**Association of Breast Pathology,
Association of Breast Surgery,
British Society of Breast Radiology,
and UK Breast Cancer Group**

NEOADJUVANT CHEMOTHERAPY: MULTIDISCIPLINARY GUIDANCE

INTRODUCTION

The use of neoadjuvant chemotherapy (NAC) and endocrine therapy in patients with breast cancer varies widely in centres throughout the UK. In other parts of the world, neoadjuvant chemotherapy has become the standard of care for specific molecular subtypes, as it allows patients with residual disease access to new drugs. In patients who do receive NAC in the UK, there is wide variation in the surgical and oncological treatment, during and on completion of NAC.

There are many reasons to account for this variation in the use of NAC. These include the perceived complexity of delivering NAC, the uncertainty regarding the benefits of NAC, and increasingly the lack of staff essential to the delivery of neoadjuvant chemotherapy, especially radiologists, oncologists and nursing staff.

This multidisciplinary guidance was developed in conjunction with the UK Breast Cancer Group (UKBCG), the British Society of Breast Radiology and Association of Breast Pathology. It is a short succinct document divided into page long sections covering all aspects of delivering NAC.

We wanted this guidance to be practical and the aims of it are:

- To simplify and demystify the delivery of NAC
- To identify which patients will benefit from NAC and those who will not
- To standardise surgery and radiotherapy in patients following NAC

I am grateful to everyone who contributed to this guidance and I hope you will find it useful.

Julie Doughty
Past President, Association of Breast Surgery

NEOADJUVANT CHEMOTHERAPY: MULTIDISCIPLINARY GUIDANCE

SECTION 1 Why Consider Neoadjuvant Chemotherapy (NACT)?

To downstage

- Inflammatory breast cancer
- Inoperable breast cancer / Locally advanced disease: T4, N2/3
  - If post-menopausal ER positive / HER2 negative consider NET

To guide post-operative therapy based on pathological response

- HER2 positive (TDM1) and TNBC (capecitabine)

Where chemotherapy will definitely be given adjuvantly* consider NACT to:

- To try to facilitate BCS +/- downstaging axilla
- To allow germline genetic testing
- To plan autologous reconstruction
- To facilitate participation on clinical trials

**See section 2*

SECTION 2 Patients Likely to Require Adjuvant Chemotherapy

HER2 positive or TNBC

- If cT≥2 or cN≥1 for NACT
- If T1b/T1cN0 only ***consider*** NACT if needed to facilitate BCS or to allow for germline testing

ER positive HER2 negative

- Only ***consider*** NACT if:
  - High risk disease in premenopausal women to try and facilitate BCS, germline testing and/or allow time to plan breast reconstruction
  - If appropriate trial available
- Avoid NACT if full surgical pathology or genomic testing required to inform decision making regarding chemotherapy
- NET should be considered in postmenopausal women for downstaging to facilitate BCS
- If genomic testing is required post-operatively and there has been treatment preoperatively (including window studies) then utilise diagnostic core biopsy rather than post-treatment surgical tissue

SECTION 3 Neoadjuvant Chemotherapy Considerations

Planning:

- Be clear on aims from outset
- Document clearly aims at MDT
- Ensure breast is fully assessed pre chemotherapy and that plan for axilla is clear
- Marker clips to localise tumour bed/nodes
- Consider timing of subsequent imaging/ clinic appointments. View a sample NACT Schedule Calculator **here**. The spreadsheet will automatically calculate the treatment dates when the start date is entered.

Patient Information

- Primary surgery is an alternative
- pCR rates will vary with phenotype
  - TNBC up to 60% with immunotherapy
  - HER2 positive up to 70%
  - ER positive HER2 negative up to 10%
- Allows response adaptive surgery to breast and nodes e.g. facilitate BCS or SLNB with dual localisation or targeted axillary surgery
- Allows response adaptive drug therapy planning
- Not all will respond and less than 3% will progress
- Patients who do not achieve pCR can still have a good prognosis

SECTION 4 NACT regimens

1. Triple Negative

Platinum based regimen recommended

- Paclitaxel +/- carboplatin followed by dose dense/3w AC/EC
- Consider addition of pembrolizumab to this schedule

The following are alternative regimens

- Dose dense/3w AC/EC followed by paclitaxel
- Docetaxel + cyclophosphamide

2. HER2-Positive

- Dose dense/3w AC/EC followed by paclitaxel plus Trastuzumab plus Pertuzumab
- Dose dense/3w AC/EC followed by docetaxel plus Trastuzumab plus Pertuzumab
- Docetaxel plus Carboplatin plus Trastuzumab plus Pertuzumab
- Where co-morbidity or frailty precludes more intensive regimen: Consider weekly paclitaxel plus Trastuzumab

3. ER-positive/HER2-negative*

- Dose dense/3w AC/EC followed by paclitaxel or docetaxel
- Docetaxel plus cyclophosphamide
- Dose dense AC/EC followed by paclitaxel +carboplatin can be considered in cases of germline BRCA1/2 pathogenic or likely pathogenic variants

**Consider endocrine therapy +/- a CDK 4/6 inhibitor in inoperable disease*
In postmenopausal patients consider commencing bisphosphonate with neoadjuvant therapy

SECTION 5 Neoadjuvant therapy in pregnancy related breast cancer

- Surgery: Can be undertaken at any time in pregnancy
- Systemic treatment protocols: Aim to follow those for non-pregnant females
- Dosing: According to actual body weight at each cycle not pre-pregnancy body weight
- Timing of systemic therapy: Avoid chemotherapy in 1st trimester and beyond 35 weeks unless weekly regimen when up to 37 weeks with monitoring of bloods can be considered
- Chemotherapy Regimens: Anthracyclines, Taxanes and platinum based regimens are all allowed but CMF to be avoided
- HER2 targeted Therapy: Not generally recommended. May be considered for short durations i.e. < 1 trimester with monitoring for an/oligohydramnios

Supportive Therapies:

- Antiemetics: Utilise methylprednisolone or hydrocortisone rather than dexamethasone. All other antiemetics allowed
- Granulocyte colony-stimulating factor: Allowed as per non-pregnancy protocols
- Monitoring: Chemotherapy may cause foetal growth retardation therefore foetal growth should be monitored

Delivery:

- The aim should be for a full term delivery given as prematurity is the biggest factor for an adverse foetal outcome

