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Review

Sentinel lymph node biopsy after neoadjuvant treatment in breast cancer: Work in progress

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Abstract

Sentinel lymph node biopsy has replaced axillary lymph node dissection (ALND) in those patients with clinically node negative axilla and nowadays, patients with low burden disease in the SLNs may spare an ALND without compromising their oncologic outcomes. In the last decade, indications of neoadjuvant treatment (NAT) have been extended to patients with operable disease and with the use of targeted therapies, rates of pathologic complete response (pCR) after NAT have increased. In the neoadjuvant setting, SLN after NAT is feasible and accurate in clinically node negative patients and it has been explored in different randomized prospective studies in patients with clinically positive axilla in the continuous effort to avoid the morbidity of ALND. The importance of identifying patients with residual axillary disease may serve not only as indicator for selecting patients with pCR to be spared an ALND but also for selecting patients for additional therapy. Future research is needed to more accurately identify residual axillary disease and the SLN after NAT is the driver for this achievement.

Keywords: Neoadjuvant treatment; Sentinel node; Breast cancer; Axillary node dissection

Introduction

Neoadjuvant treatment is a widely accepted treatment for breast cancer and has been proved to be equally effective option when compared to adjuvant therapy. Advantages are in vivo determination of an individual tumor's chemosensitivity, reduce micrometastatic disease and decrease disease burden to allow less extensive surgery.[1] It is increasingly used in node negative breast cancer patients to downstage the tumor facilitating breast conservative surgery. In recent years, increasing rates of tumor downstaging have been reported, rates that have approached 94%, and more important, pCR is achieved by around 20–40% of patients after NAT.[2–6] Pathologic complete response has been associated with a better prognosis and overall survival.[7,8]

There is also evidence that NAT downstage involved axillary nodes. Early studies have shown that NAT can completely clear axillary metastases as assessed by standard histologic examination in approximately 23% of patients with locally advanced breast cancer,[9] rates that have increased to 40–60% with the use of anti-Her2 therapies.[10] It is important to understand the extent to which the initial disease is eliminated and its contribution to the risk of loco regional recurrence, along with the question of how response to NAT should affect decisions for adjuvant systemic and radiation therapy treatments.[10,11]

For many years, the standard treatment of the axilla after NAT has been an ALND. Staging the axilla with SLN biopsy after NAT may spare women from the morbidity of an ALND, supported by the knowledge from clinical trials in the adjuvant setting that axillary local control is also influenced by systemic therapy.[12]

The sequencing of SLN and NAT has been extensively debated.[13] The never-ending debate on whether is better doing the SLN before of after NAT is getting to an end. There are some advantages and disadvantages in both ways, although the main indication for doing it after NAT is to take advantage of the increasing pCR obtained from the newest targeted therapies and to translate into a more conservative axillary surgery. It allows the patient with

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clinically occult axilla to avoid an ALND if the nodal metastases are eradicated with chemotherapy and the results of the nodal status after NAT are also a prognostic indicator.[11]

SLN before NAT have shown to have higher identification rates that after NAT, and the strongest argument for SLN before NAT is that knowing the pathological status of the axilla before NAT may influence loco-regional treatment, mainly radiation therapy. But, several studies have suggested that it is likely that accurate staging after NAT is a more meaningful predictor of loco regional recurrence (LRR) than accurate staging before NAT.[14,15] Current data also suggest that in the majority of patients the pathologic stage after NAT has more prognostic value.[16] Response to systemic therapy may prove to be a powerful tool for selecting patients with node-positive disease at diagnosis who can avoid radiotherapy.[15] Ongoing trials are enrolling patients to answer whether the response to NAT will more accurately guide loco-regional treatment in clinically node positive patients after NAT versus before NAT.

Other advantages of SLN after NAT include a single surgical procedure, while two procedures are needed if the SLN is done before. This review will focus on the actual indications for SLN after NAT and the management of the axilla in the neoadjuvant setting.

