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REVIEW ARTICLE

Targeted Axillary Dissection: A Review Covering Technical Aspects, Current Recommendations and the Future

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ABSTRACT

For clinically node positive patients with breast cancer, traditionally the gold standard for management of the axilla has been axillary lymph node dissection. This however has been associated with a high rate of morbidity including lymphoedema and shoulder stiffness. With the introduction of neo-adjuvant systemic therapy many patients undergo pathological complete response within the breast and axilla, particularly in certain molecular subtypes of breast cancer propelling interest in de-escalation surgery to reduce this morbidity.

Targeted axillary dissection is a procedure combining targeted lymph node biopsy, removing a previously marked node with confirmed cancer prior to neo-adjuvant systemic therapy and sentinel lymph node biopsy. The aim of the procedure is to accurately re-stage the axilla in patients with known nodal metastases after systemic therapy and reduce the morbidity associated with axillary dissection. Current meta-analyses have demonstrated that performing targeted axillary clearance has a consistently lower false negative rate when re-staging the axilla compared to sentinel or targeted node biopsy alone. This has led to a huge increase in popularity for the procedure. However, long-term data for oncological outcomes and morbidity are still lacking.

This review article aims to provides an overview of targeted axillary dissection. Focusing on technical aspects, including clip selection, number of clipped nodes and localization techniques for identifying the clipped node prior to surgery. The improved false negative rates of targeted lymph node dissection compared to sentinel node biopsy in clinically node positive patients converting to clinically node negative patients after neo-adjuvant systemic therapy. Pathological and radiological factors that may help in predicting nodal response to neo-adjuvant systemic therapy. Current guidelines/ recommendations for patient selection and management of residual disease within the axilla based on limited data and future studies aiming to clarify treatment decisions for this group of patients.

**Introduction**

The axilla plays a key role in the staging and management decisions for breast cancer patients. Historically axillary lymph node dissection (ALND) was performed for local disease control and prognostic information. However, ALND carries significant morbidity including the risk of lymphoedema, sensory loss and shoulder dysfunction impacting quality of life. Newer breast cancer treatment models aim to de-escalate surgical management of the axilla to reduce this morbidity.

From the late 1990s, sentinel lymph node biopsy (SLNB) revolutionised staging for breast cancer patients with clinically node-negative disease. Lymphoedema rates are reported as approximately 2% for SLNB compared to 13-25% for ALND.1 The false negative rate for SLNB is 7.3% (0-29% in systematic reviews).2 A positive sentinel node indicates the need for further management, in the form of completion ALND or radiotherapy depending on the burden of disease.

The Z-0011 trial in 2005 showed that in select patients receiving surgery plus whole-breast irradiation plus adjuvant systemic therapy, SLNB alone was non-inferior to ALND (n=891).1 The AMAROS randomised controlled trial (RCT) recruited 4823 patients with positive sentinel node(s) to either ALND or axillary radiotherapy. Axillary recurrence rates were higher in the radiation group, 1.19% (95% CI 0.31-2.08) versus 0.43% (95% CI 0.00-0.92), but there was no difference in disease-free or overall survival. Axillary clearance resulted in higher rates of lymphoedema at all timepoints (1 year, 3 years, and 5 years).3

Neoadjuvant systemic therapy (NAST) has become increasing popular in breast cancer management over the last couple of decades. For selected node positive patients NAST may lead to a pathological complete response (pCR) in the axilla in around 40% of patients, and this has led to an interest in de-escalating axillary surgery.4 As demonstrated in the ACOSOG Z1071 and SENTINA studies, SLNB alone for node positive patients following NAST has a false negative rate (FNR) of 13%, and this was felt to be unacceptably high.4,5 Some of the SLNB studies for node positive breast cancer treated with NAST noted when the most abnormal node was marked with a clip and removed the false negative rate was improved. This led to the introduction of the targeted lymph node biopsy (TLN). By combining TLN and SLNB, to improve staging accuracy further the targeted axillary dissection (TAD) was invented.