SECTION 6 Imaging Assessment

Pre treatment diagnosis

- Standard imaging to assess breast and axilla: Digital Mammography (DM) and ultrasound (US) as a minimum
- Contrast examination before NACT
  - If patient may be candidate for BCS post NACT, to exclude multifocal or multicentric disease
  - MRI or contrast enhanced mammography (CEM) probably equivalent
  - Particularly relevant for HER2 positive disease
- Biopsy confirmation of unexpected multifocal or multicentric disease prior to NACT
  - All areas to have tissue markers if BCS being considered
- N1 axillary disease – consider marker to biopsied node pre NACT to facilitate targeted axillary surgery
- Whole body staging: as per Royal College of Radiologists (RCR) guidance
  - No requirement to stage if ≤ T2 tumours and ≤N1 disease

Monitoring – RCR guidance

- MRI if performed at baseline
  - Best correlates with final pathology
  - CEM may have similar accuracy (limited evidence to date)
  - If MRI not available – repeat DM + US post NACT
  - Consider imaging mid treatment if using risk-adapted therapies

NB: artefact from some non-wire localisation devices at MRI

- Can be up to 4cm
- May prevent MRI response assessment in breast and axilla

SECTION 7 Clinical Assessment Prior to Surgery

Monitoring

- Oncological assessment for disease progression and toxicity
- Surgical assessment to plan surgery
- If evidence of disease progression, surgery to proceed as soon as safely possible

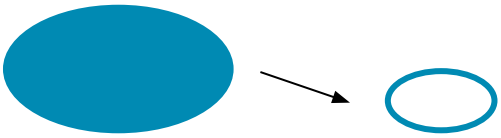
Timing of Surgery

- From 3 - 4 weeks and within 8 weeks after 3 weekly chemotherapy
- 2 weeks after weekly chemotherapy
- HER2 positive breast cancer: HER2 directed therapy to continue until surgery
- Need neutrophil count >1

SECTION 8 Response to Neoadjuvant Chemotherapy – patterns

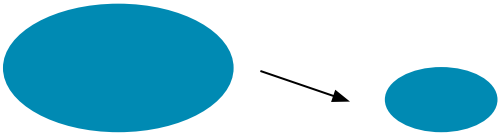
pCR

- No clinical abnormality
- Imaging – normal or residual mass that may be fibrosis alone
- Surgery: smaller WLE around clip
- Pathology – no cancer – specimen should contain marker and show evidence of chemo response



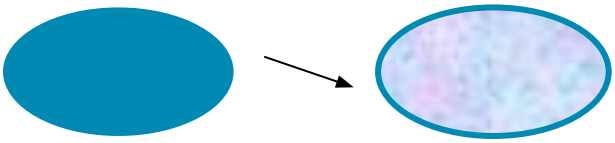
Concentric shrinkage

- Examination – smaller mass
- Imaging – smaller residual mass or may be normal
- Surgery: WLE around clip
- Pathology – smaller lesion, well circumscribed, margins clear, may be downgraded



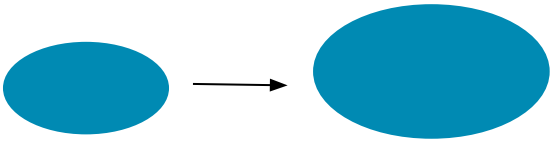
Honeycomb effect

- Examination – normal
- Imaging – may be normal or residual mass
- Surgery – smaller WLE around clip
- Pathology – cancer cells throughout specimen
- In this scenario consideration needs to be given to excising the original footprint. Re-iterate to the patient that this is still a response to chemotherapy

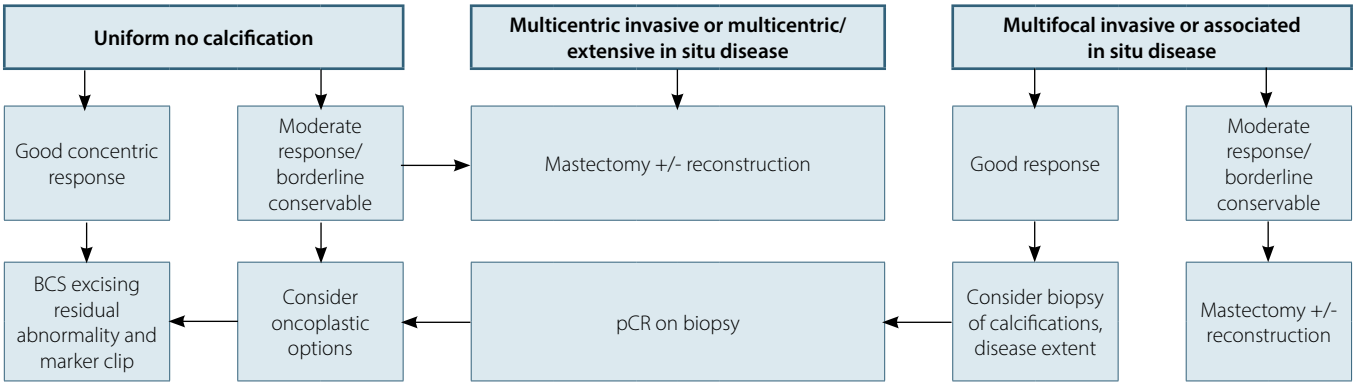


No response or progression – less than 3%

- Examination – larger mass
- Imaging – same or larger
- Pathology – larger lesion
- Should pick up on monitoring during chemo
- Usual to switch chemo, may need to operate sooner, poorer prognosis

