) when an I-125 seed was used. In 35.2% of cases, the clipped lymph node proved not to be the sentinel lymph node. The authors reported a FNR of 7.2% for the clipped lymph node technique and 4.2% for the I-125 seed technique (38) (*Table 2*).

The efforts made to reduce the FNR in these circumstances reflect the absence of data from randomized clinical trials on oncological safety. Nevertheless, data from single centers suggest that axillary recurrence could be very low (39-42). In a consecutive cohort of 688 patients submitted to NACT at the European Institute of Oncology and followed up for ten years, axillary recurrence was 1.6% in the initially cN1/2 group (n=123) (40). The higher rate of false-negative results was considered to pose no clinical risk and the SLNB technique was recommended to be used

Table 2 Identification rates and false-negative rates with clipped lymph node and targeted axillary dissection

Author	Clipped lymph node not identified	False-negative rate of clipped lymph node	False-negative rate with targeted axillary dissection
Boughey *et al.* (16)	37%	7.2%	1.4%
Caudle *et al.* (18)	23%	4.2%	2.0%
Kuemmel *et al.* (38)	22%	7.2%	4.2%

Table 3 Studies of patients submitted to sentinel lymph node biopsy without axillary dissection who had initially positive axillary lymph nodes prior to neoadjuvant chemotherapy

Author	Initial axilla	Number of patients	Regional recurrence
Piltin *et al.* (42)	cN1/2	159	<1.0%
Kahler-Ribeiro-Fontana *et al.* (40)	cN1/2	123	1.6%
Barrio *et al.* (41)	cN1	234	<1.0%
Wong *et al.* (39)	cN1/2	58	0%

in these circumstances irrespective of the number of lymph nodes resected or whether dual-tracer mapping or clipping of the axillary lymph node is used (in 50% of cases in that series, only one SLN was resected) (40). In another analysis conducted at the McGill University Medical School, including 58 cN1/2 patients who obtained clinical complete response and in whom SLNB was used, there was no axillary lymph node recurrence during follow up (39). In a series of 769 consecutive patients with positive lymph nodes submitted to NACT at the Memorial Sloan Kettering Cancer Center, 555 had clinical complete response and in 234 cases (42%) axillary dissection was avoided through the use of dual-tracer mapping and the identification of at least three lymph nodes (41). After 4 years of follow-up, there was only one case (0.4%) of axillary recurrence synchronous with local recurrence in the entire cohort and that case consisted of a patient who had refused radiotherapy (41). In another study conducted at the Mayo Clinic with 159 initially cN1/2 patients submitted to SLNB without axillary dissection, one patient had axillary lymph node recurrence over a short follow-up time (42) (*Table 3*).

The RTOG 1304/ NSABP B51 study will provide definitive data on this subject (43). The search for a lower FNR remains most relevant, since, even if there is no locoregional effect of a higher FNR, identifying a residual lesion could be crucial when deciding on whether to use systemic adjuvant therapy with capecitabine for triple-negative tumors or olaparib for patients with the BRCA mutations and trastuzumab emtansine (T-DM1) in HER2 disease. Studies with these drugs have shown important benefits in women with residual disease following NACT (20-22).

Positive SLN following NACT

In recent years, following publication of the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 (Z11) study (44), there has been an increasing tendency to omit axillary dissection, even in patients with SLN metastases after NACT (23,24). Indeed, the Z11 study showed excellent locoregional control with the omission of additional axillary surgery in patients with positive SLN. However, as in other studies that also evaluated the omission of axillary dissection at upfront surgery, patients submitted to NACT were not included in those analyses (45-49). Furthermore, residual disease following NACT means resistance to systemic treatment, hence the possibility of a high residual burden of disease. Single center analyses have shown high residual cancer burden in around 60% of cases after NACT irrespective of the extent of metastasis (micro- or macro-metastasis) or of the subtype of the disease (26-28). This rate compares with the rate of 27% found in the Z11 trial and 13% for micro-metastasis alone (IBCSG 23-01) at upfront surgery (44,49). It is reasonable to assume that the results found at upfront surgery may not have the same outcome following NACT.

The NSABP B-18 and B-27 studies evaluated the role of anthracyclines or of anthracyclines associated with taxanes as neoadjuvant therapy for patients submitted either to breast-

Table 4 Oncological outcomes in studies that evaluated sentinel lymph node biopsy alone compared to axillary lymph node dissection when residual axillary disease is present.

