

Extended Sentinel Node Biopsy in Breast Cancer Patients who Achieve Complete Nodal Response with Neoadjuvant Chemotherapy

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ABSTRACT

Neoadjuvant chemotherapy (NAC) can eradicate axillary disease in breast cancer (BC) patients. Sentinel node biopsy (SNB) in patients with positive axilla who accomplish complete clinical response after NAC is a new opportunity for changing paradigms and decreasing the extension and the morbidity of axillary surgery. The aim of this article is to review the limits of SNB in this setting and present the current status of an expanded modification of this technique. False-negative rates (FNRs) of conventional SNB exceed the threshold of 10%, and are not acceptable. The extended SNB (ESNB) entails the removal of at least 3 lymph nodes (LNs) including the sentinel node (SN) mapped by dual tracers and a marked lymph node (LN) that was found previously metastatic. This node by node removal procedure greatly reduces the FNRs of the procedure. Despite that axillary lymph node dissection (ALND) is still the standard of care for patients with involved LNs before NAC, the ESNB is a valid option for selected patients in whom axillary positive disease is converted to negative. When ESNB is negative in such cases (immunohistochemistry included), the omission of ALND seems to be safe.

Keywords: Breast cancer, neoadjuvant chemotherapy, sentinel node biopsy

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Introduction

Neoadjuvant chemotherapy (NAC) for breast carcinoma (BC), in combination with personalized targeted therapy, allows for high rates of pathologic complete response (pCR) (1-3).

Sentinel node biopsy (SNB) is safe after successful NAC in patients with clinically-negative axilla (3-5). For BC patients with positive lymph nodes (LNs) prior to NAC the standard surgery for treating the axilla has been axillary lymph node dissection (ALND), but as NAC enables downstaging of axillary disease, SNB in patients with clinically nodes positive (cN+) axilla who accomplish complete clinical response (yc N0) is an opportunity for changing paradigms.

This article reviews the role of SNB after NAC for BC treatment and presents the current status of a modification of this technique, the extended sentinel node biopsy (ESNB), in patients with initially positive axilla who achieve favorable response with NAC.

Impact of neoadjuvant chemotherapy on nodal burden

Numerous studies have demonstrated the disappearance (on average 40%) of LNs infiltration after anthracyclines and taxane-based regimens, in association with single or dual anti-HER-2 therapy for patients with HER-2 positive (HER-2+) disease (6-11).

BC is a heterogeneous disease and the chance of nodal pathologic complete response (pCR) strongly depends on molecular parameters. For Al-Hilli et al. (12), and Mamtani et al. (13), nodal pCR varied greatly based on immunohistochemical (IMH) classification, as shown in Table 1. The overall rates of nodal pCR were, respectively, 37.7% and 49.2% according to these authors. With advancements in the understanding of tumor subtypes, NAC is increasingly focused on HER-2 + and triple negative subtypes and less frequently used in hormone receptor-positive disease.

In the preoperative phase, ensuring that NAC is effective to downstage the LNs, is based on the comparison between nodal evaluation at diagnosis and after NAC, by physical examination and ultrasonography, that is considered the imaging technique of choice to monitor the

Table 1. Different breast cancer subtypes and nodal pathologic complete response with neoadjuvant chemotherapy

	ER+, HER-2 – (%)	ER+, HER-2 + (%)	ER –, HER-2 + (%)	ER–, HER-2 – (%)
Al-Hilli et al. (12)	20.2	47.7	61.3	47.3
Mamtani et al. (13)	20.5	70.2	96.6	47.2

Table 2. Meta-analyses estimating the false-negative rate (FNR) of the sentinel node (SN) biopsy after neoadjuvant chemotherapy in node-positive patients converted to node-negative

	n	Nodal positivity at diagnosis	FNR (%)
Fu et al. (19)	2471	clinical/ultrasonographic	14* (95% CI :10%-17%)
Van Nijnatten et al. (22)	1395	microscopic	15.1** (95% CI: 12.7%-17.6%)
El Hage Chehade et al. (23)	3398	microscopic	13 (95% CI: 10.8%-15.6%)
Simons et al. (24)	2002	microscopic	17 (I ² = 38.66%, p=0.05)

*FNR: 8.7% if the SN positivity includes immunohistochemical examination
 **FNR: 10.4% if at least two SNs were retrieved

