Neoadjuvant Treatment – A Surgical Perspective

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Neoadjuvant Treatment – A Surgical Perspective

- Potential advantages of neoadjuvant treatment
- Patient selection
- Pathway and key decision making
- Local and regional treatment after neoadjuvant treatment
- Adjuvant systemic treatment (focus on HER2 positive)

Neoadjuvant Treatment

Systemic treatment of breast cancer prior to definitive surgical treatment

- Chemotherapy
- Endocrine therapy
- Targeted treatments (anti-HER2)

Neoadjuvant Treatment

Systemic treatment of breast cancer prior to definitive surgical treatment

- **Chemotherapy**
- Endocrine therapy
- **Targeted treatments (anti-HER2)**

Neoadjuvant Treatment – Potential advantages

- Inoperable locally advanced / inflammatory breast cancer

  Downstage to operable

- Operable breast cancer requiring mastectomy

  Downstage to facilitate breast conservation

- Operable breast cancer suitable for breast conservation

  Downstage to improve cosmesis

Neoadjuvant Treatment – Potential advantages

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- Operable breast cancer suitable for breast conservation

  Downstage to improve cosmesis

De-escalate local treatment – breast and axilla

Neoadjuvant Treatment – Potential advantages

- Facilitate genetic testing
  - Mainstream testing e.g. TNBC <60 years
  - Definitive cancer surgery and risk reducing surgery in gene carriers
- Facilitate early adoption of newer treatments
  - e.g. dual anti HER2 treatment
- Monitoring of response ‘Response directed therapy’
  - Discontinue ineffective treatment and substitute with alternative
- Prognostic value
  - Pathological complete response pCR
  - Post surgical systemic treatment if residual disease

NeST

Neoadjuvant Systemic Therapy in Breast Cancer

A prospective multicentre cohort study

Stuart McIntosh

On behalf of the NeST Study Steering Group

Prospective Audit

- December 2017 – November 2018

- 37 Breast Units
- 1258 patients

- Chemotherapy 88%
- Endocrine 12%

NeST
Neoadjuvant Systemic Therapy in Breast Cancer

Indications

- Surgical downstage 37%
- Facilitate dual anti HER2 treatment 33%
- Inoperable 19%
- Improve cosmesis 17%
- Facilitate genetic testing 9%
- Inflammatory breast cancer 6%

Indications –Standard of Care

- Triple negative
- HER2 positive
- Locally advanced breast cancer T ≥ 3 and / or N ≥ 2 M0

Triple negative HER2 positive

ER positive HER2 negative Chemotherapy

or

ET +/- CDK 4/6 inhibitor

Safety Concerns

Traditional approach: Surgery first

If NACT:

? Higher local recurrence

? Impact on prognosis

Long term outomes for neoadjuvant vs adjuvant chemotherapy in early breast cancer

- Meta-analysis of individual patient data

- 10 randomised trials 1983-2002
- 4756 women
- Median follow up 9 years

EBCTCG, Lancet Oncology 2018

Long term outomes for neoadjuvant vs adjuvant chemotherapy in early breast cancer

	NACT		Adjuvant Chemo
Breast conservation	65%		49%
Local recurrence (15 yrs)	21%	**5%** (3%)	16%

Long term outomes for neoadjuvant vs adjuvant chemotherapy in early breast cancer

At 15 years	NACT	Adjuvant Chemo
Distant recurrence	38%	38%
Breast cancer mortality	34%	34%
Overall mortality	41%	41%

Long term outomes for neoadjuvant vs adjuvant chemotherapy in early breast cancer

At 15 years	NACT	Adjuvant Chemo
Distant recurrence	38%	38%
Breast cancer mortality	34%	34%
Overall mortality	41%	41%

Equal survival to the same chemotherapy given after surgery

Small increase in local recurrence

Pathological Complete Response (pCR)

The absence of residual invasive (+/- in situ) cancer on standard haematoxylin & eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy

EMA and FDA standard definition

Neoadjuvant Treatment Response can be Assessed Using Pathological Complete Response

Pathological complete response (pCR) definitions:

- The absence of residual invasive (± *in situ*) cancer on haematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy[1]
- Despite pCR being used as an endpoint in numerous trials assessing neoadjuvant systemic therapy for breast cancer, to date there is no uniform definition. However, the European Medicines Agency's (EMA) preferred definition for registration directed neoadjuvant trials is **total pCR** (tpCR)[2]

pCR[2]	Alternatively known as…	Definition
ypT0 N0	German breast group (GBG) pCR	Eradication of invasive and *in situ* disease from breast and lymph nodes
ypT0/is ypN0	**Total pCR (tpCR)**	**Eradication of invasive cancer from breast and lymph nodes**
ypT0/is	Breast pCR (bpCR)	Eradication of invasive cancer from the breast