Targeted axillary dissection is a relatively new introduction to breast cancer management and long-term outcomes regarding morbidity and oncologic outcomes are still awaited. This article reviews the technical aspects, current recommendations and future considerations of TAD.

## **Performing targeted axillary dissection**

TAD requires marking one or more abnormal lymph nodes and then accurate localisation of the node at the time of surgery. A number of methods have been described; these may be used in isolation or combination, and each varies in rates of detection, cost, patient comfort and risk profile. Some marking devices require no additional localisation procedures. Where possible node marking should be performed prior to NAST.

Most commonly nodes will be marked with a metal clip deployed at time of initial biopsy, and later require a second localisation procedure such as a hookwire or tattooing. There is a risk of failed detection at the second procedure; for example, the SenTa multi-centre registry trial of clip-based TAD quote a clipped node detection rate of 78% (329/423 patients).6 Other risks of clipping the node include clip migration along the biopsy tract

or dislocation by haematoma, both affecting localisations.

The ILINA trial found a higher success rate of 95.7% (44/46 patients) for clipped node identification using intra-operative ultrasound alone.7 Other approaches such as magseed and radar reflectors do not require a metal clip.

### **Clip type**

There are many manufacturers and over 30 clip shapes available. These are most commonly titanium or stainless steel, or non-metal alternatives such as carbon-coated ceramic. Some are embedded in carrier material such as collagen or hydrogel to reduce risk of migration and improve ultrasound visibility. All clips are visible on mammogram (MMG) but with variable ultrasound visibility and rates of MRI safety and artefact.

A retrospective study by Hyde et al compared 139 clipped axillary nodes and found a localisation rate of 76% (106/139 patients) using ultrasound and radioactive seeds. Of their most commonly used clips the coil-shaped marker was most successfully localised at 85% (50/59).8 There is still a lack of head-to-head data comparing each clip type but suggests clip choice is an important consideration when performing TAD.

### **Clip localisation**

Similar to impalpable or clipped breast lesions, hookwires can be used to localise the axillary clipped node. Hookwires are readily available to most breast units, however, must be sited on the day of surgery and has a risk of wire migration and discomfort for the patient. Success is dependent on the expertise of the radiologist and the imaging visibility of the clipped node. Identification rates vary in literature. For example, the ASTR article describes flexible marking wires to previously clipped metastatic nodes and had an identification rate of 98.4% (63/64 patients).9 Similar success rates are described by Balasubramanian (92% or 23/25 patients) and García-Novoa (100% of 42 patients).10,11 In contrast, the German CLIP study described 30 patients undergoing ultrasound or mammogram-guided wire marking of a targeted lymph node; 24 were successfully wire localised, and then selective removal of the clipped node was only possible in 17/24. Their trial concluded that wire localisation for TLNB after NAST is “not appropriate for routine clinical use”.12

Another method is tattooing using a sterile carbon suspension or purified dye. Under ultrasound guidance, hyperechoic carbon particles are injected into cortex and peri-nodal tissue +/- a tract to the skin or overlying skin marker. Tattooing can take place months in advance or can be performed closer to the operation date which theoretically decreases ink migration. Tattooing is conceptually simple and low cost without need for expensive ancillary equipment. However, in cases of difficult direct visualisation a more extensive dissection may be required. Other considerations are that blue dye for SLNB may be masked by the carbon tattoo, and ipsilateral arm skin tattoos may cause confusion. Studies quote identification rates between 64% (Goyal et al, 14/22 NAST patients) to 100% (Patel et al, 47/47 patients).13,14

The TATTOO trial, a multicentre prospective trial of clinically node-positive breast cancer patients undergoing tattoo localisation, is the largest feasibility trial for carbon tattooing.15,16 In their protocol the largest and/or biopsy-proven metastatic node was injected with carbon suspension, SLNB was undertaken at individual surgeon discretion and completion ALND was in accordance with national guidelines (mandatory in Sweden, and optional in Germany for negative staging procedure). The analysis only included those who proceeded to completion ALND to calculate false negative rates. Of 149 patients, a tattooed node was identified in 94.6% of cases (however 3.5% of these did not identify nodal tissue in the histopathology specimen). For patients who also underwent SLNB, TAD was successful in identifying a sentinel and/or tattooed node in 98.7% of cases (147 of 149). The FNR was 6.7% in patients clinically node negative post NAST (4/65 patients).16 All false-negative TAD procedures were performed in the first two years of the trial, suggesting a learning curve.