Management of clinically node negative axilla

Reported experience of SLN after NAT has been variable in terms of identification and false negative rates (FNR). Single institution studies with small sample size have reported identification rates of 72–100% and FNR of 0–33%.[17–22] In three studies with larger experience in SLN after NAC,[23–25] identification rates in clinically node negative patients only varied between 85% and 97%.

One of the most experience reports on SLN after NAC compared the accuracy of SLN after NAT in 575 patients to 3171 patients with upfront SLN biopsy.[25] They found SLN identification rates in the NAT group of 97.4%, highlighting the fact that there was a learning curve in the NAC setting, and that the technique improved after. In the patients who were cN0 at the time of diagnosis, FNR of SLN biopsy done before versus after chemotherapy were virtually identical (4.2% versus 5.9%).

The largest multicenter study data comes from the NSABP B-27[26] in which 428 patients treated with NAT underwent SLN followed by ALND. They reported identification rates of 85% and FNR of 11%, with lower FNR when a radioisotope was used (8%) instead of blue dye (14%). This study included patients with clinically negative and positive axillary nodes before NAT, but the FNR was not significant different between both groups. Other multicenter study, the GANEA that included 195 patients who underwent SLN after NAT using dual tracer reported FNR of 11% with no significantly differences depending on node status before NAT.[23]

Meta-analyses that combine data on clinically node negative and node positive patient show FNR for SLN after NAT between 10.5% and 15.1%[27–29] (Table 1). These rates are lower when considered the clinically node negative patients only and are around 5.9–9.4%.[28,29] In the meta-analysis by van Deurzen et al.,[28] including 27 studies that comprise 2148 patients, rates are roughly comparable to that of SLN biopsy in general, 10.5%. The pooled SN identification rate in studies restricted to clinically node-negative patients (N = 5 studies, 266 patients) was 92.7% compared to 88.2% in studies restricted to clinically node-positive (N = 3 studies, 342 patients). Tan et al.,[30] in a meta-analysis that included only clinically node negative patients after NAT, showed identification rates of 94.3% with FNR of 7.4%, values comparable to those for the SLN in the early breast cancer.[31,32]

To compare the performance of SLN biopsy prior and after NAT, van der Heiden-van der Loo et al.,[33] in a population based study, compared 980 patients with clinically node negative patients with SNB before NAT and 203 patients with clinically node negative patients with SNB after NAT. The SN identification rate before NAT was somewhat higher than after NAT (98% versus 95%; $p = 0.032$), showing that after NAT the SLN biopsy can identify a very high proportion of patients. It seems that the idea that NAT may interfere with the anatomy of the lymphatic drainage resulting in lower IR is not sustained in the newest studies. They have also demonstrated that patients who had SN after NAT more often had a negative SN (54% versus 67%; $p = 0.001$) and had less axillary dissection than patients with SN before NAT (45% versus 33%; $p = 0.006$). This study supports the idea that more patients may spare an ALND if the SLN is performed after NAT than before.

Whether different mapping agents make a difference in the SLN after NAT in clinically node negative patients has not been supported,[30] although FNR in clinically node negative patients is worse in whom only one sentinel node could be identified during surgery, compared to two or more sentinel nodes (14.3% versus 4.3%).[34]

In conclusion, for patients with clinically node negative before NAT, SLN after NAT is acceptable and in those patients with clinically node negative after NAT no additional ALND is necessary.

Table 1
Meta-analysis of SLN after NAT.

Author	Patients	N status pre treatment	Identification rate (%)	False negative (%)
Xing et al., 2006	1273	cN0/cN1	89.7	12
Kelly et al., 2009	1799	cN0/cN1	89.6	8.4
Van Deurzen et al., 2009	2148	cN0/cN1	90.9	10.5
Tan et al., 2011	449 (cN0)	cN0	94.3	7.4
van Nijnatten et al., 2015	1395	cN1	92.3	15.1