Axillary management in node-positive breast cancer in patients undergoing neoadjuvant chemotherapy: NAC-AX Delphi consensus study

Authors

Mr. James Lucocq[1], Mr. Lachlan Dick[1], Dr. Andreas Karakatsanis[2], Dr. Susie X. Sun[3], Dr. Jennifer Tseng[4], Professor Judy Boughey[5], Professor Oreste Gentilini[6], Professor Thorsten Kühn[7], Professor Michael Dixon[1], Professor John Benson[8], Professor Cliona Kirwan[9], Mr. Kenneth Elder[1]

Affiliations

1. Edinburgh Breast Unit, Edinburgh, United Kingdom
2. Uppsala University, Sweden
3. The University of Texas MD Anderson Cancer Centre, Houston, USA
4. City of Hope Orange County, Irvine, USA
5. Mayo Clinic, Rochester, USA
6. San Raffaele Hospital, Milan, Italy
7. University Hospital Ulm, Germany
8. University of Cambridge and Addenbrookes Hospital, Cambridge, United Kingdom
9. University of Manchester and University Hospital of South Manchester, United Kingdom

Study Overview

Neoadjuvant chemotherapy (NAC) is widely administered to patients with locally advanced and operable breast cancer with involved axillary nodes and produces an axillary pathological complete response (pCR) in 20-41% of patients.[12] The optimal strategy to stage and treat patients with nodal metastasis after NAC remains uncertain.[2,3] While axillary lymph node dissection (ALND) clears all nodes from level 1 and 2 and is accurate in defining post-NAC nodal status, it produces significant morbidity and as nodes are frequently down-staged post-NAC, a search for the optimal minimally invasive axillary procedure post-NAC has explored a number of alternative procedures.

Poor clinical prediction of pathological response and suboptimal identification rates of sentinel nodes can lead to false reassurance in sentinel lymph node biopsy (SLNB).[4] Previous studies (e.g. ACOSOG, SENTINA and SN FNAC) have reported a FNR of SLNB of up to 14.2% even in ycN0 patients following NAC.[5–7] Despite this, in patients that achieve pCR following NAC, SLNB has proved to have acceptable short-term axillary recurrence rates.[8,9]

With a view to reduce the false negative rate (FNR), a marked lymph node biopsy (MLNB) strategy has evolved whereby the positive node is clipped and removed without SLNB.[10,11] Since then the targeted axillary dissection (TAD) approach has emerged which combines MLNB with SLNB.[12] MLNB and TAD have demonstrated promise in reducing the FNR and boast high identification rates; however, studies including meta-analyses are marked by notable heterogeneity (e.g, ycN0 vs. ycN+ or ypN0 vs. ypN1) and the incorporation of selection bias.[13–18]

Overall, there is significant variation in axillary management and the role of minimally invasive techniques in patients with positive lymph nodes who receive neoadjuvant chemotherapy. There is variation in node localisation techniques, surgical strategy (e.g. SLNB, MLNB, TAD), decision to perform ALND and subsequent surgical management following formal pathology. The present Delphi consensus study aims to determine best practice and make international consensus recommendations for the role of minimally invasive axillary techniques in lymph node positive patients undergoing neoadjuvant chemotherapy.

Study Period

The study will be open from April to July, 2025. The link and QR-code to the first round can be found here: https://forms.gle/xnvXDX5ZmuPf9MwU9

Panellists

Panellists will be identified primarily through national and international membership associations and invited by email to take part. Panellists will provide their consent prior to enrolment but can

withdraw from the Delphi study at any time. The aim is to include at least 500 breast oncology surgeons.

Inclusion criteria

- Panellists must be a consultant or attending breast oncology surgeon actively practicing in their respective healthcare systems
- Panellists must be practicing in an OECD (Organisation for Economic Co-operation and Development) Country
- Panellists must be proficient in English to ensure clear understanding of the Delphi questions and responses
- Panellists should have a willingness to participate in multiple Delphi rounds (up to three rounds) and respond within the specified timelines

Exclusion criteria

- Surgeons without specific expertise or practice in breast oncology surgery
- Surgeons currently employed in non-clinical roles or administrative positions without active patient care responsibilities

Aims

- To determine best practice for the role of minimally invasive axillary techniques in lymph node positive patients undergoing neoadjuvant chemotherapy

- To make international consensus recommendations that inform the development of future axillary management guidelines for lymph node positive patients undergoing neoadjuvant chemotherapy

Data collection and Analysis

Background data will be collected including the panellist's Country of practice and the number of years they have been practicing as a breast oncology surgeon. Following this, the participant will answer several questions relating to staging/assessment, marking strategy, SLNB and TAD. The questions in the Delphi consensus study were derived firstly from a review of the current guidelines, and a comprehensive review of the literature. Areas of uncertainty not addressed by current guidelines were identified. Final questions were selected through expert opinion from breast surgical oncologists, ensuring relevance to contemporary clinical practice.