The use of radioactive iodine seeds (I125) was first described as the MARI procedure (“marking the axillary lymph node with radioactive iodine”) in 2015, with identification rates for targeted nodes of 97% (97/100) and FNR 7% (7/100).17 This was then combined with SLNB in the RISAS trial, recruiting 227 patients from the Netherlands for TAD and then completion ALND following NAST – the results are awaited.18 Note users must adhere to radiation safety protocols when using iodine seeds, and these vary between countries and even individual institutions. There is a finite preoperative interval due to radioactive decay (half-life of approximately 60 days). The patient is exposed to a small dose of ionising radiation, and to reduce this exposure many countries legislate a time frame (e.g. 5 days preoperatively in the US).

Magnetic seeds are 5x1mm metallic seeds deployed by an 18-gauge needle at time of biopsy or later in treatment. These are temporarily magnetised in the presence of a probe for targeted removal. The Magseed trial recruited 40 patients for USS-guided Magseed placement and selective excision under Sentimag probe guidance and specimen X-ray. They report 100% success rate.19 Other Magseed studies report similar success rates, such as Greenwood et al (97% identification rate, 37/38)20 and Simons (98%, 49/50).21 The obvious limitation of magnetised markers is the increased artefact on MRI which can affect post-treatment imaging. These are MR conditional (1.5T and 3.0T) but extinction phenomenon affects evaluation of a diameter around the seed, so may be inappropriate for patients requiring MRI surveillance of the primary tumour. Some brands are compatible with standard metal instruments and others required non-ferrous instruments due to interference. The seeds, probe and non-ferrous instruments can be a significant cost.

Radar-localised reflectors (RLR) can be placed at time of tissue diagnosis or prior to surgery. They rely on infrared light and a sterile handheld sonar device for node detection. The probe can detect to 6cm depth and notes distance from the tag to aide localisation. In a 101-patient series RLR was feasible in 90.5% (86/95) with 9 patients removed due to technical failure (improper placement or unable to identify a target).22 Limitations include nickel allergy, signal loss (e.g. in large haematomas or if deactivated by electrocautery). They may create minor artefact on MRI, but this is less pronounced than by magnet or RFID tag. Again, the reflectors and probes can be a significant cost.

In radio-isotope occult lesion localisation (ROLL) additional technetium is injected into the clipped node under ultrasound guidance, if the clipped node is not a sentinel node on SPECT-CT, prior to surgery. A 38-patient series found identification rate of 97.4% for the clipped node (noting that the clipped node was the sentinel node in 55.3% of cases, 21/38).23 The learning curve for this approach is minimal.

### **Number of clips**

An area of controversy is the number of nodes localised. TAD describes removing sentinel nodes and a targeted node. In most patients this allows for adequate staging of the axilla, with the assumption that the most abnormal node is biopsied and clipped, and this will best reflect response to neoadjuvant chemotherapy. However nodal metastases may have heterogenous response to NAST.

Lim et al’s series removed all sonographically abnormal nodes without SLNB. From 21 nodes in 14 patients, the first clipped node had FNR of 7% which decreased to 0% by adding a second clipped node, without the need for SLNB.24

The authors noted that marking more nodes may increase the accuracy of axillary staging and improve oncological outcomes but at the cost of increased technical challenge, patient discomfort, cost and procedural time. Removing a greater number of nodes also increases risk of morbidity. Inability to retrieve a single clip could result in additional procedures or progression to ALND.

