Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy Structured Reporting Protocol (1st Edition, 2023)

Includes the International Collaboration on Cancer Reporting (ICCR) dataset content.

Royal College of Pathologists of Australasia (RCPA) content is boxed in red

PROTOCOL SCOPE

S1.01 DEMOGRAPHIC INFORMATION

Family name

Given name(s)

S1.03 ACCESSION NUMBER

Date of birth

DD – MM – YYYY

Patient address

Date of request

DD – MM – YYYY

Sex

- ◯ Male
- ◯ Female
- ◯ Intersex/indeterminate

Ethnicity

- ◯ Unknown
- ◯ Aboriginal/Torres Strait Islander (AU)
- ◯ Māori (NZ)
- ◯ Other ethnicity:

G1.01 COPY TO DOCTORS

S1.04 PRINCIPAL CLINICIAN

Requesting doctor - name and contact details

Patient health identifiers (e.g. MRN, IHI or NHI)

Mandatory fields (standards) are in **bold** (e.g., **S1.03 ACCESSION NUMBER**).
Optional fields (guidelines) are in grey (e.g., **G1.01 COPY TO DOCTORS**).

☐ Indicates multi-select ◯ Indicates single select

Clinical information

S1.02 CLINICAL INFORMATION *(if provided on request form)*

OR

◯ Information not provided

Neoadjuvant treatment(s) *(if provided)* (select all that apply)

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

Pre-treatment tumour characteristics *(if provided)*

◯ Information not provided

Laterality

Site(s) and # of tumours

Date of diagnosis

Imaging size at diagnosis

Cancer subtype

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 *(if provided)* (select all that apply)

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

Result: ◯ Positive ◯ Negative

Method of localisation (e.g., clip, carbon, hook wire, radioactive pellets, magnetic seeds)

Number of fiducial markers (e.g., clips) placed

Location of nodes and clips

Other clinical information *(if provided)*, ***specify***

S1.05 OPERATIVE PROCEDURE - BREAST

- ◯ Not specified
- ◯ Excision (less than total mastectomy)
  - ◯ Therapeutic wide local excision
  - ◯ Re-excision
- ◯ Total mastectomy
  - ◯ Simple mastectomy
  - ◯ Nipple-sparing mastectomy
  - ◯ Skin-sparing mastectomy
- ◯ Additional specimens, *specify*

S1.06 OPERATIVE PROCEDURE - AXILLA (select all that apply)

- ☐ Sentinel lymph node biopsy
- ☐ Targeted non-sentinel lymph node biopsy (dissection)
- ☐ Other non-sentinel lymph node biopsy
- ☐ Axillary lymph node dissection
  - ☐ Level I
  - ☐ Level II
  - ☐ Level III
- ☐ Other regional lymph node(s) biopsy, *specify*
- ☐ Other, *specify*

G1.02 COLD ISCHAEMIC TIME AND TIME IN FIXATIVE

- ◯ Compliant with RCPA guidelines
- ◯ Other, *specify*

Macroscopic information

S2.01 SPECIMEN LATERALITY

- ◯ Left
- ◯ Right
- ◯ Not specified

G2.01 SPECIMEN DIMENSIONS

mm x mm x mm

G2.02 SPECIMEN WEIGHT

g

G2.03 SPECIMEN DETAILS

Depth of tissue excised

Skin to deep fascia ◯ Yes ◯ No

Specimen includes (select all that apply)

☐ Skin ☐ Nipple ☐ Skeletal muscle

S2.02 TUMOUR SITE (select all that apply)

- ◯ 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*

S2.03 NATURE AND SITE OF ALL BLOCKS

G2.04 OTHER MACROSCOPIC COMMENTS

Microscopic information

S3.01 TUMOUR FOCALITY

- ◯ 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

Morphology of multiple foci [b]

◯ Distinct ◯ Similar

Histological tumour type	
Histological tumour grade	
Receptor status	
Cellularity	
Size	mm

[a] *See also S3.03 Tumour dimensions.*

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

S3.01 TUMOUR FOCALITY CONT.

