Management of the Axilla

GUIDANCE

NICE

- Sentinel node biopsy (SNB) to stage breast cancer where ultrasound is negative
- Post SNB, offer RadioTx or ANC to if >1 macromet
- Can omit if 1-2 LNs +ve **and** are having both whole breast radiotx and systemic therapy
- Do not offer treatment if micromets or ITCs.

ABS Consensus (2015, awaiting likely update in 2024/5)

- Sentinel node biopsy (SNB) to stage breast cancer where ultrasound is negative.
- If 1-2 nodes and T1-2, they will receive adjuvant chemo (+/-endocrine) and radiotherapy to the breast then they can be enrolled in POSNOC (see below, now closed)

Additional guidance

Royal College of Radiology suggests patients who have BCS and receive whole breast RadioTx, are T1, G1-2, ER+, Her2 neg, and post-menopausal you can omit axillary treatment.

Staging of the Axilla – Sentinel node biopsy

NSABP B32 Lancet Oncology 2010 - Justified use of SNB

- 5.6K
- Clinically node negative
- Stratified for
    - age (> or <50),
    - tumour size
    - WLE vs Mx
    - Radiotx rate 82% and systemic therapy 85%
- Two arms

1. SLNB
2. SLNB + ANC

OS, DFS, LRR equated when SNB negative so established this practice as safe

OS 91.8% at 8 years

New Start programme '04-'06 - training and validation of SNB in UK.

SOUND (Sentinel Node Vs Observation After Axillary Ultra-souND)

- Randomised patients of any age, with T1 tumours and ultrasound negative axilla to SLNB vs no axillary intervention.
- Recuited 93.8% of planned
- 57 of the 1463 included had a "doubftful" node on USS but underwent FNA/biopsy demonstrating a negative node. The remainder had conclusive negative axilla on ultrasound.
- 1405 included in intention to treat analysis (excluded patients whom discountinued intervention)
- Of note, in the SLNB group, patients with metastases on SNB had to proceed to ANC.
- Median age was 60 (IQR 52-68) years, 87.8% had ER+, HER2- disease.
- 8.6% had macromets post SNB. 4 patients (0.6%) had 4 or more positive lymph nodes.

Matched pretty well for systemic and radiotherapy intervention in both arms. The radiotherapy regimen was the 3 weeks course (now more commonly de-escalated to 5 days in the UK following FAST-see Rdaiotherpay cheat sheet)

- 5.7yrs follow-up with SNB/omission:
- 12/11 (1.7/1.6%) locoregional relapses, 13/14 (1.8/2.0%) distant metastases, and 21/18 (3.0/2.6%) deaths occurred.
- The 5-year cumulative incidence of distant metastaseswas 2.3% in the SLNB group and 1.9% in the no axillary surgery group

They concluded that the omission of SNB is safe and non-inferior to SNB. However, they do acknowledge that the information obtained can guide systemic therapy e.g. particularly in pre-menopusal women and therefore it should be used if finding mets would alter their adjuvant therapy. An additional consideration is that the knowledge of a negative axilla on SNB can be a pre-requisite for de-escalation of other treatments e.g. radiotherapy so this is also something ot consider.

It is likely that in the UK, both staging and treatment of the axilla will alter in the coming years. In early breast cancer (meet Z011 criteria) in over 70s Americans now omit SLNB.

INFLUENCE trial Ann Surg Oncol 2024

In many centres, the use of both blue dye and Tc99 (RI) as in the original New Start Programme is not practiced because of the effects of blue dye – tatooing and anaphylaxis. The INFLUENCE trial was a non-inferiority trial using Indocyanine Green (ICG) as a tracer and showed that this alone was just as good. This has yet to fully replace Tc99 injection.