## **Patient selection for targeted axillary dissection**

As there are no long-term outcomes for oncological safety for TAD patient selection remains controversial. Both ESMO and AGO guidelines (discussed later) recommend TAD can be considered for patients who convert from cN1 to cN0 after NAST; ESMO suggests for cN2-3 disease data does not support routine use, and AGO recommends caution for cN2 disease as false negative rates are likely to be higher.

Multiple studies have included patients with N2-3 disease in the axilla. Hartmann et al included 13/75 (17.3%) patients with N2 disease but did not comment separately on the success of the procedure on this subgroup.25 The Danish Cancer Institute’s management algorithm for the MARI procedure involves for cN1 clipped node (CN) negative patients no further treatment is given, for cN2 CN negative patients or cN1 CN positive patients radiotherapy to the axilla is performed and for cN2 CN positive patients ALND is recommended.26

In practice, the EUBREAST international survey on axillary management for node-positive breast cancer patients treated with NAST showed significant variation in practice among 349 surveyed physicians.27 For cN2 patients converting to cN0 (277 responders) 45.1% recommended level 1-2 ALND, 30.3% TAD, 13.4% SLNB and 2.5% TLNB. For patients with residual disease post-surgical staging variations also exist. For isolated tumour cells (ITC’s) 30.6% of 257 responders recommended ALND +/- radiotherapy (RTx), RTx alone 33.1% and 32.3% no specific treatment. For micrometastases 57.7% of 253 responders recommended ALND +/- RTx, 30.4% RTx and 11.9% no specific treatment. For macrometastases 67.9% of 246 responders recommended ALND +/- RTx, 32.1% RTx and 0% no specific treatment. Both ESMO and AGO suggest patients with ypN+ disease should undergo or strongly consider completion axillary lymph node dissection (cALND). Therefore, oncological outcomes for these patients are desperately needed to clarify the optimum treatment pathway for these individuals.

## **Predicting nodal response to neo-adjuvant systemic therapy**

Since many guidelines recommend ALND for residual disease in the axilla, factors that are predictive of pathological complete response in the axilla should aid in patient selection for TAD.

### **Pathological Factors**

Molecular subtypes of breast cancer are well known to have varying response rates to NAST. In a large meta-analysis published in JAMA in 2021 response rates between the four subtypes varied in the axilla. Pathological complete response rates were 13% (156 patients) for luminal A cancers, 33% (468 patients) for luminal B cancers, 47% (14,521 patients) for triple negative cancers (TNBC) and 65% (764 patients) for ERBB2 positive cancers.28 Therefore, TNBC and ERBB2 positive breast cancers are more likely to benefit from axillary de-escalation surgery. Elamin et al also noted absence of residual disease in the breast was predictive for axillary pCR (P=<0.001) and negative lympho-vascular invasion was strongly predictive for axillary pCR (P=<0.001), however these factors may only be determined at the time of surgery currently.29 Kim et al identified cN2-3 disease, Grade 1-2 compared to grade 3, low Ki-67 to have significantly lower rates of pathological complete response in the axilla on univariate analysis (P=<0.001) in their study of 290 patients.30

### **Radiological Factors**

Kim et al also noted no lymphadenopathy on ultrasound of the axilla post-NAST was associated with pCR of the axilla (P=<0.001) on univariate analysis and axillary lymphadenopathy post-NAST had the strongest independent association with residual LN metastasis on multivariate analysis (odds ratio 13.8; P<0.001).30 A reduction of <50% of tumour volume in the breast on MRI was also predictive of residual disease in the axilla (adjusted odds ratio, 3.2). Corsi et al noted 67.6% of 1064 patients with ypN+ disease had lymphadenopathy on ultrasound alone post-NAST.31

The sensitivity of MRI to detect persistent lymph node metastases is moderate and reported between 61-72%32, however specificity is also moderate with one study with abnormal post-NAST nodes found only 58% contained viable tumour.33 For F18FDG-PET/CT the sensitivity, specificity, PPV and NPV for detecting residual disease in the axilla was 47.5%, 76.7%, 73.0% and 52.3% in one study of 171 women with node positive disease prior to NAST.34 Of note, when combined with ultrasound of the axilla the specificity and PPV improved to 100%.