The first round of the Delphi will be used to collect diverse viewpoints and identify areas of disagreement or uncertainty. Panellists will be given 4 weeks to respond to the questions. Responses will be collated, and consensus will be defined a priori as a median score >75%.[19] Questions with less than 25% agreement will be considered for exclusion and questions with 25-75% agreement will be included in round two. At the end of round 1, panellists will have the opportunity to suggest changes or additional questions for round 2.

Before the second round each panellist will be provided with their own response as well as the collective response of the entire panel using the collated and de-identified data via email. This will allow each panellist to reconsider their responses. The second round will then include a revised set of questions focused on areas of contention and areas of greatest uncertainty. Panellists will have 4 weeks to respond. Panellists who did not respond to the first round would not be eligible to contribute to further rounds. The study will conclude with a third round to reach consensus, only if required.[20]

Authorship

Each participating consultant or attending surgeon will be eligible for an authorship position on all papers that result from the investigation. Any publication, presentation or abstract on collected data will acknowledge all authors.

Legal compliance

All investigators and study site staff will comply with the requirements of the data Protection Act 2018 and the General Data Protection Regulations (GDPR) with regards to the collection, storage, processing, and disclosure of personal information and will uphold the acts core principles.

Data Processing for Analysis

Data will be stored on secure computers at an NHS site in the form of a password protected database. Data will be processed and analysed by the team at the Edinburgh Breast Unit, United Kingdom. Only the chief investigators (J.L. and K.E.) will have access to the full dataset.

Funding

The study is funded by NHS Lothian Charity.

Endorsement

This study is endorsed by Association of Breast Surgeons (ABS), American Society of Breast Surgeons (ASBrS), Breast Surgeons of Australia and New Zealand (BreastSurgANZ), European Society of Surgical Oncology (ESSO) and Breast Surgery International (BSI).

Long Term Data Storage

De-identified data will be stored in accordance with GDPR on a secure password-protected database and for 5 years after the study findings are published in order to ensure that findings are verifiable.

Appendix 1. Delphi Study Questions

The following abbreviations are used throughout the Delphi consensus study:

ALND – Axillary Lymph Node Dissection

CT – Computed Tomography

FNR – False Negative Rate

MLNB – Marked Lymph Node Biopsy

MRI – Magnetic Resonance Imaging

NAC – Neoadjuvant Chemotherapy

PET – Positive Emission Tomography

SLNB – Sentinel Lymph Node Biopsy

TAD – Targeted Axillary Dissection

USS - Ultrasound

Section 1. Participant information

1. How many years have you been a consultant/attending breast oncology surgeon (board certified)?
2. Gender
3. Age group <40; 40-49; 50-59; ≥60
4. In which country do you practice?
5. Do you work in the public or private sector (or both)?
6. How many breast surgeons work in your institution?
7. Approximately how many breast cancers does your institution manage each year? <150; 150-300; ≥300
8. Do you regularly manage patients undergoing NAC for breast cancer?
9. Do you have access to axillary marking and localisation methods in your institution?