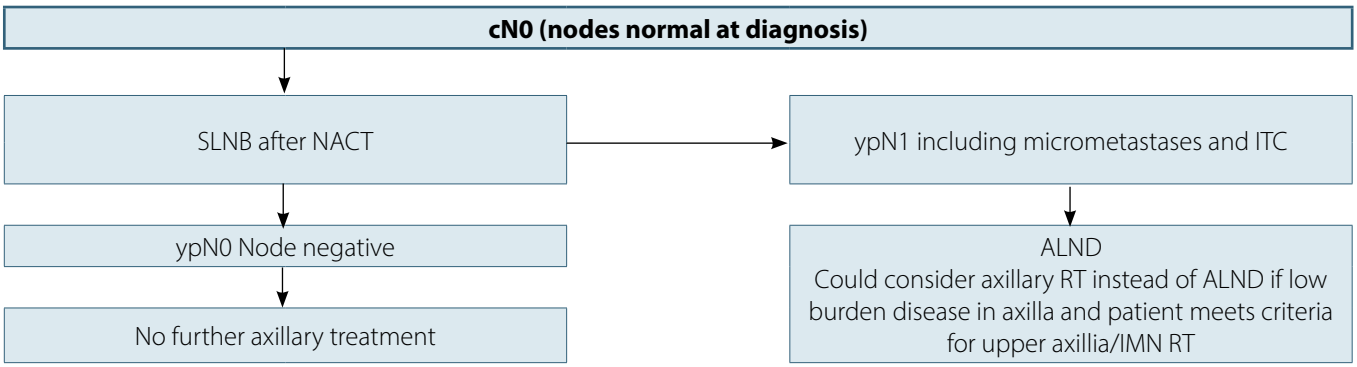


SECTION 9 Surgery to the Breast post Neoadjuvant Chemotherapy

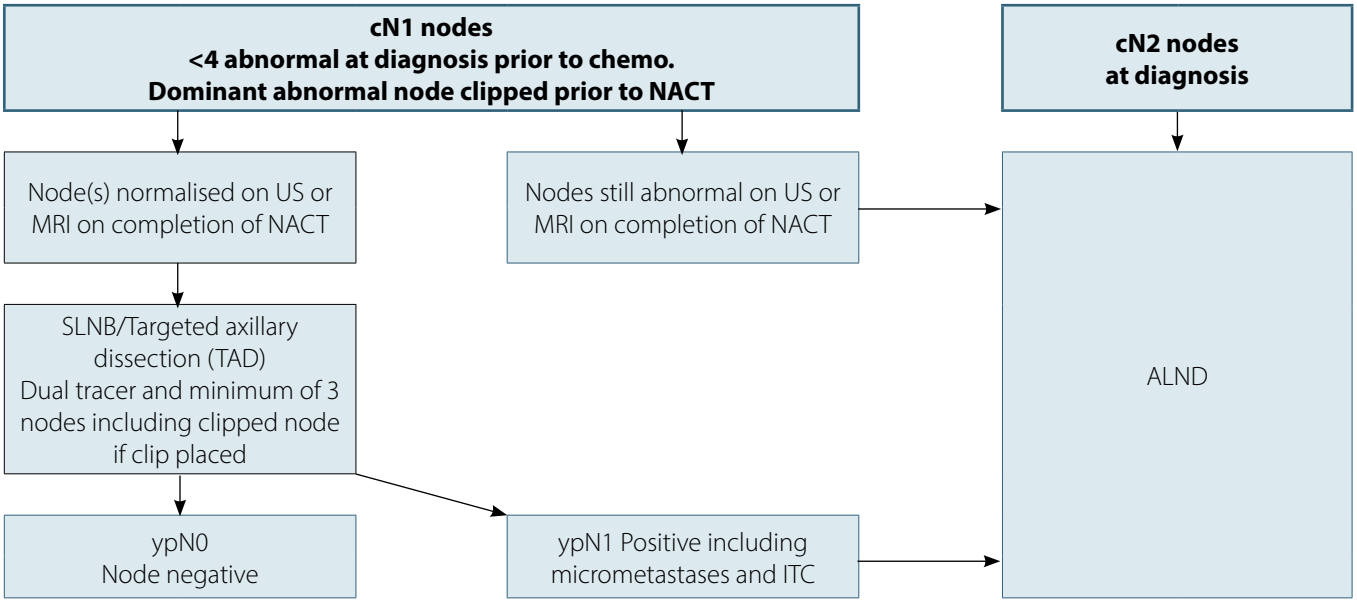


SECTION 10 Axillary Surgery post Neoadjuvant Chemotherapy

Axillary surgery post NACT



Axillary surgery post NACT



SECTION 11 Pathology

- Specimens often more complicated to handle, and report, particularly if there is good response to NACT, with more extensive sampling (and sometimes immunohistochemistry) needed
- Lymph node yield is often lower post NACT
- Response/tumour bed is seen histologically as fibrosis, oedema, foamy macrophages, inflammation, scattered haemosiderin; cancer cells can be subtle
- Definitions of complete pathological response (pCR) have varied but no residual invasive tumour in breast (may have DCIS) and in lymph nodes is a good prognostic feature
- Pathologists should report degree of response; no single system is mandated, but residual cancer burden (RCB) is used in some centres, and in clinical trials **(MD Anderson Cancer Center Residual Cancer Burden Calculator)**
- The International Collaboration on Cancer Reporting have provided a standardised data set for reporting pathology specimens post NACT. See Appendix 1

SECTION 12 Post operative systemic therapy

1. Triple negative

If no pCR

- Neoadjuvant chemotherapy regimen containing anthracycline, taxane +/- carboplatin: Capecitabine 6 or 8 cycles (Omission reasonable after platinum based neoadjuvant regimen given lack of data)
- For patients with germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants consider Olaparib when funded

Independent of pathological response

- If pembrolizumab was used prior to surgery continue for a further 9 cycles

2. HER2-positive breast cancer

Pathological complete response

- cN0 with no pathological evidence of nodal scarring: Trastuzumab max. 14 cycle. *Consider total 6 months of trastuzumab*
- cN>1or cN0 with evidence of nodal scarring indicative of response: Trastuzumab plus pertuzumab max. 14 cycles

Residual Disease

- Trastuzumab emtansine: max. 14 cycles

Residual Disease in breast and/or the axilla, ER positive and post-operative therapy with single agent trastuzumab

- Neratinib for 1 year

3. ER Positive/HER2 Negative

No pCR

- For patients with germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants olaparib when funded

4. ER Positive

- For all patients adjuvant endocrine therapy for at least 5 years

5. Postmenopausal women

- Offer adjuvant bisphosphonates if not commenced neoadjuvantly
- If Bisphosphonates commenced neoadjuvantly they should be continued independent of the pathological response

SECTION 13 Adjuvant Radiotherapy

Adjuvant Radiotherapy to Breast/Chest wall

- Decision to treat based on tumour size/nodal status at presentation pre-NACT
- Consider post-surgical findings including number of lymph nodes containing fibrosis (highly suggestive of previous positive nodes)
- Offer RT in all cases of BCS
- Offer PMRT
  - > 5 cm or T4 tumour
  - ≥4 nodes involved (includes fibrotic nodes)
  - close or involved margins
- Consider PMRT
  - for all patients with node positive cancer, especially if grade 3, young age, poor response to NACT, ER-ve