### **Risk prediction tools**

Multiple risk prediction tools to determine likelihood of axillary pCR by combining imaging and pathological information available to clinicians have been developed. The most recent, published in 2021 including 1950 patients and externally validation showed a sensitivity of 71% and specificity of 73% (AUC 0.77, 95%CI 0.75-0.80).31 They incorporated post-NAST breast clinical complete response (y/n), post-NAST axillary status (positive/negative), NAST regimen, ki67, molecular subtype, histological type and clinical tumour stage.

## **Accuracy of axillary staging post neo-adjuvant systemic therapy (false negative rates)**

Pesek et al published a meta-analysis on the FNR of sentinel node biopsy for node negative patients in 2012.35 For the 9220 patients the overall FNR was 7.0% (CI: 6.1-7.9%). Using dye and tracer as opposed to a single agent reduced the false negative rate to 5.9% (CI: 4.8-7.1%). A false negative rate under 10% has been deemed an acceptable cut off for accurately staging the axilla and SLNB is the recommended method for staging the axilla in node negative patients.

The SENTINA study demonstrated that for cN+ patients who convert to cN0 after NAST the overall FNR for SLNB followed by ALND was 14.2% (CI: 9.9-19.4%).5 This was seen as too high for accurately staging the axilla. For patients with only one node removed at SLNB the FNR was 24.3%, for two nodes 18.5%, but for 3 or more nodes removed 5%. Therefore, removing three sentinel nodes was seen as an accurate method of staging the axilla for N+ patients converting to N0 post-NAST. This however only occurred in a third of the patients and therefore remains unreliable. A recent meta-analysis by Simons et al, included 17 studies and 2002 patients, reviewed the FNR for SLNB for patients with cN+ disease converting to cN0 post-NAST.36 The overall FNR was 17% with a range of 8-40%. This potentially means 1 in 6 patients would have missed residual disease using SLNB alone.

Swarnkar et al published a further meta-analysis looking at targeted lymph node biopsy (TLN) and TAD for cN+ patients converting to cN0 post-NAST.37 For TLN they identified 9 studies with 366 patients. The overall FNR was 6.0% with a range of 0-15.6%. For TAD they identified 13 studies with 521 patients. The overall FNR was 5.2% with a range of 0-7.3%. Although statistically the overall FNR was not different between these two techniques (p= 0.484) TAD consistently remained below the 10% cut off for acceptably staging the axilla and therefore is likely to be the most reliable method currently for staging this group of patients as opposed to ALND. In both TLN and TAD the implementation studies had higher FNR compared to later studies after the technique had been refined. These results were confirmed by the SENTA study, a multicentered prospective registry published in 2022.6 In this study TLN was performed in 423 patients with an identification rate (IR) of 77.8% and FNR of 7.2%, and TAD was performed in 229 patients with an IR of 86.9% and FNR of 4.3%.

## **Factors affecting accuracy of targeted axillary dissection**

Results from the ACOSOG Z1071 (Alliance) study found that for 170 patients undergoing SLNB where a clip had been placed into the abnormal node prior to NAST (but not localized at the time of surgery) and the clip was not identified during the SLNB the FNR increased from 6.8% to 19.0%.4 All of these patients had cN1 disease prior to NAST and at lease 2 SLN’s removed. Caudle et al found 23% of clipped nodes (CN) were not sentinel nodes (SN) in their study during surgery.38 They noted if the number of abnormal lymph nodes was >4 on initial ultrasound then the CN was significantly more likely to be a non-SN. In the SenTa studythe CN was not the SN in 36.2% of patients at the time of surgery.6 Therefore, it is important to localize the clipped node prior to surgery. The SenTa study identified 4 factors on multivariate analysis that negatively impacted identification rates of the clipped node including, ≥3 suspicious LN’s at diagnosis (IR 67.7%), ycN0 status (IR 73.8%), inability to detect CN prior to surgery on ultrasound (IR 45.0%) and study center <20 cases (IR 69.3%).