Author	Patients	Duration of follow-up	Oncological outcome
Ling *et al.* (52)	161	3 years	92.6% with SLNB *vs.* 96.4% with AD; P=0.616[†]
Chun *et al.* (53)	324	71 months	91.2% with SLNB *vs.* 91.4% with AD; P=0.594[‡]
Almahariq *et al.* (54)	1,617	5 years	71% with SLNB *vs.* 77% with AD; P=0.01[§]

Oncological outcome evaluated: [†], regional control; [‡], axillary recurrence; [§], overall survival. SLNB, sentinel lymph node biopsy; AD, axillary dissection.

conserving surgery with radiotherapy or to mastectomy without radiotherapy associated with axillary dissection. A combined analysis of these studies (50), which evaluated 335 locoregional recurrences (12.6% in mastectomized patients and 10.3% following breast-conserving surgery), found high accumulated 10-year regional recurrence rates in patients with initially positive axillary lymph nodes that remained positive following NACT and axillary dissection (7.5% in women ≥50 years of age and 8.7% in those <50 years of age at breast-conserving surgery with radiotherapy). More recent studies have produced controversial results. A study conducted in the Netherlands (51) using initial axillary ultrasonography reported four cases of regional recurrence (4/118 or 3.4%) after three years of follow-up in patients with residual disease in the SLN following NACT who had fewer than four affected lymph nodes at axillary ultrasonography and who were given only radiotherapy as additional axillary treatment, without axillary dissection. Another two retrospective studies involving a small number of patients found no differences in terms of oncological outcome (52,53). On the other hand, a study conducted using the National Cancer Database (54) included 1,617 women initially cN1 submitted to NACT and compared axillary dissection with SLNB associated with axillary radiotherapy in a design similar to that of the ongoing prospective randomized study conducted by the ALLIANCE group (A11202). Better survival rates were associated with axillary dissection. In an exploratory analysis, the authors reported similar survival rates in hormone receptor (HR)-positive tumors and metastasis in a single lymph node (*Table 4*).

Omitting axillary surgery in good responders

SLNB allowed similar prognostic information to be obtained; however, although morbidity is less than with axillary dissection, the procedure is not without complications. The largest study on SLNB (NSABP-B32) found numbness in 7.5% of cases, paresthesia in 6% and lymphedema of the ipsilateral upper limb in 8% in an evaluation performed 36 months after the procedure (4-7). This led to an ongoing debate on whether surgical procedures on the axilla should be avoided under specific circumstances such as when information on axillary status would not affect the decision regarding whether to use systemic or regional therapy or when prior evaluation with imaging tests would enable the negative predictive value of the lymph nodes to be established with a high degree of certainty. The problem of omitting axillary surgery under these conditions with excellent responders is that evaluating the presence of residual disease is very important when making a decision regarding adjuvant therapy. Indeed, in patients with initially positive axilla who achieve clinical complete response to NACT, SLNB will identify residual disease in more than 50% of cases (16).

In HER2-positive breast cancer, the results of the KATHERINE randomized clinical trial (21) showed that the use of T-DM1 in patients with any residual lesion increases disease-free survival. In triple-negative breast cancer, the CREATE-X randomized clinical trial evaluated the addition of capecitabine for patients with residual disease and confirmed that its use increased disease-free and overall survival (20). More recently, the adjuvant use of olaparib in patients with the BRCA gene mutations and residual disease after NACT was associated with better invasive disease-free survival in the OlympiA study (22). Therefore, ignoring pathologic lymph node status in such cases could result in the omission of treatments capable of changing relevant clinical outcomes. On the other hand, the KEYNOTE-522 study (55), which used pembrolizumab associated with chemotherapy as neoadjuvant therapy in triple-negative tumors, showed that the addition of immunotherapy increased pathologic complete response and disease-free survival. It can also be used as adjuvant therapy irrespective of the presence of a residual lesion. In this case, knowledge

Table 5 The probability of disease in the lymph node in patients with cT1/2cN0 tumors submitted to neoadjuvant chemotherapy and with pathologic complete response in the breast

Author	Number of patients	HER2	Triple-negative
Barron *et al.* (30)	5,377	HR-positive: 2.1%; HR-negative: 1%	1.6%
Samiei *et al.* (31)	986	HR-positive: 1.6%; HR-negative: 0%	1.5%
Tadros *et al.* (32)	116	0%	0%
van der Noordaa *et al.* (33)	89	0%	0%

HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

Table 6 Ongoing studies to evaluate the role of axillary ultrasonography in omitting sentinel lymph node biopsy at upfront surgery or after neoadjuvant chemotherapy

Study	Upfront surgery	Neoadjuvant chemotherapy
SOUND (34)	Yes	No
INSEMA (35)	Yes	No
VENUS (36)	Yes	Yes
EUBREAST-01 (37)	No	Yes

of pathologic lymph node status would not affect the indication of pembrolizumab. However, a combination of pembrolizumab and capecitabine in patients who used the immunotherapy drug as neoadjuvant therapy and did not achieve pathologic complete response was not evaluated. Another relevant factor in relation to lymph node status is the indication of regional radiotherapy for those patients with positive axillary lymph nodes following NACT. The current tendency is to recommend it in cases of axillary lymph node metastasis following neoadjuvant treatment (56,57). Nevertheless, with the previously presented data on the extremely low likelihood of positive axillary lymph nodes, we believe that the number needed to treat (NNT) to prevent regional recurrence in cases in which radiotherapy is omitted could be very high.