Section 2. Staging and assessment

Background

The National Comprehensive Cancer Network (NCCN), the National Institute of Health and Care Excellence (NICE) and the American College of Radiology (ACR) recommend an axillary ultrasound (USS) for patients who are either clinically node-negative or positive.[21–23] NICE and ACR recommend that an USS-guided core biopsy or FNA is performed for suspicious axillary nodes prior to NAC.[22,23]

Both the ACR and American Society of Breast Surgeons (ASBrS) guidelines state that axillary sampling should not be performed prior to systemic therapy.[22,24]

When the axilla has previously been evaluated prior to systemic therapy, the ACR advocate for a repeat USS after treatment.[22]Alternatively, the American Society of Breast Surgeons (ASBrS) advise that a SLNB can be performed if no nodes are palpable after treatment, and report that axillary USS is not reliable enough to determine surgical approach.[24]

PET can identify nodal metastasis and its sensitivity (43%-79%) and specificity (66%-93%) has been reported.[25,26] Axillary lymph nodes may be visible on an MRI breast with and without IV contrast; prospective trials have demonstrated varying sensitivities (65%-97%) and specificities (50%) for predicting nodal metastases.[27,28]

The following questions all relate to patients who have had pathologically proven nodal metastasis prior to NAC:

1. Should re-imaging of the axilla be performed to assess for treatment response following NAC if the nodes are now non-palpable?
    - Definitely required
    - Probably required
    - Neutral
    - Probably not required
    - Not required

2. Should re-imaging of the axilla be performed to assess for treatment response following NAC if the nodes are still palpable?
    - Definitely required
    - Probably required
    - Neutral
    - Probably not required
    - Not required

3. In patients who now have non-palpable nodes following NAC but have evidence of ongoing disease on USS following NAC, should further investigation be performed prior to surgery?
    - Yes - MRI
    - Yes – PET/CT
    - Yes – USS and repeat biopsy
    - No – proceed to minimally invasive technique (e.g. SLNB/TAD)
    - No – proceed to ALND

4. In patients who still have palpable nodes following NAC but have evidence of a partial response to treatment on USS following NAC, should further investigation be performed prior to surgery?
    - Yes - MRI
    - Yes – PET/CT
    - Yes – USS and repeat biopsy
    - No – proceed to minimally invasive technique (e.g. SLNB/TAD)
    - No – proceed to ALND

5. If an MRI scan also demonstrated nodal metastasis prior to NAC, should MRI be repeated following NAC to assess the axilla if there is equivocal response based on examination or USS?
    - Definitely
    - Probably
    - Neutral
    - Probably not
    - Definitely not

Section 3. Marking of Nodes

Background

In node-positive breast cancer, key studies (e.g. ACOSOG Z1071, SENTINA and SN FNAC) have reported a FNR of SLNB of 12.6-14.2%, even in ycN0 following NAC.[5–7] With a view to reduce the false negative rate (FNR), a marked lymph node biopsy (MLNB) strategy has evolved whereby the positive node is clipped and removed without SLNB.[10,11] Localisation techniques can then be employed to identify and then remove the marked node.[29–31] Since then, the targeted axillary dissection (TAD) approach has emerged which combines MLNB with SLNB: the marked node can be localised and removed and a SLNB can be performed.[12] Meta-analyses have reported a FNR of TAD of approximately 6%.[10,32]

In patients who are initially node-positive, SLNB has proved to have acceptable short-term axillary recurrence rates in those with a breast and nodal complete pathological response.[8,9] In patients that downstage from positive to negative, axillary recurrence is rare.[33] A recent study by Montagna et al. did not find any significant difference in axillary recurrence rate between SLNB and TAD in this setting.[33] To the best of our knowledge, there are no widely available guidelines which specify on the marking of axillary lymph nodes.

1. Is the marking of pathologically-proven axillary nodes essential?
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly disagree

2. When should patients with clinically positive lymph nodes (palpable nodes and/or radiologically abnormal nodes) for whom NAC is planned, receive a marker in the biopsied node?
   - At the time of the biopsy
   - After confirmation of malignancy
   - Following complete staging
   - Marker is not required

3. If three or more lymph nodes are abnormal on imaging prior to NAC, how many abnormal nodes should have a marker sited for localisation?
    - All should have a marker sited
    - Two should be marked (most suspicious)
    - One should be marked (most suspicious)
    - None should be marked

4. If two or more lymph nodes are abnormal on imaging (at least one biopsy proven) prior to NAC, should both be marked for localisation?
    - Both should be marked (most suspicious)
    - One should be marked (most suspicious)
    - Neither should be marked

5. Which localisation techniques are available to you to localise axillary lymph nodes?
    - Magseed
    - Radar device (e.g. Savi-Scout)
    - I-125 radioactive seed
    - Radiofrequency device
    - Charcoal Tattooing
    - Intra-operative Ultrasound
    - Wire
    - Skin marking
    - Other
    - None