Adjuvant nodal Radiotherapy

- **cN0 to ypN0:** No further axillary treatment
  - If fibrosis in nodes, offer axillary RT. Consider omitting axillary RT if 1 out of at least 2 SLNs shows fibrosis post-NACT and baseline axillary imaging excludes macroscopic axillary disease
- **cN0 to ypN1:** ALND recommended
- Nodal RT can be considered as an alternative in individual cases with low burden disease (ITC or micromets) and who also require upper axilla/IMC nodal RT
- Upper axilla (levels 3-4) should be considered if ≥4 nodes positive, usually with internal mammary chain (IMC) radiotherapy unless patient is unfit or a heavy smoker
- Offer IMN RT for all T4, all N2-3 & T3 N1
- Consider IMN RT for N1 pts with high-risk features, e.g. unfavourable biology and medial/lower half breast tumour
- IMC is treated in conjunction with axillary nodes
- **cN1 to ypN0 following TAD:** offer axillary RT OR no further treatment of the axilla within a clinical trial
- **cN+ to ypN1 following TAD:** for ALND + RT to axilla above surgical dissection ± IMC
- Ideally surgeon will mark the most superior part of the axillary dissection with a clip

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APPENDIX 1 Standardised data set for reporting pathology specimens post NACT

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Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy Histopathology Reporting Guide

ICCR

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in grey text are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

◯ Information not provided

Neoadjuvant treatment(s) (select all that apply)

◯ Information not provided
☐ Hormonal therapy
☐ Chemotherapy
☐ Anti-HER2 targeted therapy
☐ Immune therapy
☐ Radiation therapy
☐ Other, *specify*

Pre-treatment tumour characteristics

◯ Information not provided

Laterality

Site(s)

Date of diagnosis

Imaging size at diagnosis

Fiducial marker placement

Diagnosis

Hormone receptor and HER2 status

Other (e.g., tumour grade, tumour cellularity, tumour infiltrating lymphocytes (TIL), Ki-67, multigene assays), *specify if available*

Pre-treatment axillary lymph node biopsy/sampling (select all that apply)

◯ Not applicable
◯ Not known
☐ Core biopsy
☐ Fine needle aspiration (FNA)
☐ Other, *specify*
☐ Sentinel node biopsy

Fiducial marker placed ◯ Yes ◯ No

Result ◯ Positive ◯ Negative

Other clinical information, *specify*

OPERATIVE PROCEDURE - BREAST (Note 2)

◯ Not specified
◯ Excision (less than total mastectomy)
- ◯ Therapeutic wide local excision
- ◯ Re-excision

◯ Total mastectomy
- ◯ Simple mastectomy
- ◯ Nipple-sparing mastectomy
- ◯ Skin-sparing mastectomy
- ◯ Modified radical mastectomy
- ◯ Radical mastectomy

◯ Additional specimens, *specify*

OPERATIVE PROCEDURE - AXILLA (select all that apply) (Note 3)

☐ Sentinel lymph node biopsy
☐ Targeted non-sentinel lymph node biopsy (dissection)
☐ Other non-sentinel lymph node biopsy
☐ Axillary lymph node dissection
- ◯ Level I
- ◯ Levels I and II
- ◯ Levels I to III

☐ Axillary lymph node level III, excision
☐ Other regional lymph node(s) biopsy
- ☐ Internal mammary
- ☐ Infraclavicular (subclavicular)
- ☐ Supraclavicular

☐ Other, *specify*

SPECIMEN LATERALITY (Note 4)

◯ Left ◯ Right ◯ Not specified

SPECIMEN DIMENSIONS

mm x mm x mm

SPECIMEN WEIGHT

g

NEOADJUVANT CHEMOTHERAPY: MULTIDISCIPLINARY GUIDANCE

Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy

SPECIMEN DETAILS

Depth of tissue excised

Skin to deep fascia ◯ Yes ◯ No

Specimen includes (select all that apply)

☐ Skin ☐ Nipple ☐ Skeletal muscle

TUMOUR SITE (select all that apply) (Note 5)

◯ Not specified

Distance from nipple _____ mm

AND

Position, *specify* _____ o'clock

OR

☐ Upper outer quadrant
☐ Lower outer quadrant
☐ Upper inner quadrant
☐ Lower inner quadrant
☐ Central
☐ Nipple
☐ Other, *specify*

TUMOUR FOCALITY (Note 6)

◯ Cannot be determined
◯ Single focus of invasive carcinoma
◯ Multiple foci of invasive carcinoma on pre-treatment imaging and on pathologic evaluation, *describe*[a]

◯ Multiple foci of invasive carcinoma within a single (fibrotic) tumour bed corresponding to a single focus on pre-treatment imaging

Number of foci

◯ Cannot be assessed

_____

is at least _____

Morphology of multiple foci[b]

◯ Distinct ◯ Similar

Histological tumour type _____

Histological tumour grade _____

Receptor status _____

Cellularity _____

Size _____ mm

[a] *See also Note 8.*

[b] *Core element if multiple foci only.*

Morphology of multiple foci[b]

◯ Distinct ◯ Similar

Histological tumour type _____

Histological tumour grade _____

Receptor status _____

Cellularity _____

Size _____ mm

Morphology of multiple foci[b]

◯ Distinct ◯ Similar

Histological tumour type _____

Histological tumour grade _____

Receptor status _____

Cellularity _____

Size _____ mm

RESIDUAL INVASIVE CARCINOMA (Note 7)

◯ Present
◯ Absent[c]

Pre-treatment tumour site identified[d]

◯ Uncertain
◯ Yes (select all that apply)

☐ Palpable/visible area on gross examination
☐ Area of concern on specimen radiograph
☐ Calcifications associated with tumour pre-treatment identified
☐ Ductal carcinoma in situ (DCIS) identified
☐ Fiducial marker (clip or equivalent) identified
☐ Surgical localization marker (wire, seed or equivalent) identified
☐ Histologic changes suggestive of tumour bed
☐ Targeted lumpectomy thoroughly sampled
☐ None of the above but likely areas thoroughly sampled
☐ A reference map documents the blocks sampled for histologic evaluation

◯ Cannot be assessed, *specify*

_____

[c] *If there is no residual invasive carcinoma then the remaining elements pertaining to residual invasive carcinoma* ***(Tumour dimensions, Tumour cellularity/composition, Histologic tumour type, Post-treatment histologic tumour grade, Tumour extension, Margin status, Post-treatment estrogen receptor, Post-treatment progesterone receptor, Post-treatment HER2 and Post-treatment ancillary studies)*** *are removed from the report.*

