Practical guidelines in axillary management after neo-adjuvant chemotherapy in breast cancer patients

K. Van Baelen, MD[1], N. Van den Rul, MD[2], S. Marquette, MD[2], L. Vansteelant, MD[2], J. Mebis, MD, PhD[3], C. Thywissen, MD[4], A.-S. Vliegen, MD[4], L. Noé, MD[5], M. Drijkoningen, MD, PhD[6], G. Orye, MD[2]

SUMMARY

In clinical practice, the diversity in the surgical management of the axilla after neo-adjuvant chemotherapy (NACT) for node positive patients is huge. Given the morbidity of axillary lymph node dissection (ALND), a trend to perform a less invasive technique is seen in both literature and clinical practice. There are three major techniques: 1) sentinel lymph node biopsy (SLNB), 2) guided removal of lymph nodes that were positive prior to NACT, and 3) Targeted Axillary Dissection (TAD) which is a combination of the previous two techniques. Criteria for patients eligible for these techniques vary widely and oncological safety cannot always be guaranteed. With this report, we aim to introduce TAD in a safe way into the clinical practice.

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INTRODUCTION

The search for a less invasive axillary surgery procedure after neo-adjuvant chemotherapy (NACT) for node positive patients, is driven by the large axillary complete response (CR) rates in these patients together with the higher morbidity rates of axillary lymph node dissection (ALND).[1-3] Axillary pathological CR (pCR) is seen in 30 – 50% of initially node positive patients.[1] When we look at the combination of breast and axilla, pCR is reached in 3% of the ER+ Her2- patients, 28% of the triple negative patients and 35% of the Her2+ patients treated with trastuzumab.[4] A Cochrane review of 2017 revealed that in comparison to ALND, a sentinel lymph node biopsy (SLNB) caused less lymph oedema, less seroma and wound infections, less subjective arm movement impairment and less sensory complaints.[2]

Furthermore, the long-term follow-up of the ACOSOG Z0011 trial showed that patients with limited axillary disease spread did not benefit from an ALND regarding disease free survival (DFS) and overall survival (OS) rates.[5] This study, however, was done in patients who had primary breast conserving surgery. Nonetheless, it raises the question if a less invasive procedure can be appropriate for node positive patients achieving axillary CR after NACT.

In 2019, a survey done by *Simons et al.* showed that the majority of surgeons would still perform a standard ALND without restaging the axilla. Nearly 40% of all the surgeons who participated in the survey would perform restrictive axillary surgery when CR is suspected: 63% SLNB, 21% SLNB together with resection of previous positive nodes,

[1]Resident Gynaecology, KU Leuven, Belgium, [2]Department of Gynaecology, JessaZH, Hasselt, Belgium, [3]Department of Oncology, JessaZH, Hasselt, Belgium, [4]Department of Radiology, JessaZH, Hasselt, Belgium, [5]Department of Radiotherapy, JessaZH, Hasselt, Belgium, [6]Department of Pathology, JessaZH, Hasselt, Belgium.

Please send all correspondence to: K. Van Baelen, MD, Laboratory for Translational Breast Cancer Research, ON IV, Herestraat 49 - bus 810, 3000 Leuven, Belgium, tel: +32 16 37 95 74, email: karen.vanbaelen@kuleuven.be.

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TABLE 1. Indications for NACT.

Indications	
Tumour type dependent	- Triple negative tumours (independent of size) - HER2-positive tumours ≥ 2cm
Tumour stage dependent	- Locally advanced cancer - Inflammatory breast cancer - To consider with stage IIA and IIB tumours
Patient dependent	- Downstaging of breast surgery*

* Downsizing of the lesion to perform breast-conserving surgery or to perform nipple or skin conserving procedures.

11% resection only of the previous positive nodes and 5% other techniques.[6]

There are two main principles that need to be considered when thinking about de-escalation of the axillary surgery: 1) the technique must have a clear advantage for the patient in comparison to ALND (e.g. less morbidity) and 2) the technique must guarantee the oncological safety with comparable DFS and OS.[1] In the Jessa Hospital of Hasselt, Belgium, we implemented Targeted Axillary Dissection (TAD), a technique in which SLNB is combined with the resection of initially proven positive nodes. For reasons of oncological safety, we have set strict criteria for the use of TAD. This report will give an overview of the literature together with an outline on the conditions followed at our hospital for the management of the axilla after NACT.