Table 3. False-negative rates of sentinel node biopsy after neoadjuvant chemotherapy in cN+ axilla converted to cN – axilla

	n	Patients	False-negative rate (%)			
			Overall	Dual tracers	2 SNs	3 SNs
ACOSOG Z1071 ²⁶	756	T0-4, N1-2	12.6	10.8	21.2	9.1
SENTINA ²⁵	592 (Arm C)	N1-2	14.2	8.6	18.5	7.3
SN FNAC ²⁷	153	T0-3, N1-2	9.6	5.2	–	4.9*

*>2 SNs

involution of LNs. This procedure is simple and also helps to guide the fine-needle aspiration or core biopsy of LNs suspected of involvement prior to beginning systemic therapy. In the same ultrasound study, once the node is punctured, a marker may be placed in the lymph node (LN) to help the surgeon find it during surgery (7-16). No imaging technique, however, is precise enough accurate to predict nodal pCR in patients treated with NAC (14-18).

Usual sentinel node biopsy after neoadjuvant chemotherapy in clinically positive axilla at diagnosis

The identification rate of sentinel node (SN) after NAC is quite acceptable (± 90%), but it is lower than the one observed in upfront surgeries, probably because of fibrotic compression over the lymphatic capillaries (19). The main limitation of SNB in this setting is its high

false negative result (FNR), estimated to be greater than 25% in initial studies (20, 21). Four meta-analyses calculated the FNR in node-positive patients converted to node-negative varying from 13% to 17% (Table 2) (19-24). In all studies, the FNR was deemed unacceptable since it was higher than 10%, the threshold adopted, based on the reasoning that it should not be greater than the rate observed in patients without NAC.

Three pivotal observational studies assessed SNB in patients with cN+ axilla who converted to ycN0 status after NAC (Table 3).

The SENTINA (SENTInel NeoAdjuvant study) was undertaken in Germany and Austria (25). In one of the study arms, 592 patients that converted from cN+ to ycN0 were treated with both SNB and axillary lymph node dissection (ALND). The SN detection rate was 80.1%, and its FNR was 14.2%. The FNR was 24.3% for women who had one SN removed, 18.5% for those who had two sentinel nodes (SNs) removed, and 4.9% for those who had at least three SNs removed. The FNR was 8.6% for patients who underwent dual SN mapping (vital dye and radiocolloid) compared with 16.0% for those who received radiocolloid alone.

The American study ACOSOG Z1071 determined the FNR of SNB after NAC, in women initially presenting with pathologically confirmed node-positive disease, when at least 2 SNs were excised (26).

Key Points

- Extended sentinel node biopsy is considered oncologically safe for patients with complete clinical response after neoadjuvant chemotherapy.
- The technique involves dual mapping sentinel node, resection of at least 3 lymph nodes, including the metastatic one marked at diagnosis.
- The omission of axillary lymph node dissection is valid option in patients with microscopically negative disease.

Positive SNs were defined as those with metastasis larger than 0.2 mm. A total of 701 women (663 cN1 and 38 cN2) were enrolled. After completion of NAC, 582 (83.0%) patients lacked palpable LNs. The SNB FNR was 12.6%, exceeding the acceptable threshold of 10%, which did not support the use of SNB in this population. Nevertheless, the authors found the following relevant factors lowering the FNR: a) the FNR was 91% when ≥ 3 SNs were examined; b) the FNR was 20.3% with single agent mapping and 10.8% when vital dye and radiocolloid were used; and c) the FNR was 11.3% when the axilla became clinically negative and 19.2% when palpable axillary LNs persisted.

In the French SN FNAC study (Sentinel Node Biopsy Following Neoadjuvant Chemotherapy), 145 patients with biopsy-proven node-positive disease (T0-3, N1-2) underwent SNB and ALND (27). Pathological examinations using IMH were mandatory if SN was negative by hematoxylin and eosin (H&E) staining. The SN identification rate was 87.6% (127/145), and the axillary pCR was 34.5%. The FNR of SNB was 8.4%.

The usual SNB is not sufficiently accurate in this setting. The highest FNR for SNB in relation to the axillary LNs accepted is 10%, taking into account its estimated value for T1-2 N0 BC cases (28). The prognostic influence of eventual malignant cell permanence in the axillary LNs is a cause of serious concern; experimentally, it was proved in mice, that LNs are foci for systemic dissemination through fine capillaries inside them (29, 30).