Morphology of multiple foci [b]

◯ Distinct ◯ Similar

Histological tumour type

Histological tumour grade

Receptor status

Cellularity

Size mm

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

S3.02 RESIDUAL INVASIVE CARCINOMA

◯ 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] *Standard element if residual invasive carcinoma absent.*

S3.03 TUMOUR DIMENSIONS [e]

◯ No residual invasive carcinoma

Maximum dimension of largest contiguous invasive focus

◯ ≤1 mm

◯ >1 mm (*specify exact measurement rounded to nearest mm*) mm

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

S3.03 TUMOUR DIMENSIONS CONT. [e]

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.*

S3.04 TUMOUR CELLULARITY/COMPOSITION

◯ 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) %

OR

Residual Cancer Cellularity (invasive only) [h]

% OR ◯ <1%, *specify* [g] %

◯ 1%
◯ 5%
◯ 10%
◯ 20%
◯ 30%
◯ 40%
◯ 50%
◯ 60%
◯ 70%
◯ 80%
◯ 90%
◯ Other, *specify* %

[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.*

[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 S3.07 for details about in situ disease.*

S3.04 TUMOUR CELLULARITY/COMPOSITION CONT.

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

Percent TILs in tumour stroma post-treatment

○ 0-10% ○ >10-30% ○ >30% OR ____ %

○ Cannot be assessed, *specify*

S3.05 HISTOLOGICAL TUMOUR TYPE

(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 CS3.05a for details of variants including medullary carcinoma.*

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

S3.06 POST-TREATMENT HISTOLOGICAL TUMOUR GRADE

- ○ 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

S3.07 CARCINOMA IN SITU

- ○ 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)

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*

S3.08 TUMOUR EXTENSION [l]

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 standard element; in all other cases it is a guideline.*

S3.09 MARGIN STATUS [m]

Invasive carcinoma

◯ 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)

Other margin, *specify* mm

◯ Involved, *specify margin/sites of involvement* [n]

Specify extent

DCIS [o]

◯ 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)

Other margin, *specify* mm

◯ Involved, *specify margin/sites of involvement* [n]

Specify extent

◯ Cannot be assessed, *specify*

[m] *Standard element for all wide local excision specimens, similar non-complete mastectomy and some complete mastectomy specimens (refer to CS3.09a).*

[n] *Involved margins are generally considered to be <2 mm; Repeat for all relevant margins; For each margin <2 mm, specify which margin and margin width (refer to CS3.09c).*

[n] *Involved margins are generally considered to be <2 mm; Repeat for all relevant margins.Repeat for all relevant margins.*

[o] *Required only if DCIS or florid LCIS or pleomorphic LCIS is also present.*

S3.10 LYMPHOVASCULAR INVASION

◯ Not identified

◯ Present

Specify extent

◯ Indeterminate

G3.01 COEXISTENT PATHOLOGY

◯ None identified

◯ Present, *specify*

G3.02 MICROCALCIFICATIONS (select all that apply)

◯ Not identified

☐ Present in DCIS

☐ Present in invasive carcinoma

☐ Present in non-neoplastic tissue

☐ Other, *specify*

S3.11 NUMBER OF LYMPH NODES EXAMINED

Total number of sentinel lymph nodes examined [p]

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

Total number of lymph nodes examined

[p] *Standard element only if sentinel lymph nodes are submitted by the surgeon.*

[q] *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*

S3.12 NUMBER OF LYMPH NODES WITH METASTATIC CARCINOMA [r]

[r] *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).*

G3.03 NUMBER OF LYMPH NODES WITH MACROMETASTASES [s]

Sentinel lymph nodes

Non-sentinel lymph nodes

Total lymph nodes

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

G3.04 NUMBER OF LYMPH NODES WITH MICROMETASTASES [t]

Sentinel lymph nodes

Non-sentinel lymph nodes

Total lymph nodes

[t] *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.*

S3.13 NUMBER OF LYMPH NODES WITH ISOLATED TUMOUR CELLS (ITCs) [u]

Sentinel lymph nodes

Non-sentinel lymph nodes

Total lymph nodes

[u] *≤0.2 mm and ≤200 cells.*

S3.14 SIZE OF LARGEST METASTASIS [v]

- ◯ Not assessable [w]

Size of largest contiguous metastatic tumour cell deposit (without intervening fibrosis) [x] mm (TNM size)