NEO-ADJUVANT CHEMOTHERAPY

The regimens for NACT often consist of an anthracycline and/or taxane and/or platinum. Depending on the tumour subtype, immunologic or targeted therapy can be associated.[7,8] The indications for neo-adjuvant therapy are shown in *Table 1*. Prior to the start of the chemotherapy, a physical examination, an axillary ultrasound (with fine needle aspiration cytology (FNAC) in case of suspicious nodes) and an MRI of the breast are performed. PET/CT is used in the case of triple negative tumours, HER2-positive tumours larger than 2 cm and locally advanced lesions. When a patient would be considered for a TAD procedure, we advise to perform a PET/CT as well to assure that there are no distant metastasis and that there is no widespread disease throughout the axilla. In patients who did not undergo a PET/CT, disease staging is performed by a chest X-ray, an abdominal ultrasound and a bone scan unless they have a lesion smaller than 2 cm.[9]

Following NACT, the clinical examination as well as an MRI or PET/CT (depending on tumour type) is performed for every patient. Supplementary, an ultrasound of axilla is repeated in patients with preceding node positive disease.

AXILLARY SURGERY

MANAGEMENT IN THE CASE OF CN0 PRIOR TO NACT

In the past, the surgery for node negative patients has already evolved from ALND to SLNB, which is now the standard in most hospitals. First, the SLNB was done prior to NACT, after the St. Gallen consensus meeting of 2015, most clinicians advanced to doing the SLNB simultaneously with the breast surgery after completion of NACT.[7] Multiple meta-analyses were performed upon this subject, proving the safety of SLNB procedures after NACT in case of a clinically negative axilla.[10–12]

In our hospital, we also perform SLNB after NACT. The sentinel lymph node (SLN) is located using only an isotope, not blue dye. Use of a single tracer in this setting has an identical identification rate compared to dual tracer methods.[10] Completion ALND is performed in case of a positive SLNB.

MANAGEMENT IN CASE OF CN+ PRIOR TO NACT WITH RADIOGRAPHIC COMPLETE RESPONSE

In this patient population, SLNB is the most studied procedure to de-escalate from the golden standard of ALND. The leading trials being the ACOSOG Z1071 trial (inclusion of 756 patients), the SENTINA trial (inclusion of 592 patients) and the SN FNAC trial (inclusion of 153 patients).[13–15] Key points of these trials are shown in *Table 2*. Within these trials, a SLNB procedure was performed with a completion ALND to measure the accuracy of SLNB in this patient population. The main conclusion of these trials was that a standard SLNB procedure performed after NACT for node positive patients had an inadequate over-

TABLE 2. Overview key points of ACOSOG Z1071, SENTINA and SN FNAC trial.

Trial	Author	Year of Publication	N° of included patients	Global FNR	FNR with Dual tracer	FNR with removal of three or more nodes	FNR if itc is seen as positive SLN
ACOSOG Z1071	Boughey	2013	756	20.3%	10.8%	9.1%	n.a.
SENTINA	Kuehn	2013	592	15.0%	8.6%	9.6% (2 or more nodes)	n.a.
SN FNAC	Boileau	2015	153	13.3%	5.2%	4.9%	9.6%

all false negative rate (FNR) of 13.3-20.3%.[13–15] A meta-analysis of seventeen studies concerning SLNB showed a pooled FNR of 17% and a pooled negative predictive value (NPV) of 57-86%, making a standard SLNB not accurate or safe enough to perform in this patient population.[1]

However, these values could be improved by implementing a number of conditions. First, the FNR could significantly improve when dual tracer method was used. The ACOSOG Z1071 reported an improvement from 20.3 to 10.8% in the FNR.[15] Whereas SENTINA and SN FNAC reported a decrease in the FNR to 8.6% and 5.2% respectively.[13,14] Nonetheless, within the meta-analysis, the decrease in FNR was not significant (16% *vs.* 13%, p=0.53).[1] Since the results of the largest trials do favour the use of dual tracer, we advise to use it during TAD procedures to enhance the identification rate and improve the FNR.

Secondly, the number of nodes removed seems to have a significant impact upon the accuracy of this technique.[1,13–15] The removal of three or more SLNs gives an FNR of 8% in comparison to 22% with < 3 SLNs (p < 0.0001).[1] The SN FNAC trial reported upon the effect of the definition of a positive SLN: when isolated tumour cells (itc), usually seen as ~negative findings, were detected, they were considered as a positive SLN. This led to a decrease of FNR from 13.3% to 9.6%.[13] Furthermore, immunohistochemical (IHC) techniques may reduce the FNR even further. However, this effect was not significant in the meta-analysis.[1]

A subgroup analysis of the ACOSOG Z1071 trial, where some patients had a clip placed in FNAC positive nodes prior to NACT, showed that in 24.1% of the patients the clipped node was not removed with the SLNB.[16] The MARI-technique (marking the axillary lymph node with radioactive iodine (I) seeds) was developed to resect only the previously positive lymph nodes.[17] At first sight, the FNR was acceptable (7%) though the NPV is only 83.3% making this procedure not accurate enough.[17]