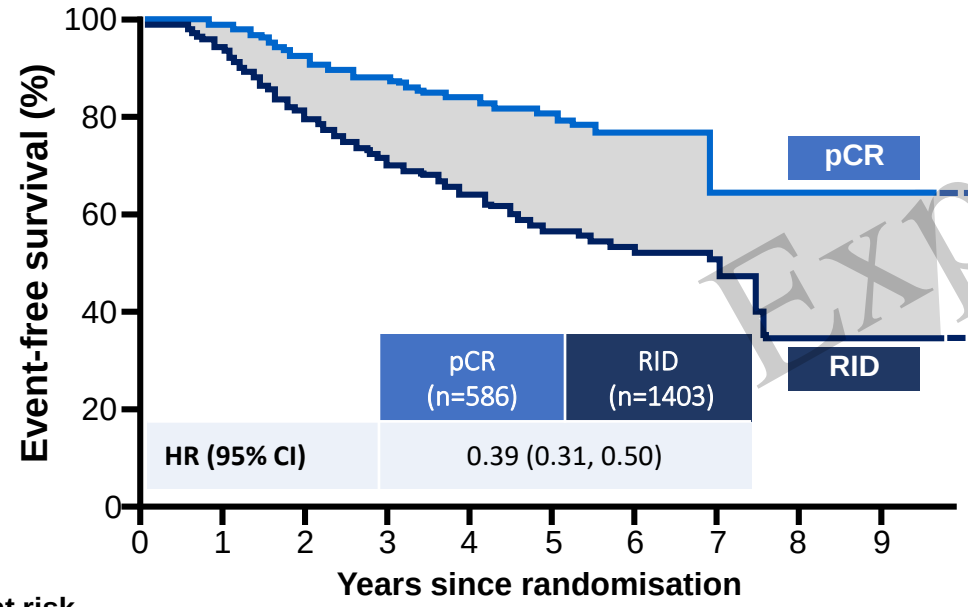
Following treatment in the neoadjuvant setting some patients may still have cancer remaining and might not have achieved a pCR. This is known as residual invasive disease and is associated with a poorer prognosis[3,4]

1. EMA guidance. The role of pathological complete response as an endpoint in neoadjuvant breast cancer studies. EMA/CHMP/151853/2014; 2. EMA. Overview of comments received on "Guideline on the role of the pathological Complete Response (pCR) as an endpoint in neoadjuvant breast cancer studies". EMA/94983/2015; 3. NICE. Technology Appraisal Guidance TA632. 2020; 4. Cortazar P *et al. Lancet* 2014;384:164–172.

bpCR, breast pathological complete response; EMA, European Medicines Agency; GBG, German breast group; N, node; pCR, pathological complete response; tpCR, total pathological complete response; T, Tumour stage.

Residual Invasive Disease After Neoadjuvant Therapy is a Predictor of Long-Term Outcomes

Association of residual invasive disease (RID) with event-free survival (EFS) in the HER2-positive subgroup of the CTNeoBC pooled analysis*



No. at risk

pCR	586	527	454	371	212	120	37	4	2	1
RID	1403	1157	918	713	436	269	106	33	3	1

Pathological complete response (pCR) = improved long-term outcomes compared to patients with RID, especially in HER2-positive breast cancer

RID (i.e. no pCR) = poorer prognosis and higher rates of recurrence than those who achieve a pCR

*Pooled analysis of 12 international neoadjuvant treatment trials (N=11955) using the ypT0/is ypN0 definition of pCR (tpCR). The analysis uses the term "No pCR" to describe RID in the breast or axilla.

Cortazar P *et al. Lancet* 2014;384:164–172.

CI, confidence interval; EFS, event-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; pCR, pathological complete response; RID, residual invasive disease; tpCR, total pathological complete response.

Neoadjuvant Pathway

- Diagnosis
- Patient selection
- Neoadjuvant treatment
- Monitor and assess response
- Plan surgery
- Detailed pathology assessment
- Post surgical radiotherapy and / or adjuvant systemic therapy

Multidisciplinary Team

Multidisciplinary Team

Neoadjuvant Pathway

- **Diagnosis**
- **Patient selection**
- Neoadjuvant treatment
- Monitor and assess response
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Diagnosis Patient Selection

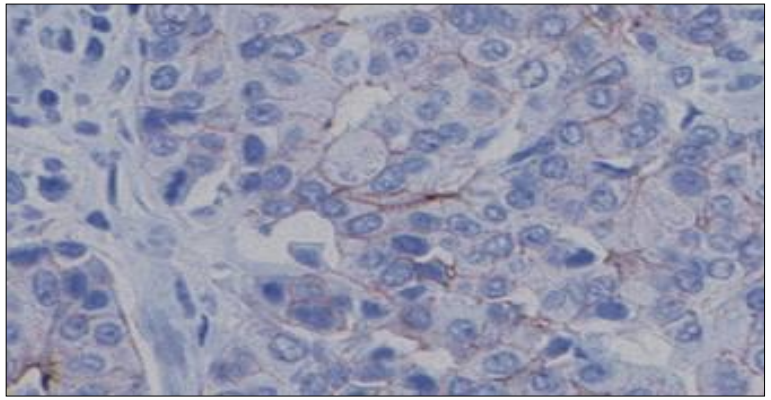
- **LABC / Inflammatory**

Diagnosis Patient Selection

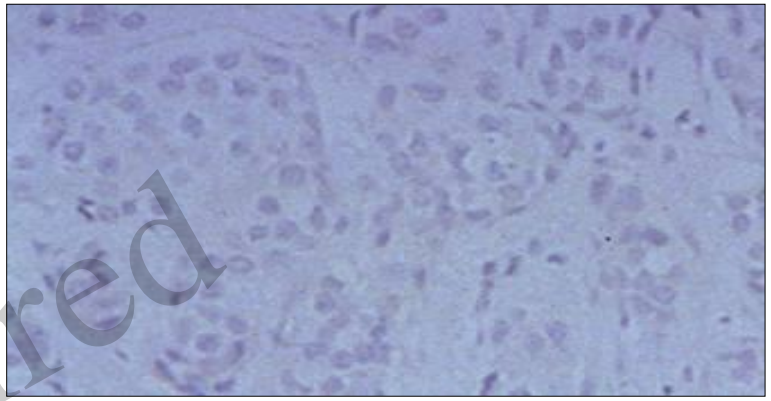
- **LABC / Inflammatory**
- **HER 2 Positive Triple Negative**