Extent of largest lymph node metastasis (with intervening fibrosis) [y] mm (RCB size)

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

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

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

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

S3.15 EXTRANODAL EXTENSION (ENE) [z]

- ◯ Not identified
- ◯ Present

Total number of lymph nodes with ENE

Largest extent of ENE mm

- ◯ Cannot be determined

[z] *This is a standard element only if macro- or micrometastases are present.*

G3.05 TREATMENT EFFECT

(These responses may be reported in the corresponding cells in Table 1A)

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

S3.16 PATHOLOGIC COMPLETE RESPONSE (pCR)

- ◯ 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

S3.17 RESIDUAL CANCER BURDEN (RCB)

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

RCB area dimensions ____ mm x ____ mm

AND

Average cancer cellularity in RCB area [aa] ____ %

____ % in situ component [ab]

OR

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

Number of lymph nodes with carcinoma [ab] ____

Extent of largest lymph node metastasis ____ mm

RCB score [ac] ____

RCB class [ac] ◯ 0 ◯ I ◯ II ◯ III

[aa] *Enter this value, and 0% for % CIS, in the RCB calculator (see CS3.17a).*

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

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

G3.06 OTHER MICROSCOPIC COMMENTS

(e.g., Presence of lymphovascular invasion in axillary fat)

Ancillary studies

G4.01 POST-TREATMENT ESTROGEN RECEPTOR (ER)

Antibody clone, *specify* ____

Testing performed ◯ Yes ◯ No

- ◯ Positive
- ◯ Low positive

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

____ % OR Range

- ◯ 1-10% [ae]
- ◯ 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* ____

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

[ae] *Classified as low ER positive.*

G4.02 POST-TREATMENT PROGESTERONE RECEPTOR (PR)

Antibody clone, *specify* ____

Testing performed ◯ Yes ◯ No

◯ Positive

Percentage of cells with nuclear positivity [ad]

____ % 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* ____

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

G4.03 POST-TREATMENT HER2

Antibody clone, *specify*

Testing performed ◯ Yes ◯ No

Testing performed on ◯ Current specimen ◯ Core biopsy, *reference*

By immunohistochemistry (IHC)

- ◯ Not performed
- ◯ Score 0 (ISH not indicated)
- ◯ Score 1+ (ISH not indicated)
- ◯ Score 2+ (ISH required)
- ◯ Score 3+ (ISH required)
- ◯ Cannot be determined, *specify*

By in situ hybridisation (ISH)

- ◯ Not performed
- ◯ Not amplified
- ◯ Amplified
- ◯ Pending
- ◯ Cannot be determined, *specify*

☐ Heterogeneity present

Percentage area of tumour occupied by the amplified cell aggregate %

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

Integrated HER2 status

- ◯ IHC score 0
- ◯ IHC score 1+: HER2 low
- ◯ IHC score 2+, ISH not amplified: HER2 low
- ◯ IHC score 2+, ISH amplified: HER2 amplified
- ◯ IHC score 3+, ISH amplified: HER2 amplified

OTHER HER2 COMMENTS

G4.04 POST-TREATMENT ANCILLARY STUDIES

- ◯ 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*

Pathological staging information

S5.01 PATHOLOGICAL STAGING (AJCC TNM 8th edition)

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)

Regional lymph nodes (pN)

S5.02 Year and edition of staging system

Diagnostic overview

S6.01 DIAGNOSTIC SUMMARY

Include: Tumour site, Tumour dimensions, Histological tumour type, Histological tumour grade, Lymph node status, Margin status, Pathological staging.

G6.01 OVERARCHING COMMENT

Contents

i. Element Checklist

ICCR The RCPA protocol includes all core ICCR dataset content.

Unique RCPA protocol content (non-ICCR content) is boxed in red.

Mandatory fields (standards) are in **bold**. Optional fields (guidelines) are in grey.