On the other hand, when the SLNB is combined with the removal of clipped nodes (= TAD) under the conditions made clear by all the previous trials, we get a technique with an excellent identification ratio, the lowest FNR reported (2-4%) and an acceptable NPV (92-97%), making this the most accurate technique available to consider instead of ALND.[1,18,19] Following the guidelines of ESMO and ASBrS, we implemented TAD in our clinical practice under strict conditions as is shown in *Table 3*.[8,20]

MANAGEMENT IN CASE OF CN+ PRIOR TO NACT WITHOUT COMPLETE RESPONSE

Although most surgeons would perform an ALND in case of persistent positive nodes after NACT, some groups would even consider restrictive axillary procedures in patients with partial or even no response to NACT.[6] We would advise against any other procedure than ALND in this setting. Current guidelines do not recommend restrictive axillary procedures without axillary CR neither.[8]

DISCUSSION

There are still a number of unanswered questions today in the literature concerning the surgical management of the previously positive axilla after NACT. No subgroup analyses were done to see if the procedures are as accurate in each subtype of breast cancer. Furthermore, nothing is said about the response of the lesion in the breast, therefore to guarantee safety we introduced the condition of complete response in the breast. Additionally, it is unclear which procedure needs to be followed when < 3 nodes are retrieved. Another issue is the variability between all the trials in inclusion criteria (e.g. number of positive nodes) and definition of positive SLNs. Consequently, we only include a maximum of two nodes and regard itc as positive SLNs. Oncological safety cannot be fully guaranteed since there are no reports on long term DFS and OS available, nor will they be available within the first years. It can only be hypothesised that TAD is as safe as ALND. Thus, ALND remains golden standard and TAD can

TABLE 3. Criteria for eligibility TAD without need for completion ALND.

Indications	
Prior to neo-adjuvant treatment	Tumour Stage: - cT1-3 - cN1 with a maximum of two clinically suspect lymph nodes, with FNAC positivity of at least 1 node - M0 Additional examinations needed: - Adequate clipping of nodes - PET/CT Only NACT (no neo-adjuvant endocrine therapy)
Following NACT	Adequate restaging (ultrasound + MRI) with: - Suspected CR axillary* - Suspected CR breast** Profound counselling of patient + informed consent Indication discussed and reported at MTB*** Procedure: - Pre-operative localisation using a hooked wire per clipped node - Dual tracer method (isotope + blue dye) - Intra-operative confirmation of presence of the clip - Resection of at least three SLN and/or clipped nodes - Resection of all clipped nodes Reporting upon: - Number of SLN - Clipped nodes SLN or not - Counts per SLN - Patent blue per SLN Pathologic report: - pCR breast - pCR axilla including absence of itc****
When not all criteria are met completion ALND needs to be performed	

*Normalisation of lymph nodes on ultrasound and MR breast.
**Absence of any contrast enhancement in the clipped lesion on MR breast or late and minor contrast enhancement suggestive for fibrotic tissue.
***MTB = Multidisciplinary Tumour Board.
****Confirmed with IHC techniques.

only be performed under strict conditions. Due to strictness of these criteria, we have only performed three TAD-procedures in our hospital since implementation six months ago. In one out of three, we had to perform a completion ALND since only two nodes could be identified. In our limited experience, we did not have any issue with clip displacement nor with retrieval of the node that was positive prior to NACT.

Perhaps the upcoming RISAS trial, a large multicentric prospective trial, can offer a solution for some unanswered questions. Its primary goal is to validate the accuracy of this combination technique. In addition, they would like to clarify the role of IHC and most important define what procedure needs to be followed when < 3 nodes are retrieved.[21]

CONCLUSIONS

ALND remains the golden standard for patients with FNAC positive lymph nodes prior to NACT. Nevertheless, we do believe that the ALND can safely be replaced by TAD in present clinical practice, in patients with radiographic complete remission after NACT when the above-mentioned conditions are strictly followed. More research is needed to: 1) better distinguish the subgroup of patients eligible for TAD, 2) refine the TAD procedure and 3) analyse the effects on disease free survival and overall survival.