Kang et al. reviewed the records of 1247 patients who had clinically axillary LN-positive status and presented negative conversion following NAC (31). Patients who underwent axillary surgery with SNB-guided decisions were compared with patients who underwent upfront ALND. Kaplan-Meier analysis showed that recurrence-free survival (axilla and distant metastases) were not significantly different between the groups (4-year recurrence-free survival: 97.8% vs. 99.0%, $p=0.14$).

Galimberti et al. (32), evaluated 147 women with clinical nodal involvement (cT1-4 and cN1-2), who converted to cN0, and were submitted to SNB. ALND was not performed if the SN was microscopically unaffected. The SN was negative in 70 (47.6%) patients and positive in 77 (52.4%) patients, that underwent ALND. After a median follow-up of 61 months. Kaplan-Meier curves were not statistically different for distant disease free survival ($p=0.54$) and overall survival ($p=0.72$) in both groups of patients.

Extended sentinel node biopsy after successful neoadjuvant chemotherapy

The first practical point for decreasing the FNR of SNB is collecting at least 3 SNs, provided the number of LNs obtained is inversely proportional to the FNR after NAC. Several authors demonstrated that it was possible to accomplish a 10% FNR, when ≥ 3 negative SNs were withdrawn (25-27). Technique matters, and the detection rate and chance to obtain at least 3 SNs are higher when dual tracer mapping was used. In contrast, random sampling of the axillary nodes is not known to affect the FNR and should not be indicated (33).

Marking nodes containing metastases before NAC and harvesting them along the dual mapped SNs (hot/blue) established ESNB as a new and more accurate method for axillary approach. The procedure entails the combination of dual SN mapping methods with the excision of the marked LN found previously involved and eventual removal of suspicious enlarged nodes. The SNs are identified by vital

dye and radiocolloid and the metastatic LN prior to NAC could be or not one of these structures; anyhow, at least 3 LNs should be retrieved.

Patient selection

Breast pCR is highly correlated with nodal status after NAC. Tadros et al. (34), in HER-2+ or triple-negative BC patients without a breast pCR, described a relative risk for positive nodal metastases after NAC of 7.4 (95% CI: 3.7-14.8), compared with those with a breast pCR. Among 237 patients (T1-2) with initial biopsy-proved N1 disease, 77 (32.4%) presented breast pCR and 160 (67.5%) had residual tumor in the breast whereas only 10.4% of the patients with breast pCR were found to have residual disease in the axilla. Conversely, in 57.5% of patients without breast pCR, metastatic LNs were detected. Thus, patients without breast pCR do not seem to be appropriate for omission of ALND after NAC.

The GANEA 2 study assessed the SNB in the neoadjuvant scenario. Among patients with a cytologically proven axillary involvement before NAC the FNR of the SNB was 11.9% (dual mapping) (35). They found that the amount of residual breast tumor allows identifying patients with a low risk of ALND involvement. For patients with negative SNB and a remaining breast tumor size less than 5.0 mm and no lymphovascular invasion, the risk of a positive complementary ALND was 3.7%.

With regard to molecular subtypes, apart from the low rates of nodal involvement with NAC in patients with luminal tumors, positive estrogen receptor (ER+) and HER-2 negative (HER-2-) the FNR of SNB in these patients is generally unacceptable. Enokido et al. (36) described the following SNB FNRs in women initially presenting with cytology-proven node positivity for each BC subtype: 42.1% for ER+, HER-2 - ; 16.7% for ER+, HER-2 +; 3.2% for negative estrogen receptor (ER-), HER-2 +; and 10.5% for ER - , HER-2 -.

Despite the paucity of data about the criteria for eligibility of cN+ patients to ESNB post-NAC, adequate patient selection is paramount for a safe procedure. In our opinion candidates for ESNB after NAC need to fulfill the following conditions:

At diagnosis: non-luminal BC subtypes (ER+HER2+; ER-HER2+; or ER-HER2 -), T1-2, cN1-2a;

After NAC: tumor complete clinical response, and conversion to a cN0 status.