6. Which localisation technique is your preference to localise axillary lymph nodes?
    - Magseed
    - Radar device (e.g. Savi-Scout)
    - I-125 radioactive seed
    - Radiofrequency device
    - Charcoal Tattooing
    - Intra-operative Ultrasound
    - Wire
    - Skin marking

- Other
- Don’t know

7. If not already marked prior to NAC, in patients who remain clinically node positive after NAC, what should be the next most appropriate course of action?
   - Mark the node before ALND
   - Do not mark the node before ALND
   - Neutral (no preference)
   - Do not know

Section 4. Sentinel lymph node biopsy (SLNB) [No marked node removal]

Background

In the ACOSOG Z1071 trial the false negative rate of SLNB following NAC in those with ≥2 lymph nodes removed was 12.6% (2 lymph nodes, 21.1%; ≥3 nodes, 9.1%). With dual mapping agents, the FNR was 10.8% vs 20.3% with a single agent. In the SENTINA trial the FNR of SLNB when ≥2 lymph nodes were removed was 14.6% and 24.3% in those with one node removed.[6] The SN-FNAC study reported the FNR as 8.4% (1 lymph node, 18.2%, ≥2 lymph node, 4.9%) and higher with dual tracers (5.2% vs. 16.0%). The ASBrS report that in patients who are initially node-positive, the false-negative rate of SLNB is minimized by the retrieval of >2 SLN, by dual mapping, and by retrieval of the biopsied/marked node'.[24]

The recent OPBC-05/ICARO study compared the 3-year rate of axillary and any invasive recurrence between ALND and no ALND in patients with residual isolated tumour cells.[34] Additional macro-metastasis were found in 5% of the ALND group and there was no significant difference in outcomes between the two groups.[34] The ATNEC trial is currently investigating the safety of omission of further axillary treatment (radiotherapy and ALND) in patients with a negative SLNB following NAC.

A recent study investigating the National Cancer Database of the USA found that in patients with residual disease following NAC (ypN1mi-2), 34% of patients underwent SLNB alone.[35] The Alliance A011202 is comparing ALND with axillary radiotherapy in ycN0 patients who remain ypN+ following NAC and results are anticipated.[36,37]

The ASBrS report that data on the use of SLNB in patients presenting with cN2 disease may be insufficient.[24]

The following questions all apply to patients with a clinically negative axilla after NAC (cN1 converting to cN0 [no palpable nodes and normal imaging]:

1. In patients undergoing a SLNB (no marked node), in your expert opinion, is single tracer sufficient to adequately assess the axilla or is dual tracer required?
   - Single tracer is sufficient
   - Dual tracer is required

- Don’t know

2. If only a single tracer is available (e.g. blue dye or technetium) in these patients, is an ALND required?
   - Definitely required
   - Probably required
   - Neutral
   - Probably not required
   - Not required

3. In your expert opinion, if SLNB (no marked node) is to be performed, what is the minimum number of nodes that should be removed for adequate staging in these patients?
   - 1
   - 2
   - 3
   - ≥4

4. In this patient group who undergo a SLNB, in those who have 1 sentinel node retrieved, what should be the next step?
   - Perform ALND during index operation
   - Await pathology – perform ALND only if positive
   - Await pathology and discuss at MDT
   - Frozen section of that node
   - Other

5. SLNB alone (2 nodes removed) is comparable with TAD for axillary staging in these patients?
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly disagree

6. SLNB alone (3 nodes removed) is comparable with TAD for axillary staging in these patients?
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly disagree

7. Based on the current evidence and your clinical practice, an ALND is required in patients if isolated tumour cells only are found in the axillary lymph nodes on pathology following SLNB (ypN0i+)?
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly disagree

8. Based on the current evidence and your clinical practice, an ALND is required if micrometastases are found in axillary lymph nodes on pathology following SLNB (ypN1mi)?
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly disagree

The following question applies to patients who are initially N2 (4-9 positive axillary nodes) but are clinically negative axilla after NAC (normal axillary ultrasound).