HER2 Testing – turnaround times

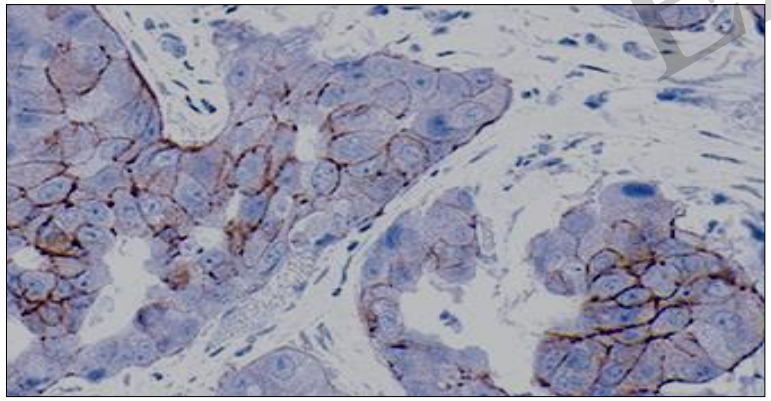
IHC HER2 scoring



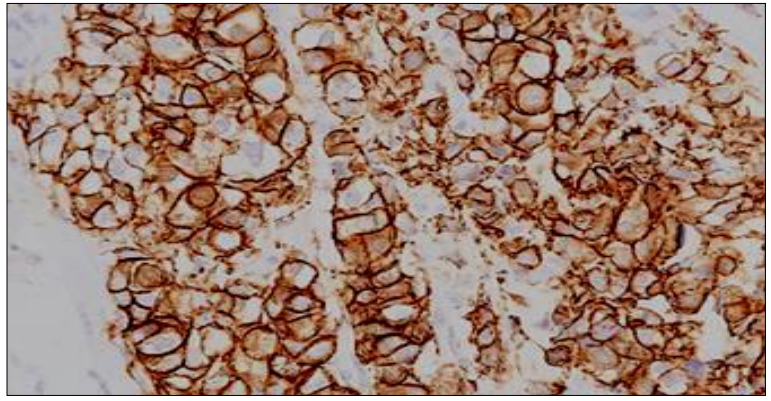
‘0’ (negative)



‘1+’ (negative)



‘2+’ (equivocal)



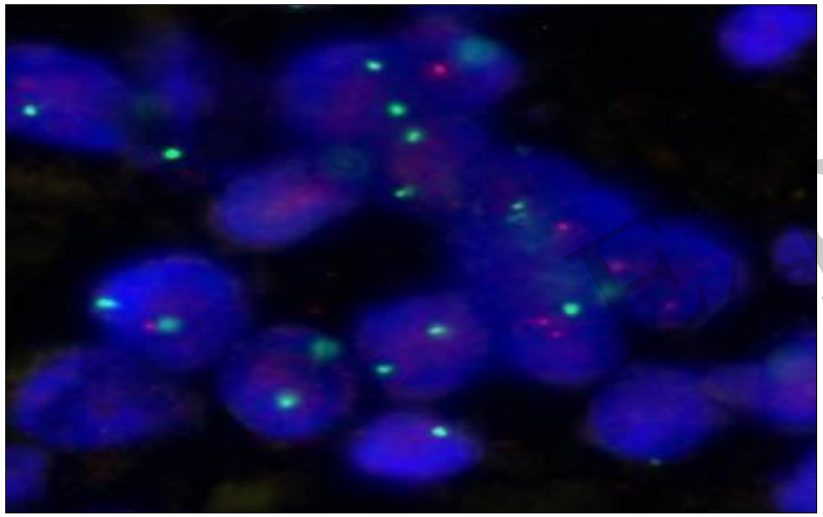
‘3+’ (positive)

With kind permission of Dako Limited

FISH scoring

No amplification/HER2-negative

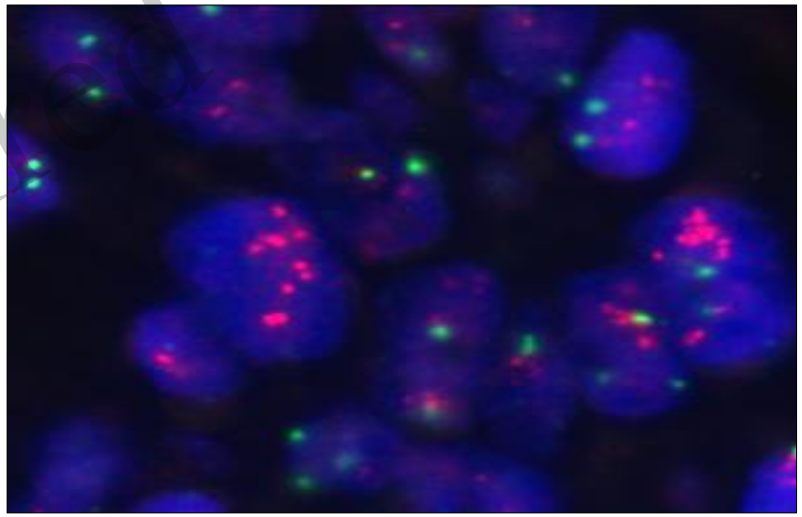
Green light = chromosome 17 control



Normal HER2 gene copy number

Amplification/HER2-positive

Red light = HER2 gene signals



Increased HER2 gene copy number

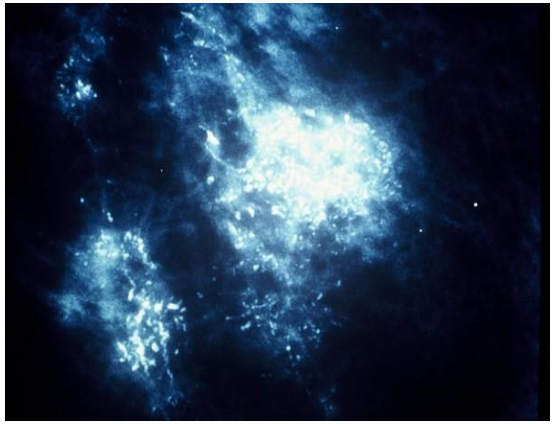
- A tumour is HER2-positive only when the ratio of HER2 signals to each chromosome 17 is 2 or more