- SNB identification in the study was 96.9%

- ICG alone = 97.9%
- ICG + RI = 100%
- ICG + blue dye = 92%

Timing of Staging in of axilla in NAC patients

- **Z1071** NAC then SNB then ANC 40% become negative and 12% false neg rate (9% if > 3 nodes)
- **SENTINA** again 14% False neg rate.
- 4 arms in this trial: in cNo disease could have a SLNB pre or post NAC then in N+ disease could have SLNB and ANC or just ANC following NAC.
- **Key finding** - SNB false negative rate in LN0 patients who have neo-adjuvant chemo was 51.6%!!!! SO should we be doing SNB pre chemo in these patients?

Micro-mets

Mirror trial - Dutch RCT that argued you should treat
IBCSG 23-01 "Milan" trial Lancet Oncol, 2015 = no difference in LRR in T1-T2 tumours

Practice both in the USA and the UK is that we do not treat micro-mets.

NOTE – this is in the non NAC patients. The question remains as to whethernodal isolated tumor cells (ITCs) after neoadjuvant chemotherapy an indication for axillary dissection?
NSABP B-51 trial includes ITCs in definition of nodal pCR (pNO)
ALLIANCE trial does not classify ITCs only as pNI (ALND vs no ALND)

The OPBC05/EUBREAST-14R/ICARO study aims to answer this and was provisionally reported at the San Antonio Breast conference showing no gain in OS when ANC is performed for ITC post NAC. Full publication awaited.

De-escalation of Treatment to the Axilla

Recommend reading the landmark paper for historical overview
The Landmark Series: Axillary Management in Breast Cancer, Carla S. Fisher, Julie A. Margenthaler, MD2, Kelly K. Hunt, and Theresa Schwartz

KEY POINT: Treatment of the axilla with ANC/RadioTx is to reduce local recurrence (low rates overall and usually within first 2 years (B-32 SNB neg LR rates~ 1%, AMAROS N1 (included micromets) i.e. very low burden ~1-2% LR post treatment, from B-04 can extrapolate that

overall axillary recurrence was 18.6% and in this trial 40% may have been node +ve, meaning about LR 7% without any adjuvants)

Z0011 10 years follow-up JAMA, 2017

- T1-2 and 1-2 +ve SLNs and received whole breast radiotx and systemic therapy (note micromets were included so may skew the burden to very low burden disease)
- Randomized to ANC or no axillary further treatment
- Non-inferiority design/analysis
- 10yr OS 86.3% vs 83.6% HR0.85, p 0.02

Planned 1900 but only recruited just over half of this so underpowered
LR - just 1 in the SNB group at 5-10yrs and none in ANC group...
Unclear if RadioTx delivered may have affected axilla also.... "planned tangential whole-breast irradiation, and adjuvant systemic therapy. Third-field radiation was prohibited"

MA-20 NEJM 2015

Showed reduced rec both local and distant but not improved survival (primary endpoint) with regional nodal irradiation (RNI) of axilla in BCS when high risk features… Eligible pts= 1-3 positive LNs OR high risk node negative – tumour > 5cm diameter or tumour > 2cm diameter and less than 10 axillary nodes removed plus either being oestrogen receptor negative, grade 3 or display evidence of lymphovascular invasion. Only 10% of the 1832 patients randomised were node negative. 85% of the patients had 1-3 positive lymph nodes.
The results from **MA 20** are important in relation to interpreting **Z0011**, since the **Z0011** investigators have claimed that patients with 1-2 positive axillary lymph nodes do not need any further regional treatment whereas **MA20** shows that RNI even in addition to ALND can result in improved disease control. There is now further support for this argument with the publication of the similar **EORTC15** and Danish Breast Cancer Co-operative trials which showed an improvement in DFS and also OS respectively.

Summary “Z11 included both micro and macrometastases (around 40% micrometastases) and showed that ALND may be omitted in women with ≤2 positive nodes undergoing breast conserving surgery (BCS) and receiving whole breast RT. Paradoxically, MA20, demonstrated improved DFS following the addition of regional RT. 51.8% (949/1832) had 1 or 2 positive nodes. 98.9% (1812/1832) had T1/T2 tumours.