9. SLNB should be offered in preference to ALND in these patients?
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly disagree

Section 5. Targeted axillary dissection (TAD)

Background

TAD has gained popularity over the last few years and has showed promise in reducing the FNR. TAD combines a SLNB with a marked lymph node biopsy (MLNB) whereby the positive node is marked, localised and removed.[10,11] Many localisation techniques have been described to identify the marked node (e.g. magnetic seeds, wire and intraoperative ultrasound).[29–31] Meta-analyses have reported the FNR of TAD of approximately 6%.[10,32] At present the use of TAD has not been incorporated into national guidelines. Studies are investigating the TAD approach in patients with positive lymph nodes who do not receive NAC (TADPOLE and TAXIS study).[38]

The following questions all apply to patients with a clinically negative axilla after NAC (cN1 converting to cN0 [no palpable nodes and normal imaging]):

1. Does your unit currently perform Targeted Axillary Dissection (MLNB + SLNB)
    - Yes (we mark and use localisation techniques to identify the node)
    - Yes (we mark the node but do not use localisation techniques)
    - No we perform MLNB (marked and localised) without SLNB
    - No

2. If TAD is performed, in addition to the marked nodes, the removal of how many sentinel nodes would you consider sufficient for axillary staging?
    - 1
    - 2
    - 3
    - 4
    - ≥5

3. If TAD is attempted and the marked node is successfully removed, but is not a sentinel node, and no sentinel nodes can be found, what is the minimum number of sample nodes that should be removed to adequately assess the axilla?
    - 0
    - 1
    - 2

- 3
- 4
- ≥5

4. In your current practice, if TAD is attempted and the marked node is successfully removed, but only sample nodes were found, this is sufficient to stage the axilla?
    - Strongly agree
    - Agree
    - Neutral
    - Disagree
    - Strongly disagree

5. If TAD is attempted but the marked node cannot be identified or retrieved via the localisation method, what should be the next step?
    - SLNB if possible, otherwise sample nodes
    - SLNB if possible, otherwise request that the radiologist insert another marker
    - SLNB if possible, otherwise ALND (same procedure or after discussion with patient)
    - ALND (same procedure or after discussion with the patient)
    - Request that the radiologist insert another marker
    - Other

6. Based on the current evidence and your clinical practice, an ALND is required if isolated tumour cells only are found on pathology following a TAD (ypN0i+)?
    - Strongly agree
    - Agree
    - Neutral
    - Disagree
    - Strongly disagree

7. Based on the current evidence and your clinical practice, an ALND is required if micrometastases are found in axillary lymph nodes on pathology following a TAD (ypN1mi)?
    - Strongly agree

- Agree
- Neutral
- Disagree
- Strongly disagree

The following question applies to patients who are initially N2 (4-9 positive axillary nodes) but are clinically negative axilla after NAC.

8. TAD should be performed in these patients?
    - Strongly agree
    - Agree
    - Neutral
    - Disagree
    - Strongly disagree

Section 6. Clinically negative (cN1 converting to cN0) following neoadjuvant chemotherapy

The following questions 1-3 relate to your current clinical practice and all apply to patients with a clinically negative axilla after NAC (cN1 converting to cN0 [no palpable nodes and normal imaging]):

1. Which axillary surgical technique should be performed in these patients?
   - SLNB
   - TAD (SLNB with removal of the marked nodes after localisation)
   - MLNB (marked lymph node biopsy after localisation, no SLNB)
   - ALND
   - Other
   - None

2. Minimally invasive techniques (e.g. SLNB or TAD) are an acceptable index axillary procedure if there is no/minimal response of the primary tumour?
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly disagree

3. Minimally invasive techniques (e.g. SLNB or TAD) are an acceptable index axillary procedure if there is partial response of the primary tumour?
   - Strongly agree
   - Agree
   - Neutral
   - Disagree
   - Strongly disagree

4. In patients with N2 disease (4-9 positive axillary nodes), who become clinically node-negative (cN2 converting to cN0), which axillary surgical technique is your preferred technique?

- SLNB
- TAD (SLNB with removal of the marked node after localisation)
- MLNB (marked lymph node biopsy after localisation, no SLNB)
- ALND
- Other
- None

5. Which outcomes are the most important primary endpoints in clinical trials investigating axillary management in patients with positive axilla who undergo NAC (please rank from most to least important)?
   - Axillary recurrence-free survival
   - Overall survival
   - Disease-free survival
   - Lymphoedema rates
   - Quality of life (e.g. BREAST-Q scores)
   - Local control (breast/chest wall recurrence)

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