[d] *Core element if residual invasive carcinoma absent.*

Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy

TUMOUR DIMENSIONS[e] (Note 8)

- ◯ No residual invasive carcinoma
- Maximum dimension of largest contiguous invasive focus
  - ◯ ≤1 mm
  - ◯ >1 mm (*specify exact measurement rounded to nearest mm*) ____ mm
- Maximum 2 dimensions of the area containing residual invasive carcinoma, representing a single residual tumour bed and including any intervening fibrosis, fat, or breast parenchyma (*specify 2 exact measurements rounded to nearest mm*)

  ____ mm x ____ mm (RCB area dimensions)

- Maximum dimension of whole tumour field (invasive + DCIS)/total extent of disease ____ mm
- ◯ Cannot be assessed, *specify*

[e] *Based on a combination of macroscopic and microscopic assessment.*

TUMOUR CELLULARITY/COMPOSITION (Note 9)

- ◯ No residual invasive carcinoma

Estimate of Residual Cancer Cellularity using one of two methods below:

Residual Cancer Cellularity (invasive and in situ)[f]

____ % OR ◯ <1%, *specify*[g] ____ %
◯ 1%
◯ 5%
◯ 10%
◯ 20%
◯ 30%
◯ 40%
◯ 50%
◯ 60%
◯ 70%
◯ 80%
◯ 90%
◯ Other, *specify* ____ %

AND

Percentage of residual carcinoma that is carcinoma in situ (CIS) ____ %

[f] *The pathologist estimates the average percent of cancer (invasive and in situ) within the area of residual invasive cancer, and then estimates the percent that is in situ component.*

[g] *Note that very low cellularity can sometimes be estimated at very low values (e.g., 0.01%) and any decimal result is acceptable.*

OR

Residual Cancer Cellularity (invasive only)[h]

____ % OR ◯ <1%, *specify*[g] ____ %
◯ 1%
◯ 5%
◯ 10%
◯ 20%
◯ 30%
◯ 40%
◯ 50%
◯ 60%
◯ 70%
◯ 80%
◯ 90%
◯ Other, *specify* ____ %

Comparison with pre-treatment cellularity if available, *specify*

Percent TILs in tumour stroma ____ % post-treatment

◯ Cannot be assessed, *specify*

[h] *The pathologist estimates the average percent of invasive cancer within the area of residual invasive cancer. Zero is entered for the percentage of cancer that is in situ disease in the RCB calculator. See Note 12 for details about in situ disease.*

HISTOLOGICAL TUMOUR TYPE (Note 10)

(Value list from the World Health Organization Classification of Breast Tumours (2019))

- ◯ No residual invasive carcinoma
- ◯ Invasive breast carcinoma of no special type (invasive ductal carcinoma, not otherwise specified)[i]
- ◯ Invasive lobular carcinoma
- ◯ Tubular carcinoma
- ◯ Cribriform carcinoma
- ◯ Mucinous carcinoma
- ◯ Invasive micropapillary carcinoma
- ◯ Carcinoma with apocrine differentiation
- ◯ Metaplastic carcinoma
- ◯ Mixed, *specify subtypes present*[j]
- ◯ Other, *specify*

[i] *Refer to Note for details of variants including medullary carcinoma.*

[j] *Tumour exhibiting more than one tumour type should be designated mixed and the types present stated.*

Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy

POST-TREATMENT HISTOLOGICAL TUMOUR GRADE (Note 11)

- ◯ No residual invasive carcinoma
- ◯ Grade 1 (scores of 3, 4, or 5)
- ◯ Grade 2 (scores of 6 or 7)
- ◯ Grade 3 (scores of 8 or 9)
  - Tubule score 1,2,3 ☐
  - Nuclear pleomorphism 1,2,3 ☐
  - Mitotic count
    - ☐ per mm^2
    - OR
    - ☐ per 10 HPF (field diameter ____ mm)
  - Score 1,2,3 ☐
  - Total score ☐
- ◯ Too small or insufficient tumour cellularity to grade
- ◯ Cannot be reliably determined due to post-treatment changes

CARCINOMA IN SITU (Note 12)

- ◯ Not identified
- ◯ Present (select all that apply)
  - ☐ DCIS
    - ◯ Negative for extensive intraductal component (EIC)
    - ◯ Positive for EIC
  - ☐ Paget disease of the nipple
  - ☐ Encapsulated papillary carcinoma
  - ☐ Solid papillary carcinoma in situ
  - ☐ Lobular carcinoma in situ (LCIS)

CLASSIFICATION OF CARCINOMA IN SITU (if present) (Note 12)

Histological nuclear grade

(Applicable to DCIS, encapsulated papillary carcinoma and solid papillary carcinoma in situ)

- ◯ Grade 1 (Low)
- ◯ Grade 2 (Intermediate)
- ◯ Grade 3 (High)

Histological architectural pattern (select all that apply)

(Applicable to DCIS only)

- ☐ Cribriform
- ☐ Micropapillary
- ☐ Papillary
- ☐ Solid
- ☐ Other (e.g., clinging/flat[k]), *specify*
  - ☐

[k] *Applies to high nuclear grade DCIS only.*

Necrosis

- ◯ Not identified
- ◯ Present
  - ◯ Central (Comedo) necrosis
  - ◯ Focal (Punctate) necrosis (<10% duct diameter)

Classification of LCIS (select all that apply)

(Applicable if LCIS is present in specimen)

- ☐ Classical LCIS
- ☐ Pleomorphic LCIS
- ☐ Florid LCIS
- ☐ Other, *specify*
  - ☐

TUMOUR EXTENSION[l] (Note 13)

Skin

- ◯ Skin is not present
- ◯ Skin is present and uninvolved
- ◯ Invasive carcinoma directly invades into the dermis or epidermis without skin ulceration
- ◯ Invasive carcinoma directly invades into the dermis or epidermis with skin ulceration (classified as ypT4b)
- ◯ Satellite skin foci of invasive carcinoma are present (i.e., not contiguous with the invasive carcinoma in the breast) (classified as ypT4b)

Nipple (including areola complex)

- ◯ Nipple tissue is not present
- ◯ DCIS does not involve the nipple epidermis
- ◯ DCIS involves nipple epidermis (Paget disease of the nipple)

Skeletal muscle

- ◯ Skeletal muscle is not present
- ◯ Skeletal muscle is free of carcinoma
- ◯ Tumour involves skeletal muscle
- ◯ Tumour involves both skeletal muscle and chest wall (classified as ypT4a)