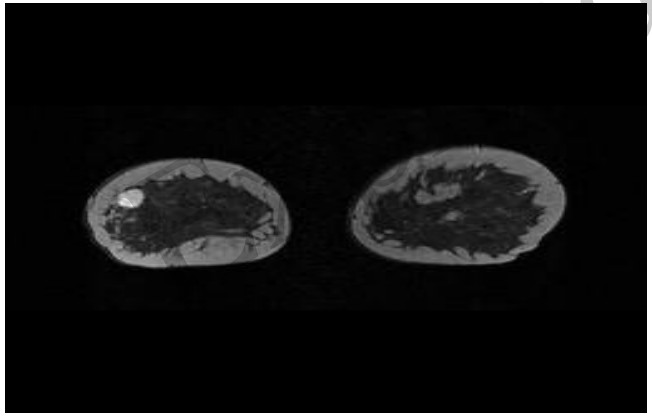
Neoadjuvant Pathway

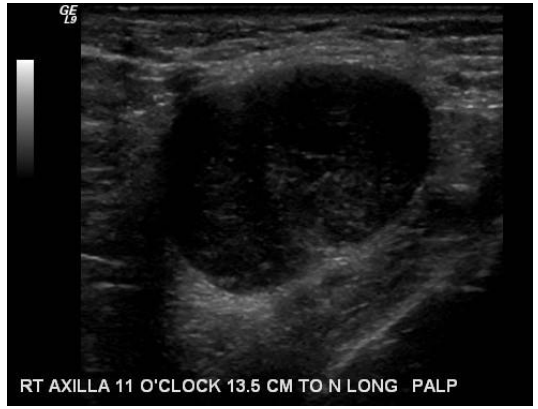
- Diagnosis
- Patient selection
- **Pre treatment planning and work up**
- Neoadjuvant treatment
- Monitor and assess response
- Plan surgery
- Detailed pathology assessment
- Post surgical radiotherapy and / or adjuvant systemic therapy

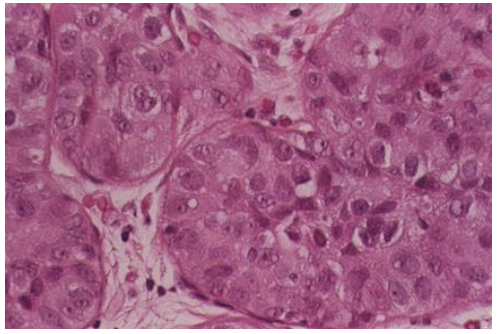
Pre treatment planning and work up

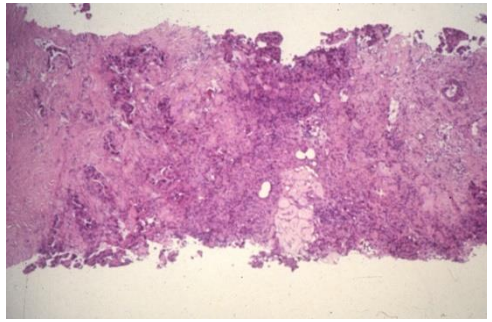
Estimate pre treatment disease in breast and axilla

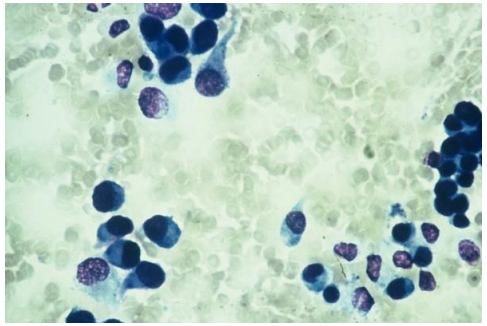













Expired
Clip everything

Neoadjuvant Pathway

- Diagnosis
- Patient selection
- **Neoadjuvant treatment**
- Monitor and assess response
- Plan surgery
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Role of Imaging in Detecting Imaging Complete Response

MRI is the gold standard

Accuracy for determining pCR:

- 57% Clinical examination
- 74% Mammography
- 79% Ultrasound
- 80% MGM & US
- 84% MRI

Crowshaw et al, Ann Surg Oncol 2011

Neoadjuvant Pathway

- Diagnosis
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- Assess response
- **Plan surgery**
- Detailed pathology assessment
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Plan Surgery

- Detailed post-treatment imaging to assess response
- MDT discussion
- Further radiological discussion
- Detailed localisation
- Surgical – radiological discussion post localisation
- Precise surgery
- Specimen x-ray