Demographic information

Clinical information

- **Clinical information***
- **Operative procedure – breast**
- **Operative procedure - axilla**
- Cold ischaemic time and time in fixative

Macroscopic information

- **Specimen laterality**
- Specimen dimensions
- Specimen weight
- Specimen details
- **Tumour site**
- **Nature and site of all blocks**
- Other macroscopic comments

Microscopic information

- **Tumour focality**
- **Residual invasive carcinoma**
- **Tumour dimensions**
- **Tumour cellularity/composition**
- **Histological tumour type**
- **Post-treatment histological tumour grade**
- **Carcinoma in situ & Classification of carcinoma in situ**
- **Tumour extension***
- **Margin status***
- **Lymphovascular invasion**
- Coexistent pathology
- Microcalcifications
- **Number of lymph nodes examined**
- **Number of lymph nodes with metastatic carcinoma**
- Number of lymph nodes with macrometastases
- Number of lymph nodes with micrometastases
- **Number of lymph nodes with isolated tumour cells (ITCs)**
- **Size of largest metastasis***
- **Extranodal extension***
- Treatment effect
- **Pathologic complete response (pCR)**
- **Residual cancer burden (RCB)**
- Other microscopic comments

Ancillary studies

- Post-treatment estrogen receptor (ER)
- Post-treatment progesterone receptor (PR)
- Post-treatment HER2
- Post-treatment ancillary studies

Pathological staging information

- **Pathological staging (AJCC TNM 8th edition)**
- **Year and edition of staging system**

Diagnostic overview

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- **Diagnostic summary**
- Overarching comment

*** Conditional**

ISBN: 978-1-76023-634-2, Publication number (SHPN): (CI) 230780

ii. Key Documentation

RCPA Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy Structured Reporting Protocol - Expert committee:

A/Prof Nirmala Pathmanathan, Pathologist (Lead author), Pathologist; Dr Brooke Beardsley, Pathologist; A/Prof Benjamin Dessauvagie, Pathologist; Prof Sunil Lakhani, Pathologist; Dr Ewan Millar, Pathologist; Prof Puay Hoon Tan, Pathologist; Dr Melissa Bochner, Surgeon; Prof Sherene Loi, Medical Oncologist; Dr Allison Rose, Radiologist; A/Prof Kirsty Stuart, Radiation Oncologist; Christina Selinger, Secretariat; Prof Gelareh Farshid (Breast Protocol Series Chair), Pathologist.

Stakeholders consulted:

- Cancer and Pathology stakeholders list consulted for each RCPA Structured Pathology Reporting of Cancer (SPRC) Protocol
- RCPA Breast lesion expert committees
- Breast Cancer Foundation NZ
- Breast Cancer Network Australia
- Breast Cancer Trials
- Breast Surgeons of Australia & New Zealand (BreastSurgANZ)
- National Breast Cancer Foundation

The RCPA protocol was externally peer reviewed during a 4 week open consultation period (see feedback).

Key Reference Documents:

- International Collaboration on Cancer Reporting (ICCR) Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy dataset
- American Joint Committee on Cancer (AJCC) Cancer Staging Manual 8th edition (including errata corrected with 8th reprint, 13th May 2021)
- World Health Organization (WHO) Classification of Breast Tumours, 2019, 5th edition (including corrigenda corrected with 3rd reprint, Sept 2020)

How to use this document:

The Royal College of Pathologists of Australasia (RCPA) Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy expert panel have reviewed and endorsed the ICCR Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy dataset and provided additional evidence-based recommendations to meet reporting needs in Australasia.

- **Standards (with S prefix)** and their respective naming conventions, definitions and value lists **must be adhered to**.
- **Guidelines (with G prefix)** are not mandatory but **are recommendations** and where used, must follow the naming conventions, definitions and value lists given in the protocol.
- The order of information and design of the checklist may be varied according to the laboratory information system (LIS) capabilities and as described in Functional Requirements for Structured Pathology Reporting of Cancer Protocols.[1]
- See Appendix 4 – Definitions for further information.

Scope:

This protocol contains standards and guidelines for the preparation of structured reports for:

- Resection specimens after neoadjuvant therapy from patients with invasive carcinoma of the breast, with or without ductal carcinoma in situ (DCIS).
- Post-treatment surgical specimens for therapeutic intent, where the neoadjuvant treatment is of a longer duration than a brief pre-operative exposure, are included.
- Ipsilateral multifocal disease should be dealt with in a single report. For bilateral breast malignancies, a separate protocol should be completed for each side. This may be under the same accession number/pathology report.