[l] *Where there is disease extension to involve skin, nipple or skeletal muscle, disease extent classification is a core element; in all other cases it is non-core.*

Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy

MARGIN STATUS[m] (Note 14)

(For wide local excision specimens and similar non-complete mastectomy specimens)

○ Cannot be assessed, *specify*

Invasive carcinoma

○ Involved *(select all that apply)*

- ☐ Anterior (superficial) — *Specify extent*
- ☐ Posterior (deep) — *Specify extent*
- ☐ Superior — *Specify extent*
- ☐ Inferior — *Specify extent*
- ☐ Medial — *Specify extent*
- ☐ Lateral — *Specify extent*
- ☐ Other margin, *specify* — *Specify extent*

○ Not involved

Specify closest margin, if possible

Distance of invasive carcinoma to closest margin

mm (< or > may be used)

○ Cannot be determined, *specify*

Distance of invasive carcinoma to other margins (< or > may be used)

Anterior (superficial)	mm
Posterior (deep)	mm
Superior	mm
Inferior	mm
Medial	mm
Lateral	mm
Other margin, *specify*	mm

[m] *Core for all wide local excision specimens, similar non-complete mastectomy and some (refer to Note) complete mastectomy specimens.*

DCIS[n]

○ Involved (select all that apply)

- ☐ Anterior (superficial) — *Specify extent*
- ☐ Posterior (deep) — *Specify extent*
- ☐ Superior — *Specify extent*
- ☐ Inferior — *Specify extent*
- ☐ Medial — *Specify extent*
- ☐ Lateral — *Specify extent*
- ☐ Other margin, *specify* — *Specify extent*

○ Not involved

Specify closest margin, if possible

Distance of DCIS to closest margin

mm

○ Cannot be determined, *specify*

Distance of DCIS to other margins (< or > may be used)

Anterior (superficial)	mm
Posterior (deep)	mm
Superior	mm
Inferior	mm
Medial	mm
Lateral	mm
Other margin, *specify*	mm

[n] *Required only if DCIS or florid LCIS or pleomorphic LCIS is also present in specimen.*

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MARGIN STATUS[m] (Note 14)
(For complete mastectomy specimens)

- ◯ Cannot be assesessd, *specify*

Invasive carcinoma

- ◯ Involved, *specify margin/sites of involvement*
- ◯ Not involved
  - Specify closest margin, if possible
  - Distance of invasive carcinoma to closest margin: mm (< or > may be used)
  - ◯ Cannot be determined, *specify*

DCIS[n]

- ◯ Involved, *specify margin/sites of involvement*
- ◯ Not involved
  - Specify closest margin, if possible
  - Distance of DCIS to closest margin: mm (< or > may be used)
  - ◯ Cannot be determined, *specify*

[m] *Core for all wide local excision specimens, similar non-complete mastectomy and some (refer to Note) complete mastectomy specimens.*

[n] *Required only if DCIS or florid LCIS or pleomorphic LCIS is also present in specimen.*

LYMPHOVASCULAR INVASION (Note 15)

- ◯ Not identified
- ◯ Present
  - *Specify extent*
- ◯ Indeterminate

COEXISTENT PATHOLOGY (Note 16)

- ◯ None identified
- ◯ Present, *specify*

MICROCALCIFICATIONS (select all that apply) (Note 17)

- ◯ Not identified
- ☐ Present in DCIS
- ☐ Present in invasive carcinoma
- ☐ Present in non-neoplastic tissue
- ☐ Other, *specify*

POST-TREATMENT ESTROGEN RECEPTOR (ER) (Note 18)

Antibody clone, *specify*

Testing performed ◯ Yes ◯ No

- ◯ Positive
- ◯ Low positive

For both options above specify percentage of cells with nuclear positivity[o]

% OR Range

- ◯ 1-10%[p]
- ◯ 11-20%
- ◯ 21-30%
- ◯ 31-40%
- ◯ 41-50%
- ◯ 51-60%
- ◯ 61-70%
- ◯ 71-80%
- ◯ 81-90%
- ◯ 91-100%

AND

Average intensity of staining

- ◯ Weak
- ◯ Moderate
- ◯ Strong

- ◯ Negative (less than 1% nuclear positivity)
  - ◯ Internal control cells present and stain as expected
  - ◯ Internal control cells absent
  - ◯ Other, *specify*
- ◯ Cannot be determined
  - ◯ Internal control cells present but no immunoreactivity of either tumour cells or internal controls
  - ◯ Other, *specify*

[o] *Percentage of cells with nuclear positivity may be reported as a specific*

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POST-TREATMENT PROGESTERONE RECEPTOR (PR) (Note 19)

Antibody clone, *specify*

Testing performed ◯ Yes ◯ No

◯ Positive

Percentage of cells with nuclear positivity°

% OR Range

- ◯ 1-10%
- ◯ 11-20%
- ◯ 21-30%
- ◯ 31-40%
- ◯ 41-50%
- ◯ 51-60%
- ◯ 61-70%
- ◯ 71-80%
- ◯ 81-90%
- ◯ 91-100%

AND

Average intensity of staining

- ◯ Weak
- ◯ Moderate
- ◯ Strong

◯ Negative (less than 1% nuclear positivity)

- ◯ Internal control cells present and stain as expected
- ◯ Internal control cells absent
- ◯ Other, *specify*

◯ Cannot be determined

- ◯ Internal control cells present; no immunoreactivity of either tumour cells or internal controls
- ◯ Other, *specify*

° *Percentage of cells with nuclear positivity may be reported as a specific number or a range if more than 10%.*

POST-TREATMENT HER2 (Note 20)

Antibody clone, *specify*

Testing performed ◯ Yes ◯ No

By immunohistochemistry (IHC)

- ◯ Not performed
- ◯ Negative (Score 0)
- ◯ Negative (Score 1+)
- ◯ Equivocal (Score 2+)
- ◯ Positive (Score 3+)

Percentage of cells with uniform, intense, complete membrane staining %

◯ Cannot be determined, *specify*

By in situ hybridization

- ◯ Not performed
- ◯ Negative (not amplified)
- ◯ Positive (amplified)
- ◯ Pending
- ◯ Cannot be determined, *specify*