Techniques

Ensuring the exact removal of the initially involved LN by malignant cells is a challenge for surgeons, because generally there is reduction in size of the downstaged LN. The utmost concerns for a valid ESNB are correct marking of the proven-positive LN and its precise excision. Thus, normally, the affected LN is tagged under ultrasound guidance, just after the nodal puncture, by inserting a metallic clip and/or a radioactive seed, and/or by injecting a charcoal suspension for tattooing.

In a landmark paper, the authors of the ACOSOG Z1071 study analyzed a subgroup of 170 patients, in whom a clip was placed in the positive LN, and the number of excised LNs was ≥ 2 (37). The clipped LN was removed separately at surgery, and radiographed to confirm that the LN contained the clip. In 107 (75.9%) cases, the marked LN was one of the SNs, and in these women the SN FNR was 6.1%. On the other hand, in 34 (24.1%) cases, the clipped LN was found in the ALND specimen, allowing a FNR of 19.0%. When the clip was

Table 4. Different methods for marking the positive axillary node

	Marker	Placement timing
Boughey et al. (37)	Titanium clip	Prechemotherapy
Donker et al. (39)	125I seed	Prechemotherapy
Caudle et al. (40)	Titanium clip and ¹²⁵ I seed	Prechemotherapy and preoperation
Choy et al. (16)	Charcoal	Prechemotherapy

not found the FNR was 14.3%. For comparison, in another subgroup of 355 patients, without clip placement, the FNR was 13.4%. It was concluded that ESNB, including the presence of the clipped LN in the removed tissue, significantly reduces the FNR.

Caudle et al. (7) performed ALND in 191 patients with biopsy-proven axillary nodes in which a clip was inserted. Nodal disease disappeared after NAC in 71 (33%) patients. In 118 patients undergoing SNB and ALND, the FNR was 10.1%. The clipped node contained metastasis in 115 patients, resulting in a FNR of 4.2% for the marked LN in relation to ALND. When the evaluation was performed for the combination of SN biopsies and clipped nodes, the FNR was markedly reduced to 1.4%. Clipped nodes were not seen in 23.1% (31/134 of patients), including six with negative SNs and metastasis in the clipped node. Accordingly, clipping positive nodes for extended SNB refines the pathologic evaluation and reduces the FNR.

Cabioglu et al. (38), in a prospective registry trial combining conventional SNB with clipped node excision, ascertained that the clipped node was the SN in 81.4% of the cases, whereas in 18.6% the clipped node was a non-SN. The possibility of clip migration was evidenced, and in 3.5% the clipped node could not be found in the specimen.

The intraoperative localization of the clipped LN is not an easy task. Therefore, other methodologies to mark the LN have been investigated, such as the placement of a Iodine-125 (125I) seed in the biopsy-proven positive LN. The node with the seed is posteriorly excised using a hand held gamma detection probe during the surgery. Donker et al. (39) described an identification rate of the seed-containing LN of 97% with this technique.

Caudle et al. (40), from the MD Anderson Cancer Center, proposed a variation of this procedure, the Targeted Axillary Dissection (TAD) method. This methodology consists of SNB and excision of the positive LN, which was first marked by a clip prior to chemotherapy, and months later, before surgery, was additionally tagged by a ¹²⁵I seed. A gamma probe optimized to ¹²⁵I activity, which is distinct from the setting used in the SN identification with Technetium-99m (99mTc), guides the removal of the LN marked with the clip and seed. Intraoperative radiography is performed to check for the presence of both markers in the tissue sample before pathologic handling. They had a FNR of 2% with TAD versus 10.6% with SNB alone.

Diego et al. (41) used the same methodology in 30 patients, and they described intraoperative finding of blue dye or ^{99m}Tc activity in the ¹²⁵I-localized LN in 73.3% of the cases.

Another strategy, proposed by Choy et al. (16), is to inject a small volume (median 0.5 mL) of sterile black carbon suspension into the

cortex of the LN and adjacent soft tissue just after the nodal fine needle aspiration. The tattooed node is visible intraoperatively even months later. Park et al. (42) approved the diagnostic performance of SNB using the technique of charcoal tattooing of cytologic-metastatic LN at presentation. The carbon nodal injection may occur before NAC, exclusive or combined with the clip, or later, preoperatively, in nodes previously marked by a clip.