The advances made in these NACT regimes, with the addition of new drugs and a more appropriate selection of patients has, on the other hand, resulted in a high rate of pathologic complete response, leading some investigators to question whether surgery could be avoided under these circumstances (30-37). In 2017, a study conducted in the MD Anderson Cancer Center with 572 cT1/2 cN0/1 patients with triple-negative and HER2-positive breast cancer who underwent NACT showed that of the 290 cN0 patients included, 116 obtained complete pathologic response in the breast (32). When pathologic response in the axillary lymph nodes was evaluated, it was found that none of the patients had axillary metastasis, showing that the likelihood of residual axillary disease following NACT and complete pathologic response in the breast in patients initially presenting with clinically negative axilla in these subtypes is very low. Another study, conducted using data from the United States National Cancer Database, included 30,281 patients and encompassed all the immunohistochemical profiles. The probability of finding a positive lymph node in cT1/2 cN0 patients with clinically negative lymph nodes following NACT was evaluated in patients who achieved pathologic complete response in the breast. Residual disease in axillary lymph nodes was found in 1.0%, 1.6%, 2.1% and 4% of cases of HER2-positive/HR-negative, triple-negative (HER2-negative/HR-negative), HER2-positive/HR-positive and HR-positive/HER2-negative tumors, respectively (30). Similar data were reported from another two studies published later (*Table 5*) (31,33).

With the routine use of axillary ultrasonography in patients with an indication for NACT, these numbers should currently be even lower in series with larger sample sizes (51,58,59). Indeed, some studies are evaluating the role of axillary ultrasonography in omitting axillary surgery, either during upfront surgery or even after NACT (34-37) (*Table 6*). The EUBREAST-01 trial (37) was conducted under the concept that the probability of axillary disease in patients with triple-negative and HER2-positive breast cancer with pathologic complete response in the breast after NACT and normal findings at axillary ultrasonography is extremely low and is evaluating omitting SLNB in such cases. The primary endpoint of the study is 3-year axillary lymph node recurrence-free survival, with the acceptable rate being ≥98.5%. The patients who did not achieve pathologic complete response in the breast will undergo further surgery for axillary management. A result of less than 96% in that study would be considered negative.

Conclusions and recommendations

Initially negative axilla (cN0) and SLNB

SLNB can be performed in initially cN0 patients following NACT without further concern with respect to the number of lymph nodes removed or the use of dual-tracer mapping, since the overall FNR is similar to that with upfront surgery and non-randomized studies have shown a low recurrence rate.

Initially positive axilla (cN1/2) and clinical complete response following NACT

In these circumstances, based on a higher FNR, the absence of randomized clinical trials for clinical outcomes and with the objective of selecting patients for adjuvant therapy when there is residual disease, tactics to reduce the FNR should be encouraged until the results of randomized clinical trials become available.

Positive SLN following NACT

Axillary dissection should be the current standard until the results of randomized clinical trials become available, since the residual axillary burden is high irrespective of the extent of the lymph node metastasis. In addition, data from non-randomized trials are debatable.

Omission of axillary surgery in good responders

Axillary surgery should be performed routinely in all cases irrespective of clinical response or findings at imaging tests following NACT, since there are no data from randomized clinical trials on oncological safety and there is a considerable risk of missing candidates for adjuvant therapy. Specific circumstances are being evaluated in clinical trials.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-22-110/coif). FPC received honoraria for lectures from Roche, AstraZeneca, MSD, Pfizer and Libbs and participated in a Data Safety Monitoring Board or Advisory Board for Roche, MSD and Pfizer. FPZ received honoraria for lectures from AstraZeneca, MSD and Novartis. AM received consulting fees from MAPE Solutions, Daiichi Sankyo, AstraZeneca and Roche; honoraria for lectures from Daiichi Sankyo, AstraZeneca and Roche; support for attending meetings/travel from Daiichi Sankyo; and participated in a Data Safety Monitoring Board or Advisory Board for MAPE Solutions, Daiichi Sankyo and AstraZeneca. RHSM received honoraria for lectures from Roche, AstraZeneca, Pfizer, and Merck Sharp and Dohme. The other authors have no conflicts of interest to declare.

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