Number of observers

Number of invasive tumour cells counted

◯ Dual probe assay

Average number of HER2 signals per cell

Average number of CEP17 signals per cell

HER2/CEP17 ratio /

◯ Single probe assay

Average number of HER2 signals per cell

Aneusomy

- ◯ Not identified
- ◯ Present

Heterogeneous signals

- ◯ Not identified
- ◯ Present

Percentage of cells with amplified HER2 signals %

POST-TREATMENT ANCILLARY STUDIES (Note 21)

- ◯ Not performed
- ◯ Performed

Ki-67 proliferation index %

Other, *specify test(s) and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

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NUMBER OF LYMPH NODES EXAMINED (Note 22)
(These values may be reported in the corresponding cells in Table 1A)

Total number of sentinel lymph nodes examined[q]	
Total number of non-sentinel lymph nodes examined[r]	
Total number of lymph nodes examined	

[q] *Core element only if sentinel lymph nodes are submitted by the surgeon.*

[r] *Non-sentinel lymph nodes include:*
1. *any lymph node submitted by the surgeon as 'non-sentinel lymph node' at the time of sentinel lymph node biopsy; and*
2. *axillary lymph nodes from an axillary lymph node dissection.*

Evidence of fiducial marker

- ◯ Not applicable
- ◯ No evidence of a fiducial marker
- ◯ Evidence of fiducial marker associated with lymph node, *specify*

NUMBER OF LYMPH NODES WITH METASTATIC CARCINOMA[s] (Note 23)
(This value may be reported in the corresponding cell in Table 1A)

[s] *This value includes the number of lymph nodes with macrometastatic (>2 mm) and micrometastatic carcinoma (>0.2 mm to 2 mm and/or ≥200 cells).*

NUMBER OF LYMPH NODES WITH MACROMETASTASES[t]

Sentinel lymph nodes	
Non-sentinel lymph nodes	
Total lymph nodes	

[t] *A macrometastasis is any tumour deposit spanning >2 mm microscopically.*

NUMBER OF LYMPH NODES WITH MICROMETASTASES[u] (Note 24)

Sentinel lymph nodes	
Non-sentinel lymph nodes	
Total lymph nodes	

[u] *A micrometastasis is any tumour deposit spanning >0.2 mm to 2 mm microscopically and/or consisting of more than 200 cells in one lymph node section but not exceeding 2 mm in extent.*

NUMBER OF LYMPH NODES WITH ISOLATED TUMOUR CELLS (ITCs)[v] (Note 25)
(These responses may be reported in the corresponding cells in Table 1A)

Sentinel lymph nodes	
Non-sentinel lymph nodes	
Total lymph nodes	

[v] *≤0.2 mm and ≤200 cells.*

SIZE OF LARGEST METASTASIS[w] (Note 26)

- ◯ Not assessable[x]

Size of largest contiguous metastatic tumour cell deposit (without intervening fibrosis)[y]	mm	(TNM size)
Extent of largest lymph node metastasis (with intervening fibrosis)[z]	mm	(RCB size)

[w] *Required only if macro- or micrometastatic carcinoma is present.*

[x] *Only to be used for cases investigated by one-step nucleic acid amplification.*

[y] *Largest contiguous metastatic tumour cell deposit determines micrometastasis versus macrometastasis for pN staging.*

[z] *Measurement used for calculation of RCB.*

EXTRANODAL EXTENSION[A] (Note 27)
(This response may be reported in the corresponding cell in Table 1A)

- ◯ Not identified
- ◯ Present
- ◯ Cannot be determined

[A] *Core element only if macro- or micrometastases are present.*

TREATMENT EFFECT (Note 28)
(These responses may be reported in the corresponding cells in Table 1B)

Treatment effect (A) – Presence of treatment effect in lymph nodes containing residual metastatic carcinoma

- ◯ Not identified
- ◯ Present
- ◯ Cannot be determined

Treatment effect (B) – Presence of treatment effect in lymph nodes without metastatic carcinoma

Number of lymph nodes with changes suggestive of treatment effect without metastatic carcinoma

PATHOLOGIC COMPLETE RESPONSE (pCR) (Note 29)

- ◯ pCR (ypT0 ypN0/cN0)
- ◯ pCR (ypTis ypN0/cN0) (residual DCIS)
- ◯ Residual invasive cancer – Not pCR
- ◯ Lymphovascular invasion only – Not pCR
- ◯ ITCs only (ypN0(i+)) – Not pCR

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RESIDUAL CANCER BURDEN (RCB) (Note 30)

- ◯ Cannot be determined
- ◯ No residual invasive carcinoma
- ◯ Residual invasive carcinoma

RCB area dimensions ____ mm x ____ mm

AND

Average cancer cellularity in RCB area[B] ____ %

____ % in situ component[C]

OR

Average invasive cancer cellularity in RCB area[B] ____ %

Number of lymph nodes with carcinoma[C] ____

Extent of largest lymph node metastasis ____ mm

RCB score[D] ____

RCB class[D] ◯ 0 ◯ I ◯ II ◯ III

[B] *Enter this value, and 0% for % CIS, in the RCB calculator (see Note).*

[C] *The number of lymph nodes with carcinoma, including the number of lymph nodes with ITCs, is used for calculating RCB.*

[D] *Core element if neoadjuvant treatment includes chemotherapy and the RCB calculator is accessible.*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[E] (Note 31)

TNM Descriptors (only if applicable) (select all that apply)

- ☐ r - recurrent
- ☐ m - multiple foci of invasive carcinoma
- ☐ y - post-therapy
- ☐ c - based on clinical or imaging studies, no histopathologic examination was performed – or lymph node assessment was done without the primary breast tumour being removed

Primary tumour (pT)

- ◯ ypTX Primary tumour cannot be assessed
- ◯ ypT0 No evidence of primary tumour
- ◯ ypT1 Tumour 2 cm or less in greatest dimension
  - ◯ ypT1a More than 0.1 cm but not more than 0.5 cm in greatest dimension
  - ◯ ypT1b More than 0.5 cm but not more than 1 cm in greatest dimension
  - ◯ ypT1c More than 1 cm but not more than 2 cm in greatest dimension
- ◯ ypT2 Tumour more than 2 cm but not more than 5 cm in greatest dimension
- ◯ ypT3 Tumour more than 5 cm in greatest dimension
- ◯ ypT4 Tumour of any size with direct extension to chest wall and/or to skin (ulceration or skin nodules)[F]
  - ◯ ypT4a Extension to chest wall (does not include pectoralis muscle invasion only)
  - ◯ ypT4b Ulceration, ipsilateral satellite skin nodules, or skin oedema (including peau d'orange)
  - ◯ ypT4c Both 4a and 4b
  - ◯ ypT4d Inflammatory carcinoma[G]