Extent of excision – breast conservation

Excise original tumour footprint

vs

Excise what is necessary guided by imaging

Extent of excision – breast conservation

Excise original tumour footprint

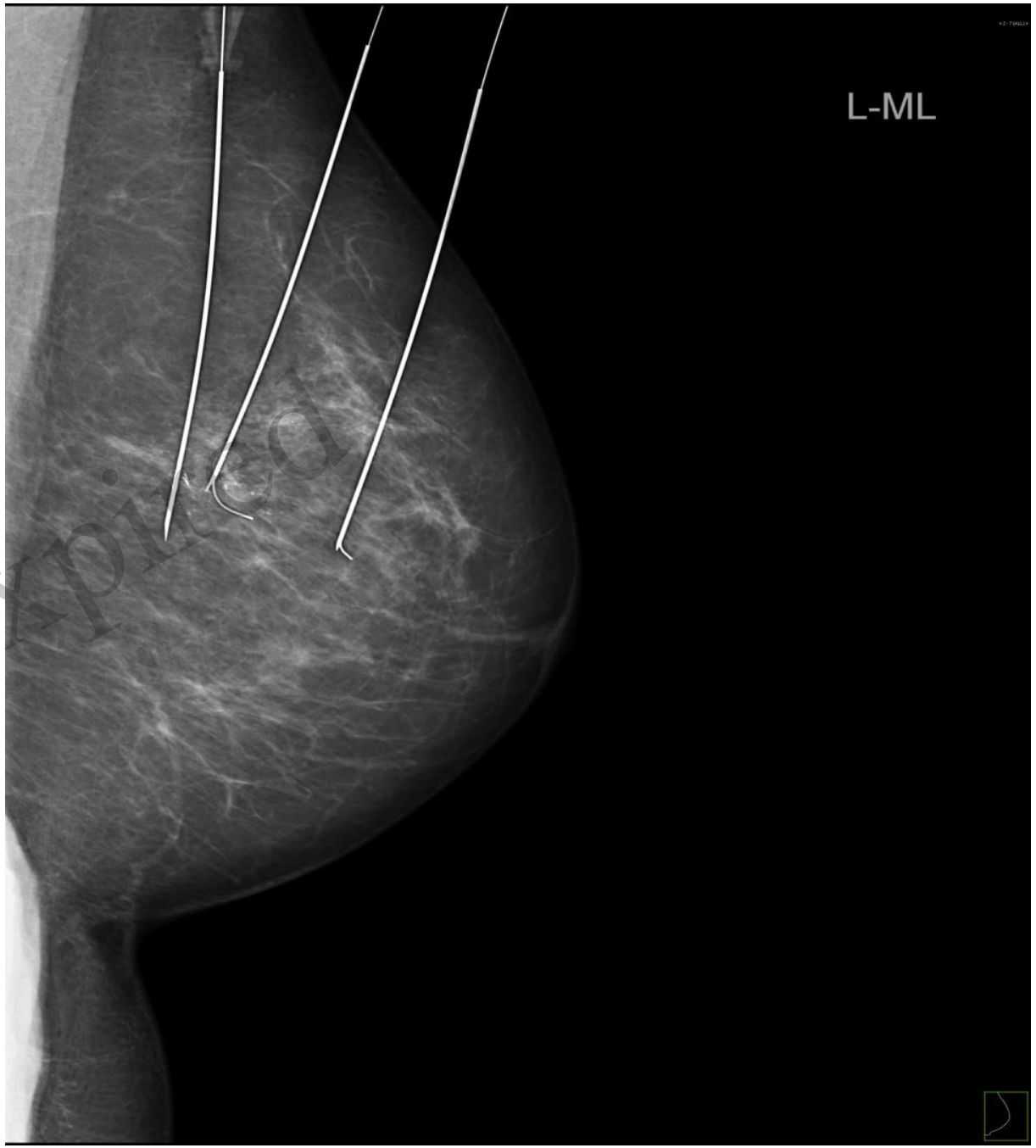
vs

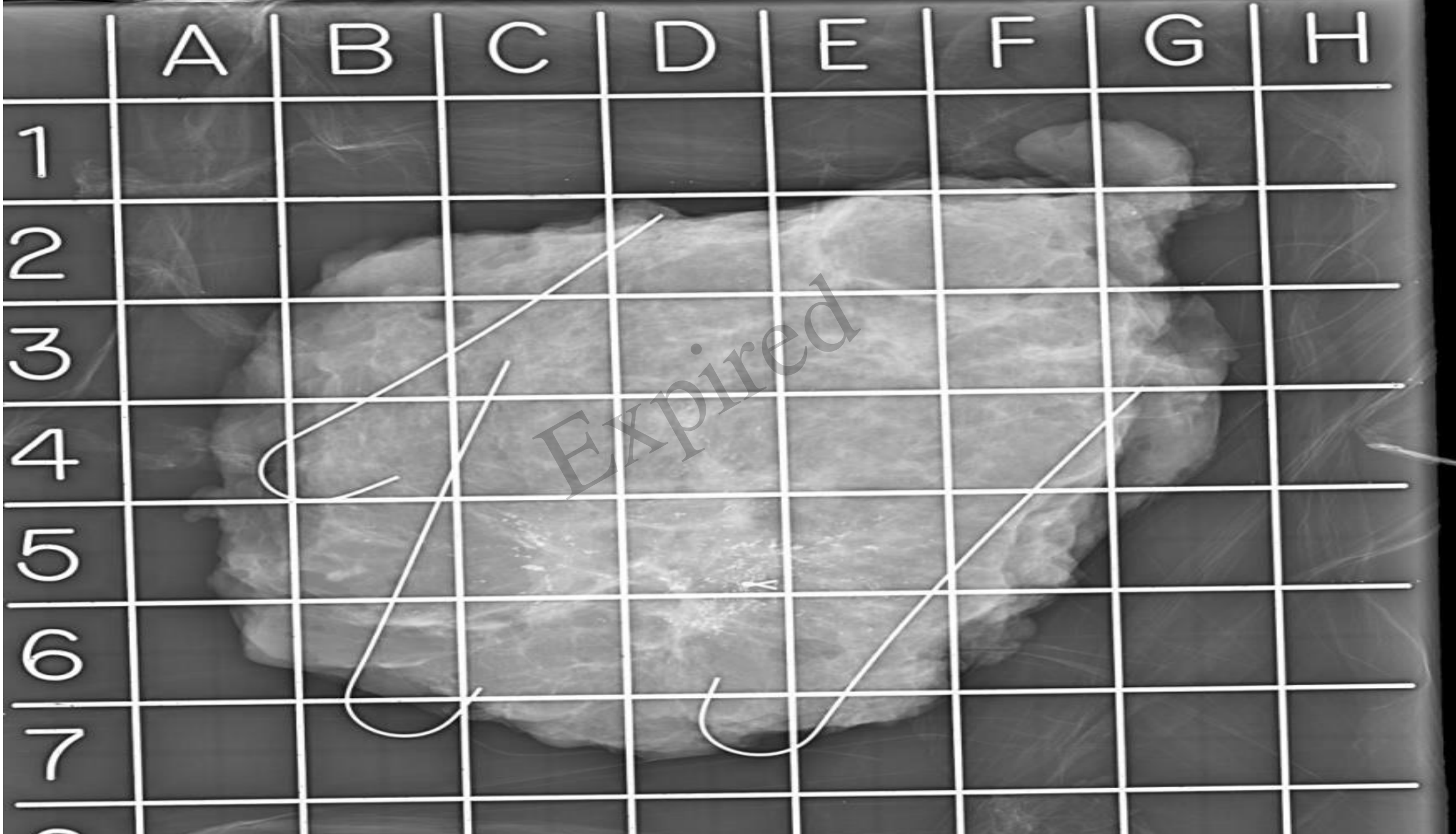
Excise what is necessary guided by imaging