The treatment de-escalation of the axilla from ANC to radiotherapy is summarised in the next section, but the next steps in de-escalation will be:
1) Systemic therapy alone in patients who meet Z11 criteria

2) Targeted Axillary dissection in those with N1 disease (see final section)
3) TAD post NAC – see below.

To answer the 1st, the POSNOC trial which closed but is yet to be publishes, is to assess whether for women with ≤2 macrometastases at SNB, systemic therapy alone is non inferior to systemic therapy plus treatment of the axilla in terms of axillary recurrence at 5 years. 1900 patients with clinically node-negative breast cancer with T1 or T2 were randomly assigned to axillary treatment (completion axillary lymph node dissection or axillary radiation therapy) or to no axillary treatment.

Radiotherapy vs ANC if node positive

Historical - B-04 has 25years f/u and showed equal survival

AMAROS Lancet 2014

- 4.8K
- Initially T1 then T2 included
- Proceeded to SNB and then 1.4k were positive and randomly allocated to:
  - Radiotx
  - ANC

Report at 10 years follow-up in JCO 2023:

- Didn't report Lymphoedema or QoL at 10 years, at 5 years it was: twice as high in ANC group (24.5% v 11.9%; P < .001)
- Ax recurrance at 10 years around 0.93% if ANC but 1.82% with Ax Radiotx, HR1.71 (not stat sig)
- No difference in DFS and OS
- LRR approx 4%
- Low event rate and underpowered
- Only 5% of patients had a high axillary burden (>3 nodes)
- Exploratory analysis showed contralateral breast cancer at 10 years was 28% AxRadiotx vs 19% ANC (no p value in paper nor supplementary data

SENOMAC

- Non-inferiority study enrolled 2766 patients across 5 countries
- Patients were clinically node-negative, T1-T3, 1-2 SNB macrometastases (metastasis size >2 mm in the largest dimension) were randomly assigned in a 1:1 ratio to completion ANC or its omission (sentinel-node biopsy only). Adjuvant treatment and radiation therapy were used in accordance with national guidelines. The primary endpoint was overall survival.
- Radiation therapy including nodal target volumes was administered to 1192 of 1326 patients (89.9%) in the SNB–only group and to 88.4% in the ANC group.

- The median follow-up was 46.8 months

The question that really remains is whether radiation can safely be omitted in the

The Axilla Post Neo-adjuvant Chemo

There is now a shift to de-escalating patients with a good response to NAC. In recent (2023) ABS guidance post NAC, patients who are N1 pre NAC can proceed to a targeted axillary dissection (TAD). This involves using a localisation technique + Tc99 or dual tracer to do a combined sample of sentinel node and the targeted (clipped biopsy proven pre NAC node). 4-6 nodes are obtained. Treatment of the axilla with proven low burden can then be de-escalated from ANC to radiotherapy and perhaps omission of radiotherapy may be a consideration to further de-escalate.

An important trial in this arena with be the **ATNEC trial**:

ATNEC - Axillary management in T1-3N1M0 breast cancer patients with needle biopsy proven nodal metastases at presentation afterbut evidence of node negative disease after neoadjuvant chemotherapy randomised to ANC/RadioTx OR no Ax treatment.

Targeted Axillary dissection (TAD) in those proceeding straight to surgery

As mentioned, ABS now recommend TAD in the context of good response to NAC.
A number of trials including TAXIS include patients who are having upfront TAD ie no NAC being given. In some centres in the UK, this practice is already being performed.

This is a brief summary of an ever-evolving topic. If you would like to read an excellent review in addition, we would recommend the review by Heidinger, M and Weber, W.P. Axillary Surgery for Breast Cancer in 2024. *Cancers* 2024, *16*, 1623 link to paper