Regional lymph nodes (pN)

(This value may be reported in the corresponding cell in Table 1A)

- ◯ ypNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathological study)
- ◯ ypN0 No regional lymph node metastasis
- ◯ ypN1 Micrometastasis: or metastasis in 1 to 3 axillary ipsilateral lymph nodes: and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected[H]
  - ◯ ypN1mi Micrometastasis (larger than 0.2 mm and/or more than 200 cells, but none larger than 2.0 mm)
  - ◯ ypN1a Metastasis in 1–3 axillary lymph node(s), including at least one larger than 2 mm in greatest dimension
  - ◯ ypN1b Metastasis in internal mammary lymph nodes not clinically detected[H]
  - ◯ ypN1c Metastasis in 1–3 axillary lymph nodes and internal mammary lymph nodes not clinically detected[H]
- ◯ ypN2 Metastasis in 4–9 ipsilateral axillary lymph nodes, or in clinically detected[H] ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis
  - ◯ ypN2a Metastasis in 4–9 axillary lymph nodes, including at least one that is larger than 2 mm
  - ◯ ypN2b Metastasis in clinically detected internal mammary lymph node(s), in the absence of axillary lymph node metastasis
- ◯ ypN3 Metastasis as described below:[I]
  - ◯ ypN3a Metastasis in 10 or more ipsilateral axillary lymph nodes (at least one larger than 2 mm) or metastasis in infraclavicular lymph nodes/level III lymph nodes
  - ◯ ypN3b Metastasis in clinically detected[H] internal ipsilateral mammary lymph node(s) in the presence of positive axillary lymph node(s): or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected
  - ◯ ypN3c Metastasis in ipsilateral supraclavicular lymph node(s)

[E] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 6th October 2020).*

[F] *Invasion of the dermis alone does not qualify as ypT4. Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle.*

[G] *Inflammatory carcinoma of the breast is characterised by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If a cancer was classified as inflammatory (cT4d before neoadjuvant chemotherapy, the cancer is still classified as inflammatory breast cancer after therapy, even if complete resolution of the inflammatory findings is observed during treatment. The post-treatment pathological classification (ypT) should reflect the extent of identified residual disease, and the pathology report should note that the pre-treatment classification was cT4d. Dimpling of the skin, nipple retraction, or other skin changes, except those in ypT4b and ypT4d, may occur in ypT1, ypT2, or ypT3 without affecting the classification.*

[H] *Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on FNA biopsy with cytological examination.Confirmation of clinically detected metastatic disease by FNA without excision biopsy is designated with a (f) suffix, e.g., cN3a(f). Not clinically detected is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.*

[I] *Definition of N3 not included in UICC TNM 8th Edition.*

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The following tables are provided for reference, and may be used as needed.

Core elements are summarised in Table 1A. Although all core elements need to be reported for accurate staging of lymph node status, reporting in table format is not required, and the same information may be provided as indicated in the reporting guide. The same applies to the non-core elements summarised in Table 1B.

Table 1A: Regional lymph node status – core elements

Type of lymph nodes	Number of lymph nodes	Status post-neoadjuvant treatment[c]	Total lymph nodes with metastatic carcinoma (size >0.2 mm)	Size of largest metastasis (mm)[d]	Only ITCs present (Yes/No)	Total lymph nodes with ITCs[e]	pN status (UICC TNM8)[f]	Extranodal extension (ENE)
SLNs[a]								
Non-SLNs[a]								
Total lymph nodes[b]								

SLNs: sentinel lymph nodes
ITCs: isolated tumour cells
ENE: extranodal extension

Status post-neoadjuvant treatment:
Information not provided
No neoadjuvant treatment given
Residual disease not identified
Residual disease present

ENE: Not identified
Present
Cannot be determined

[a] *Core elements only if SLN biopsy was performed; if no SLN biopsy was performed report only total number of lymph nodes (LNs).*

[b] *The total number of LNs removed includes the number of SLNs (if SLN biopsy was performed) + number of non-SLNs. Non-SLNs are all the LNs that are not submitted as SLNs by the surgeon. If an axillary lymph node dissection has been performed without a SLN biopsy, only the total number of LNs needs to be given.*

[c] *If the LNs were obtained post-neoadjuvant treatment, it is strongly suggested to provide the non-core information summarised in Table 1B.*

[d] *If the size cannot be measured (e.g., LN removed in several pieces and multiple pieces involved by the metastatic process) the largest measurable size should be given as 'at least' size. If one-step nucleic acid amplification was used for nodal staging the size will be not assessable; the CK19 mRNA copy numbers can be given alternatively as a quantitative value. (Macrometastasis: one-step nucleic acid amplification assay result with >5000 CK19 mRNA copy number/µL lisate; Micrometastasis: one-step nucleic acid amplification assay result with CK19 mRNA copy number between 250 and 5000/µL lisate).*

[e] *ITCs are tumour deposits spanning ≤0.2 mm and ≤200 cells in a single LN profile. LNs with ITCs are not counted as metastatic LNs for pN stage. LNs with ITCs are counted in the number of lymph nodes with carcinoma for RCB calculation.*

[f] *If SLN biopsy was performed the minimum number of LNs required for staging purposes is one (sentinel) LN. If no SLN biopsy was performed, non-SLNs usually are obtained by axillary LN dissection (level I + level II +/- level III axillary LNs, depending on regional practices).*

Table 1B: Regional lymph node status post-neoadjuvant treatment – non-core elements

Tumour regression	Number of lymph nodes WITH residual carcinoma	Number of lymph nodes WITHOUT residual carcinoma	Total number of lymph nodes
Not identified			
Present			
Cannot be determined			
Total lymph nodes examined			

APPENDIX 2 Relevant Trials

Just as neoadjuvant therapy generally requires good multidisciplinary working, so all trials in the neoadjuvant/post-neo-adjuvant space require engagement from across the multidisciplinary team.

These trials are all multidisciplinary in nature but are listed according to where they might sit in the patient pathway.

The list is not exhaustive and does not include trials of treatment post NACT/NET

Neo adjuvant chemotherapy:

- **PARTNER**
- **ROSCO**

Neoadjuvant or pre op endocrine therapy:

- **EndoNET**
- **POETIC-A**
- **PIONEER**

Surgery:

- **ATNEC**
- **NOSTRA – feasibility study**