Can we avoid operating altogether ?

Plan Surgery:

Breast




A
B
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1
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6
7
Expired

The Axilla

Axillary Surgery Following Neoadjuvant Chemotherapy

Multidisciplinary Guidance

UK Breast Cancer Group
Association of Breast Surgery
British Society of Breast Radiology
National Coordinating Committee for Breast Pathology
Faculty of Clinical Oncology of The Royal College of Radiologists

Ashu Gandhi, Charlotte Coles, Andreas Makris,
Amit Goyal, Elena Provenzano, Anthony Maxwell, Julie Doughty

Axillary Staging: Pre-NACT

Axillary ultrasound +/- biopsy

↓ ↓

Node positive **Node negative**

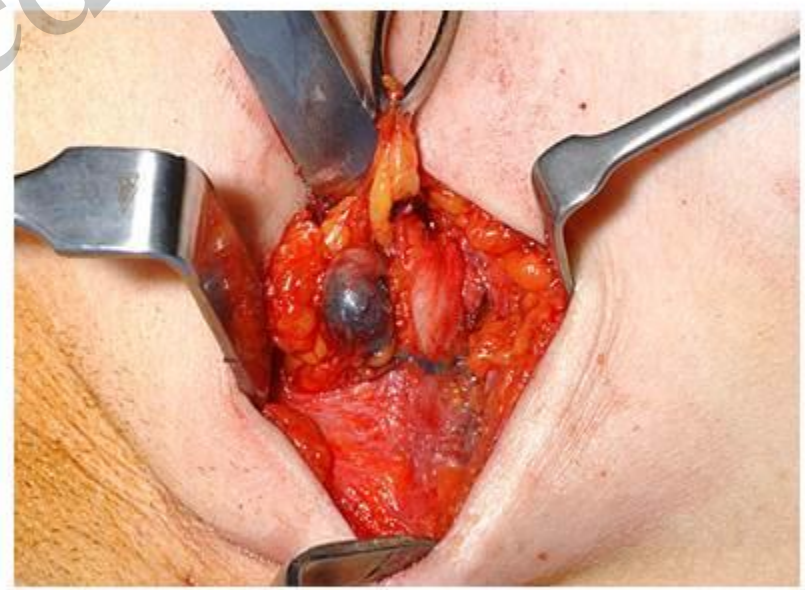
Pre NACT Assessment

Node negative (cN0)

Sentinel Node Biopsy

Before

OR



After

Node negative disease at presentation (cN0)

Clinical and radiological: normal axilla

SLNB : Pre- or post – neoadjuvant chemotherapy

Comparable identification & false negative rates

Sentinel Node Biopsy Before

SNB positive (macromets) pre-NACT:
- post NACT treatment: ANC or RT (or POSNOC)
- facilitates planning in patients considering immediate recon

Repeat SNB after NACT not recommended:
- identification rates (~60%), false negative rates (~ 50%)

Committed to TWO operations: SNB then post NACT
May delay commencement of chemotherapy

Committed to axillary treatment regardless of NACT response

Loss of prognostic information: NACT effect on nodes (RCB)