The concordance between the pathologic results for both the charcoal tattooed nodes and the nodes containing blue dye or radiocolloid was analyzed by Kim et al. (43). In 45 cases the tattooed nodes were not identified in the surgical field in only 1 (2.2%). In 25 cases (56.8%) there was concordance between the SN and the tattooed node, they were the same structure. In the final pathological results, 18 (40.0%) patients had metastatic nodes. The sensitivities of the SNB, charcoal marked node biopsy, and the combination radiocolloid and/or tattooed node biopsy, for axillary metastasis identification, were 61.1%, 66.6%, and 77.8%, respectively.

The different techniques, employed in order to facilitate the identification of the node previously containing malignant cells in the surgical field, are summarized on Table 4. All of them entail the placement of a marker under ultrasound guidance. Each method has pros and cons.

A clipped lymph node is not easily identified during the surgery, since it is not visible nor detected by a probe. A nodal radiography is mandatory to confirm the harvesting precision. Besides, we must consider that hazardous spontaneous clip migration is possible. On its turn the radioisotopic seed placing is more complex and requires interaction between the services of Nuclear Medicine and Ultrasonography. Moreover, the 5-6 months permanence of a radioactive source in the human body is theoretically undesirable, and in some countries federal laws do not allow this type of procedure. To circumvent this problem, in the TAD method the ¹²⁵I seed is placed in a second-step procedure after NAC, some days prior the surgery.

The method of node tattooing with black carbon is simple, cheap, and the ink injection could be done at the same moment of the puncture for cytology/histopathology. It is easier to find a tattooed node than a clipped one, and the excised node radiography is not needed. The sole precaution is not to inject excessive volume of carbon suspension inside the node, since it may interfere with the microscopic analysis.

The value of the isolated tumor cells and micrometastases in the sentinel node

Low-volume SN disease after NAC is not an indicator of a low risk of additional positive axillary nodes. In contrast with its role in adjuvant treatment, it is likely that isolated tumor cells (ITCs) or micrometastasis in the SN after NAC, remnants of nodal disease that were not sensitive to chemotherapy, have a different meaning, and could have a negative impact on the evolution of the patients. Of note, patients with micrometastases in the SN after NAC have high rates (12%-64%) of positive non-SNs (44-46).

In the SN FNAC trial, FNR improved from 13.3% to 8.4% when IMH had been used (27). The importance of IHC was also evident in the ACOSOG Z1071 study: the trial's FNR was 8.7% when any ITC-positive node was included compared with 12.6% without IHC (37).

For Moo et al. (46) 17% of the patients with ITCs and 64% of the patients with micrometastasis in the SN had additional nodal metastases at ALND.

A meta-analysis conducted by Fu et al. (19) estimated that the SN FNR reduced from 16.0% to 8.7%, if ITC detected by the additional IHC, was considered positive.

There are typical findings in the metastatic LNs which had negative conversion after NAC. Chemotherapy effects on the positive node include fibrosis, hemosiderin deposits, laden macrophages, increased vascularity and a foamy histiocytic infiltrate. Malignant cells may be scattered through a fibrotic LN, and cytokeratins-IMH may be useful to confirm suspicious morphology (47). In clinical practice, cytokeratin staining should be added to achieve a more accurate ESNB result when the excised LNs are negative according to H&E analysis (9, 48).

Intraoperative evaluation of SNs could prevent a second surgery by indicating immediate ALND. Rubio et al. (45), after performing SNB and completing ALND in the same patients after NAC, demonstrated that frozen sectioning of the SNs is effective, with sensitivity ranging from 78.5% for micrometastasis and ITC to 100% for macrometastasis. In the experience of the Memorial Sloan Kettering Cancer Center the FNR of the frozen section of the SN was 6.2% and minimal involvement of the SN in the final pathology was an indication for ALND (46).

Conclusion

ALND is still the standard procedure for the management of the axilla of BC patients with metastatic lymph nodes before NAC. Nevertheless, ESNB (dual SN mapping, resection of at least 3 LNs, including the metastatic one marked at diagnosis) is considered a valid option for selected patients with axillary positive disease that is converted to negative after NAC. In patients with negative microscopic findings in the excised LNs (IMH included), the omission of ALND seems to be oncologically safe. Future research studies focusing specifically on prognosis of the treated patients are needed for definitive judgement.

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