Exclusions:

- A separate RCPA protocol is available for reporting resection specimens from patients with invasive breast cancer without neoadjuvant therapy.
- A separate protocol for reporting DCIS without carcinoma, microinvasive carcinoma (≤1 millimetres (mm), encapsulated papillary carcinoma and solid papillary carcinoma) is available.

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- Surgically removed lymph nodes are covered by a separate RCPA protocol and can be used in conjunction with this protocol, as appropriate.
- A separate RCPA protocol is under development for phyllodes tumours.

Background:

For background information about this protocol, refer to chapter iv. Background.

Changes compared to the ICCR dataset:

All 2023 ICCR dataset content is incorporated.

Additional RCPA standards and guidelines to the ICCR dataset were developed by the RCPA Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy expert panel for this edition. Unique RCPA elements are shaded red.

The following items were modified from the ICCR dataset:

- Clinical information, when provided, is a standard to report. However, the clinical information sub-elements are optional, depending on the information received.
- Operative procedure Axilla - Axillary lymph node dissection sub-values are optional and modified.
- High nuclear grade encapsulated papillary carcinoma and solid papillary carcinoma of high nuclear grade is considered as in situ disease at the discretion of the reporting pathologist, regardless of hormone receptor and HER2 status. These entities can be reported using the RCPA DCIS protocol rather than the RCPA Invasive breast carcinoma protocol.
- Margin status layout has been simplified.
- Post-treatment estrogen receptor, progesterone receptor and HER2 testing was moved to Ancillary studies.
- Pathological staging recommendation is for AJCC TNM staging.

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iii. Evidentiary Support

ICCR Includes ICCR dataset content.

RCPA protocol content (non-ICCR content) is boxed in red. Mandatory fields (standards) are in **bold**. Optional fields (guidelines) are in grey.

DEMOGRAPHIC AND CLINICAL INFORMATION

S1.01 - S1.04, G1.01 For **additional** RCPA commentary and recommendations see Appendix 6 – Pre-analytical

S1.01 **Demographic information provided on the request form and with the specimen must be recorded.**

S1.02 **Clinical information - as documented on the request form must be recorded verbatim.**

CS1.02a ICCR

It is imperative to alert the pathologist that the specimen has been resected following neoadjuvant therapy. Residual invasive carcinoma post neoadjuvant therapy is often difficult to identify grossly. Without the information that the specimen is post neoadjuvant therapy and information regarding the location and size of tumour foci prior to treatment, appropriate sampling of the correct area of the breast is not possible. Information about the type of treatment received and prior diagnosis helps the pathologist to know what to expect in terms of response to treatment and helps to guide the extent of initial sampling.

Fiducial markers are radiological clips or other markers placed at the site of the primary breast tumour(s) pre-treatment to indicate the location of the tumour bed in case of excellent clinical/ radiological response to therapy. The placement of fiducial markers should be documented and communicated to the pathologist as they help the pathologist identify the pre-treatment tumour site. Fiducial marker placement in biopsied lymph nodes with removal of the marked lymph nodes improves the accuracy of sentinel lymph node biopsy after neoadjuvant therapy. If an intra-operative specimen x-ray has been carried out in the operating theatre the findings should be communicated to the pathologist.

Pre-treatment clinical-radiologic nodal status in the axilla is important information to guide handling and interpretation of axillary surgical specimens. The clinical-radiologic findings may include needle biopsy results from a suspicious node. If a pre-treatment axillary sentinel lymph node excision was performed and there was nodal metastasis, then response in the lymph nodes cannot be evaluated with accuracy and the residual cancer burden (RCB) and ypTNM staging become invalid. Positive lymph nodes removed before neoadjuvant therapy are given a clinical N stage.

Pre-treatment assessment of cancer cellularity by area (percent tumour cellularity) is compared with post-treatment tumour cellularity in some methods of response grading. Centres that use those response assessments may prefer to collect this optional information.

There is accumulating evidence in the literature that the presence of tumour infiltrating lymphocytes (TIL) provides important prognostic and predictive information for some molecular subtypes of breast cancer.[2] Pre-treatment assessment of TILs, estimated as a percentage of stromal area, is optional.