Sentinel Node Biopsy After

cN0 pre NACT & negative SNB post NACT: No axillary treatment required

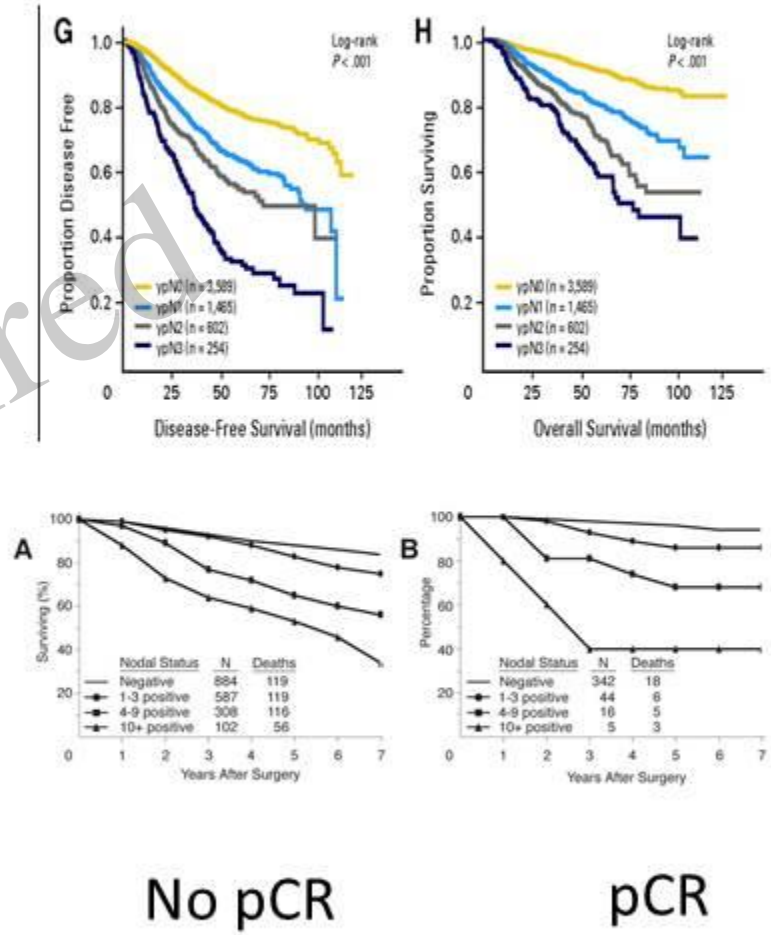
Positive SNB post NACT or evidence of treatment response treat as for node positive

Only one surgical procedure usually required

Greater prognostic information:
NACT effect on nodes (RCB)

Significance of nodal response

- Nodal status post chemotherapy is a strong predictor of outcome
- Neo Tango – 6% residual disease in axilla despite pCR in the breast
- Residual nodal disease an independent predictor of poor prognosis, even in presence of pCR in the breast



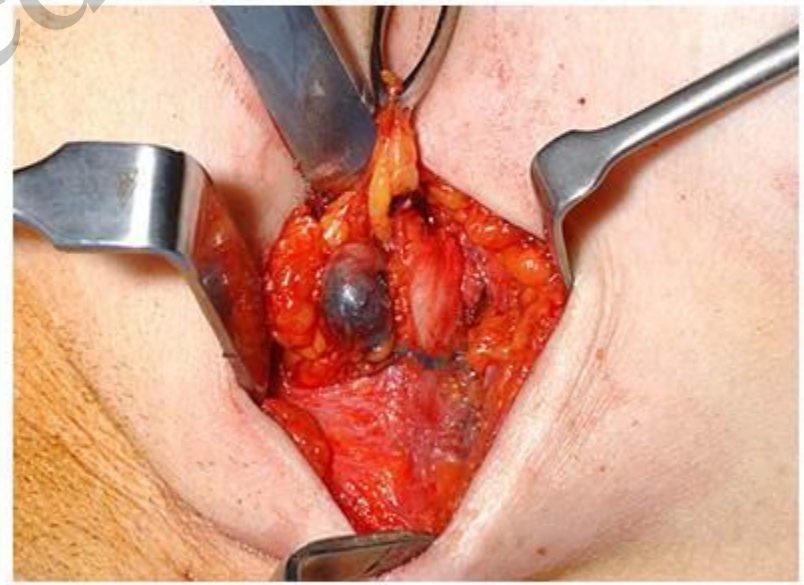
No pCR pCR

von Minckwitz G et al. JCO 2012;30:1796-1804

Sentinel Node Biopsy Node negative (cN0)

Before

OR



After

Pre NACT Assessment

Node positive (cN1)

Pre NACT Assessment: node positive (cN1)

Ultrasound assessment of the axilla:
- number of axillary nodes that appear to be involved
- any evidence of extra-nodal spread

If extensive disease may decide that post NACT axillary treatment required regardless of treatment response

Potential to de-escalate treatment

Post NACT Assessment: node positive (cN1)

MDM discussion

Post NACT Assessment: node positive (cN1)

- Response in breast may correlate with axilla
- Good response rates with triple negative tumours and HER2 + tumours treated with dual blockade
- Axillary USS (+/- Bx) may identify residual disease
- SNB may be an option if evidence of good response

Post NACT Assessment: node positive (cN1)

If SNB is an option:

- False negative rates can be reduced by:
  - using dual radio-isotope & blue dye technique
  - taking 3 or more SNB
  - marking positive node pre NACT (clips, tattoo, seeds)

- If no SNB identified proceed to ANC

Neoadjuvant Pathway

- Diagnosis
- Patient selection
- Neoadjuvant treatment
- Assess response
- Plan surgery
- **Detailed pathology assessment**
- Post surgical radiotherapy and / or adjuvant systemic therapy

Detailed pathology assessment - Breast

- Residual disease - Residual Cancer Burden (RCB)
- Evidence of response
- Clear margins
- ? Need for further surgery

Detailed pathology assessment - Axilla

- Residual disease - Residual Cancer Burden (RCB)
- Evidence of response
- ? Need for further local treatment

Post NACT SNB: node positive (cN1)

Complete pathological response

No evidence base – Trials

NSABP B51/RTOG 1304 - Axillary radiotherapy

Post NACT SNB: node positive (cN1)

Malignant sentinel node(s)

Residual disease: macro / micro / ITC

No evidence base

Alliance A011202 Trial (Comparison of axillary node dissection vs axillary radiation in patients who have positive sentinel node biopsy after neoadjuvant chemotherapy)