KEY MESSAGES FOR CLINICAL PRACTICE: AXILLARY MANAGEMENT OF cN+ WITH CR AFTER NACT

1. ALND remains the golden standard procedure.

2. TAD can be introduced only under strict conditions:

Prior to NACT

- Limited axillary disease (max. 2 FNAC+ nodes)
- PET/CT needs to confirm limited axillary disease and no distant metastasis
- Adequate clipping of nodes by skilled radiologists

Following NACT

- Adequate restaging: radiographic CR in breast and axilla

Procedure

- Dual tracer
- Removal of three nodes, which must all be SLN and/or clipped nodes
- Intra-operative confirmation of removal clipped nodes

Pathology report

- itc are seen as positive SLN on IHC

3. When one of these conditions cannot be met, completion ALND is strongly advised.

REFERENCES

1- Simons JM, van Nijnatten TJ, van der Pol CC, et al. Diagnostic Accuracy of Different Surgical Procedures for Axillary Staging after Neoadjuvant Systemic Therapy in Node-positive Breast Cancer: A Systematic Review and Meta-analysis. Ann Surg. 2019;269(3):432–42.

2- Bromham N, Schmidt-Hansen M, Astin M, et al. Axillary treatment for operable primary breast cancer. Cochrane Database Syst Rev. 2017; 1(1):CD004561.

3- Wetzig N, Gill PG, Zannino D, et al. Sentinel Lymph Node Based Management or Routine Axillary Clearance? Three-year Outcomes of the RACS Sentinel Node Biopsy Versus Axillary Clearance (SNAC) 1 Trial. Ann Surg Oncol. 2015;22(1):17-23.

4- Straver ME, Rutgers EJ, Rodenhuis S, et al. The relevance of breast cancer subtypes in the outcome of neoadjuvant chemotherapy. Ann Surg Oncol. 2010;17(9):2411-8.

5- Giuliano AE, Ballman K v, Mccall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial HHS Public Access. JAMA. 2017;318(10):918–26.

6- Simons JM, Maaskant-Braat AJ, Luiten EJ, et al. Patterns of axillary staging and management in clinically node positive breast cancer patients treated with neoadjuvant systemic therapy: Results of a survey amongst breast cancer specialists. Eur J Surg Oncol. 2020;46(1):53–8.

7- Gnant M, Thomssen C, Harbeck N. St. Gallen/Vienna 2015: A brief summary of the consensus discussion. Breast Care (Basel). 2015;10(2):124-30.

8- Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) †. Ann Oncol. 2018;29(8):1634-57.

9- Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †. Ann Oncol. 2019;30(8):1194-220.

10- Xing Y, Foy M, Cox DD, et al. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. Br J Surg. 2006;93(5):539-46.

11- Tan VK, Goh BK, Fook-Chong S, et al. The feasibility and accuracy of sentinel lymph node biopsy in clinically node-negative patients after neoadjuvant chemotherapy for breast cancer - A systematic review and meta-analysis. J Surg Oncol. 2011;104(1):97-103.

12- Gui G. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer (Br J Surg 2006: 93: 539-546). Br J Surg. 2006;93(8):1025–6; author reply 1026.

13- Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: The SN FNAC study. J Clin Oncol. 2015;33(3):258–64.

14- Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): A prospective, multicentre cohort study. Lancet Oncol. 2013; 14(7):609–18.

15- Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: The ACOSOG Z1071 (alliance) clinical trial. JAMA. 2013;310 (14):1455–61.

16- Boughey JC, Ballman K v., Le-Petross HT, et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer

(T0-T4, N1-N2) who receive neoadjuvant chemotherapy: Results from ACO SOG Z107 1 (Alliance). Ann Surg. 2016;263(4):802–7.

17- Donker M, Straver ME, Wesseling J, et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients the MARI procedure. Ann Surg. 2015;261(2):378–82.

18- Caudle AS, Yang WT, Krishnamurthy S, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: Implementation of targeted axillary dissection. J Clin Oncol. 2016;34(10):1072–8.

19- Siso C, de Torres J, Esgueva-Colmenarejo A, et al. Intraoperative Ultrasound-Guided Excision of Axillary Clip in Patients with Node-Positive Breast Cancer Treated with Neoadjuvant Therapy (ILINA Trial): A New Tool to Guide the Excision of the Clipped Node After Neoadjuvant Treatment. Ann Surg Oncol. 2018;25(3):784–91.

20- American Society of Breast Surgeons. Consensus Guideline on the Management of the Axilla in Patients With Invasive/In-Situ Breast Cancer Purpose. n.d.

21- van Nijnatten TJ, Simons JM, Smidt ML, et al. A Novel Less-invasive Approach for Axillary Staging After Neoadjuvant Chemotherapy in Patients With Axillary Node-positive Breast Cancer by Combining Radioactive Iodine Seed Localization in the Axilla With the Sentinel Node Procedure (RISAS): A Dutch Prospective Multicenter Validation Study. Clin Breas Cancer. 2017;17(5):399–402.