The SenTa study also noted the only false negative TAD results were seen when the clipped node and the sentinel node were the same node and only one node was retrieved, FNR 18.1%. Ideally at least one clipped node and one sentinel node should be removed for accurate TAD. Most patients were initially imaged and staged with mammogram, ultrasound, PET-CT and MRI.

## **Sentinel lymph node biopsy for clinically node-positive patients post neo-adjuvant systemic therapy**

Kahler-Ribeiro-Fontana et al recently published their long-term outcomes for patients treated with NAST and staged with SLNB, including both cN0 and cN1-2 from Milan. For 466 cN0 patients the axillary failure rate was 1.5% and 1.8% for the 222 cN1-2 (211 cN1, 11 cN2) patients after 9.2 years follow up.39 Overall survival at 5 and 10 years was 91.3% and 81.5% for cN0 patients and 89.8% and 80.1% for the cN1-2 patients. Of the cN1-2 patients 123/222 were sentinel node negative with 2 axillary recurrences. Of the 99/222 SLNB positive patients 90/99 (91%) underwent cALND. For the remaining patients 2/9 developed axillary recurrence, both in patients with micrometastases. Regional radiotherapy was not mandatory. The potentially elevated false negative rates with SLNB for cN+ patients post-NAST did not seem to affect the rates of local recurrence, distant recurrence or overall survival. Current AGO guidelines recommend using caution when managing patients with cN+ disease converting to ycN0 disease based on SLNB due to the potentially higher false negative rates.40 The ESMO guidelines (2020) do allow SLNB for patients who have converted to ycN0 status, however any residual disease should prompt cALND.41

## **Targeted axillary dissection for clinically node-positive patients post neo-adjuvant systemic therapy**

For cN+ patients who become ypN0 after NAST and TAD there is currently no long-term data to support recommendations. If the FNR is 10% then the estimated probability of compromising overall survival or disease-free survival would be around 1/2000 patients and 1/10,000 patients if the FNR was 2%.37 Further trials are still required to determine the safety of de-escalating surgery for ypN1 patients post-TAD.

Recommendations from AGO (2021) for the surgical management of the axilla include patients undergoing TAD should have >2SLN’s removed with no untargeted axillary sampling and immunohistochemical evaluation should be performed to detect isolated tumour cells and micrometastases. If the axilla is normal (ycN0) after NAST on clinical and ultrasound examination, then TAD and ALND are considered equivalent for patients with limited axillary involvement (N1 disease prior to chemotherapy). For patients with N2 disease prior to chemotherapy TAD should be used with caution due to the potentially higher false negative rates40. For patients with ypN1 lymph node involvement including micro-metastases cALND is recommended. For patients with ypN0(i+) disease, isolated tumour cells, cALND should be considered. These recommendations are not universal. Sweden, Norway and Finland still only recommend ALND. Italy routinely perform SLNB without marking the suspicious nodes. The NCCN guidelines recommend carrying out TAD as an optional procedure. Further RCT are needed to clarify the best surgical approach.

## **Radiotherapy post neo-adjuvant systemic therapy**

A recent meta-analysis looking at adjuvant locoregional radiation therapy in breast cancer patients with pCR after NAST included 13 studies. They found a significant reduction in locoregional recurrence (HR 0.59; 95% CI 0.42-0.81), however no significant difference on disease free survival or overall survival.42 As all these studies were non-randomized the risk of bias was thought to be moderate and the grade of evidence was felt to be very low or low. Current AGO recommendations include patients who have ypN1mic or ypN+ who do not undergo ALND should receive radiotherapy to the axilla. Patients who convert from node positive to ypN0 after (TAD / SLNB) additional radiotherapy can be considered.43 Further studies are required to clarify the benefit of radiotherapy particularly for patients with a pathological complete response after NAST.