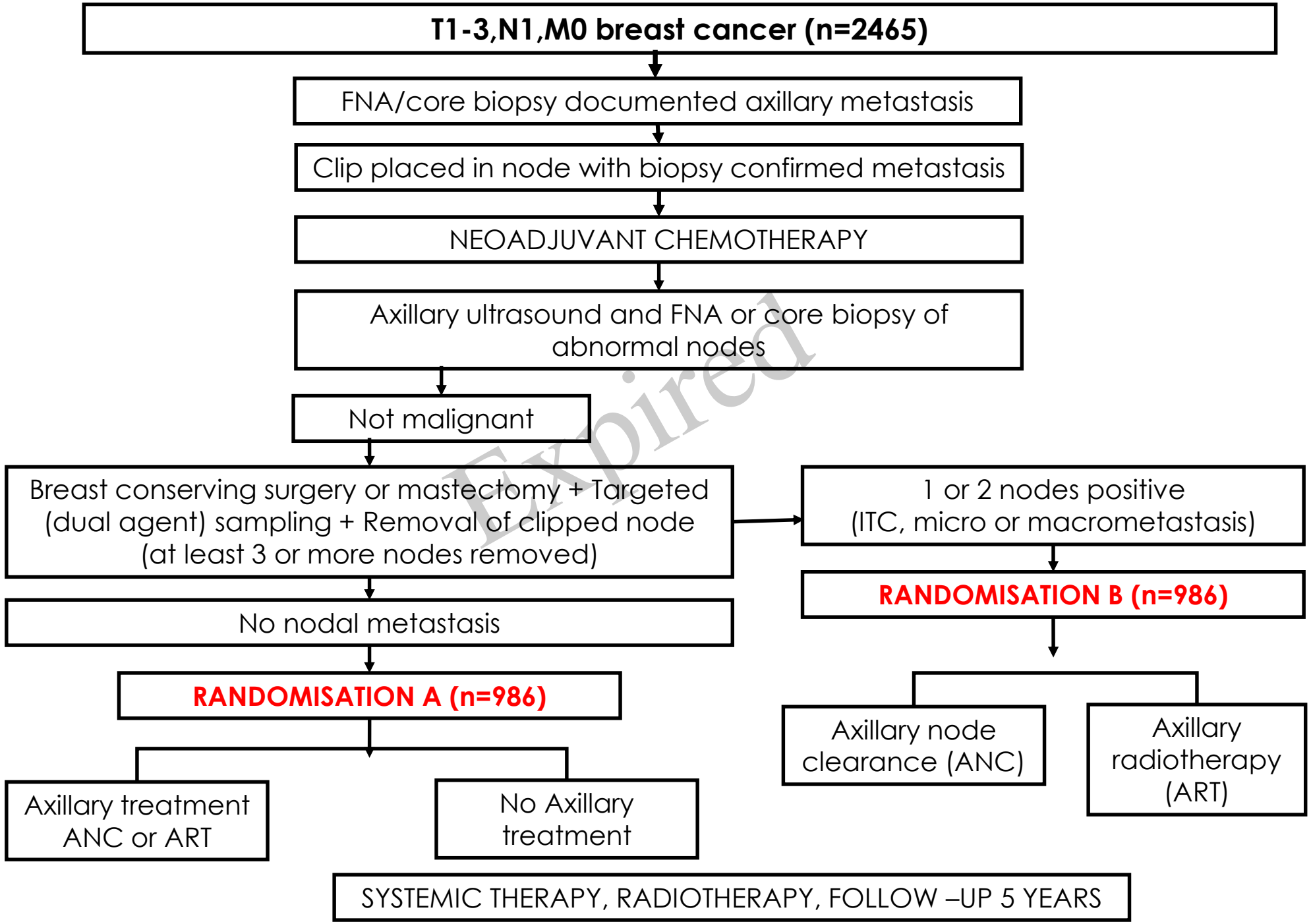
ANC – standard of care (not axillary radiotherapy)

ATNEC Trial

Adaptive platform study evaluating the optimal management of axilla in patients with **T**1-3N1M0 breast cancer after **Ne**oadjuvant **C**hemotherapy

Amit Goyal (Chief Investigator)

Royal Derby Hospital, Derby, United Kingdom


T1-3,N1,M0 breast cancer (n=2465)
FNA/core biopsy documented axillary metastasis
Clip placed in node with biopsy confirmed metastasis
NEOADJUVANT CHEMOTHERAPY
Axillary ultrasound and FNA or core biopsy of abnormal nodes
Not malignant
Breast conserving surgery or mastectomy + Targeted (dual agent) sampling + Removal of clipped node (at least 3 or more nodes removed)
No nodal metastasis
RANDOMISATION A (n=986)
Axillary treatment ANC or ART
No Axillary treatment
1 or 2 nodes positive (ITC, micro or macrometastasis)
RANDOMISATION B (n=986)
Axillary node clearance (ANC)
Axillary radiotherapy (ART)
SYSTEMIC THERAPY, RADIOTHERAPY, FOLLOW –UP 5 YEARS

Neoadjuvant Pathway

- Diagnosis
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- Detailed pathology assessment
- **Post surgical radiotherapy and / or adjuvant systemic therapy**

Local treatment Post NACT

- Surgery to breast
  - breast conserving or mastectomy
- Surgery to axilla
  - SNB or ANC
- Radiotherapy:
  - to breast post BCS
  - to chest wall post mastectomy
  - to axilla +/- other LN areas (SCF, IMC)

Local treatment Post NACT

- Surgery to breast
  - breast conserving or mastectomy **or NIL**
- Surgery to axilla
  - SNB or ANC **or NIL**
- Radiotherapy:
  - to breast post BCS
  - to chest wall post mastectomy
  - to axilla +/- other LN areas (SCF, IMC)

Neoadjuvant Treatment – A Surgical Perspective

- Potential advantages of neoadjuvant treatment
- Patient selection
- Pathway and key decision making
- Local and regional treatment after neoadjuvant treatment
- **Adjuvant systemic treatment (focus on HER2 positive)**

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