## **Future Insights**

The main limitation to routine implementation of TAD has been a lack of data regarding oncological safety. Multiple studies are now recruiting to determine the safety of downstaging axillary surgery for patients undergoing NAST.

The French GANEA 3 trial (ClinicialTrials.gov identifier: NCT03630913) is a prospective multicenter cohort study. They plan to recruit 385 patients with T1-4N+M0 (biopsy proven) breast cancers treated with NAST. Patients will undergo TAD followed by ALND to determine the true FNR for TAD.

### **Residual disease following neo-adjuvant systemic therapy**

The Alliance A011202 trial (ClinicialTrials.gov identifier: NCT01901094) is a multicentred phase 3 randomised controlled trial (RCT) with over 2000 enrolled patients. The study has two arms including (cT1-3N1) breast cancer patients post-NAST. Patients with residual disease (one lymph node with >0.2mm deposit) after SLNB are treated with either ALND and nodal RTx (undissected axilla, supraclavicular and internal mammary nodes) or axillary and nodal RTx alone. The second arm of the study will evaluate patients with pCR or isolated tumours (<0.2mm) on SLNB. They will undergo either no further treatment or axillary and nodal RTx. Study endpoints include overall survival (OS), local recurrence and lymphoedema rates.

The swiss TAXIS trial (ClinicialTrials.gov identifier: NCT03513614) will included T1-3N1-2M0 breast cancer patients post-NAST. Patients will be restaged by targeted axillary surgery, removing the clipped node, sentinel nodes and any palpable lymph nodes. Patients with residual disease will be randomized to ALND or RTx to axilla and regional nodes. Outcomes will include OS, local, regional and distant recurrence.

The Italian Neo NOD 2 trial will include patients with T1-3N+M0 breast cancer patients.44 This is a non-randomised non-inferiority study. Patients staged with SLNB with micrometastases only in at least 3 sampled nodes will be compared to patients with pCR. No further axillary surgery or radiotherapy will be performed. Outcomes include OS and disease-free survival.

### **Pathological complete response post neo-adjuvant systemic therapy**

The NSABP B-51/TROG 1304 trial (ClinicialTrials.gov identifier: NCT01872975) is a RCT for patients with T3N1 breast cancer treated with NAST. They have recruited over 1600 patients. Patients with pCR in the nodes, diagnosed on SLNB or ALND, can proceed to RTx of the regional lymph nodes or no further treatment. Study endpoints include overall survival and local recurrence.

The British ATNEC trial (ClinicialTrials.gov identifier: NCT04109079) will include T1-3N1M0 breast cancer patients with confirmed nodal metastases treated with NAST. Patients with pCR (including micrometastases and isolated tumour cells) will be randomized to either ALND or axillary RTx. SLNB or TAD can be used to stage the axilla, however at least 3 lymph nodes must be removed.

### **Genomic testing**

A genomic test developed at the MD Anderson Cancer Centre to predict chemo-sensitivity to taxane-anthracycline based chemotherapy. The Austrian AGO-35 trial, which has finished recruitment, is an observational trial for breast cancer patients with node positive disease, excluding distant metastases who undergo NAST. The study will evaluate the microarray-based genomic test as a predictor of axillary lymph node response. The aim will be to predict chemo-sensitivity to enable omitting ALND.

## **Conclusion**

The use of de-escalation surgery in the axilla in the patient with cN1 disease prior to NAST is becoming increasingly popular. Currently TAD seems to have the consistently lowest false negative rates, but morbidity data and oncological outcomes are still awaited for comparison with other treatments. Guidelines generally recommend proceeding to cALND with residual disease post-NAST. Further data is required to determine if additional de-escalation is warranted.

### **Conflicts of interest**

The authors have no conflicts of interest to declare.

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