CS1.02b

Established pathogenic variants for breast cancer predisposition genes (e.g., *BRCA1*, *BRCA2*, etc.) should be documented.

CS1.02c

Any clinical information received in other communications from the requestor or other clinician should be recorded together with the source of that information.

For optimal patient treatment, it is important that pathologists to receive key clinical information with the specimen. An Exemplar Request Information Sheet is provided in Appendix 1.

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S1.03 **Pathology accession number - The pathology accession number of the specimen must be recorded.**

S1.04 **Principal clinician - The principal clinician involved in the patient's care and responsible for investigating the patient must be recorded.**

G1.01 Copy to doctors - requested on the request form should be recorded.

S1.05 **The nature of the breast operation must be recorded.**

CS1.05a ICCR

The nature of the operation or procedure(s) performed is important to ensure appropriate pathological examination protocols are followed, and accurate clinical correlation and post-operative management discussion take place. The nature, extent, focality of the abnormality and patient choice can influence the type of operation. Multiple procedures may be performed and sent as separate specimens which require cross correlation. The forms of surgical procedure used to manage breast disease are considerable and more specific detail of the specimen can be provided.

S1.06 **The nature of the axilla operation must be recorded.**

CS1.06a ICCR

The metastatic involvement of the axillary lymph nodes has specific clinical, treatment and prognostic implications. Nodal status post neoadjuvant treatment shows a strong association with overall and disease-free survival,[3] and is independent of response in the breast.

Accurate staging requires that all submitted lymph nodes be accurately designated by the surgeon.

Currently, in some countries (e.g., United States, Canada, Singapore, many European countries) an axillary lymph node dissection does not routinely include level III lymph nodes.

G1.02 Cold ischaemic time (≤1 hour) and time in fixative (6-72 hours) should be documented to be within the prescribed range.

CG1.02a

The American Society for Clinical Oncology (ASCO)-College of American Pathologists (CAP) emphasise cold ischaemic time of ≤1 hour as a crucial aspect of quality assurance.[4,5] This is particularly relevant for antigen preservation.

Time stamps for tissue removal and for placement in formalin are to be specified by the surgeon, as required by RCPA[6] and ASCO-CAP.[7]

Similarly, the laboratory should verify on each report that fixation time meets RCPA[6] and ASCO-CAP requirements.[7]

The RCPA Fixation of Tissues Guideline can also be consulted.[6]

MACROSCOPIC INFORMATION

See Appendix 7 – Specimen Handling and Macroscopic Guidelines

Detailed fixation and specimen handling instructions are available from the RCPA online Macroscopic Cut-up Manual.

S2.01 **The specimen laterality must be recorded.**

CS2.01a ICCR

Specification of the side and site in the breast is important for clinical correlation and accuracy of the patient medical record.

For bilateral invasive breast tumours, a separate dataset should be completed for each side.

G2.01 The specimen dimensions should be recorded.

G2.02 The specimen weight should be recorded.

G2.03 Other specimen details should be recorded.

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S2.02 **Tumour site must be recorded.**

CS2.02a ICCR

A clock face delineation and measure of distance from the nipple are a more accurate indicator of site than quadrant alone. Specification of the site in the breast is important for clinical correlation, post-operative management discussion and accuracy of the patient medical record, especially when there are multiple lesions for correlation with radiology/prior biopsies.

S2.03 **The nature and site of all blocks must be recorded.**

CS2.03a

The use of specimen photographs or diagrams to illustrate the block key is strongly encouraged.

G2.04 Other macroscopic comments should be recorded.

CG2.04a

A descriptive or narrative field should be provided to record any macroscopic information that is not recorded in the above standards and guidelines, and that would normally form part of the macroscopic description.

MICROSCOPIC INFORMATION

S3.01 **Tumour focality must be recorded.**

CS3.01a ICCR

Presence of a single tumour focus is the most common clinical situation, but breast cancer can present with multiple tumour foci because of several scenarios (see ICCR Invasive carcinoma of the breast dataset[8]).

Identification of the presence of multiple tumour foci requires further clarification through measurement of the main foci, the overall extent of disease (DCIS and invasive foci) and their type, grade and receptor status to determine which of the forms of multifocality is present. Ipsilateral multifocal disease, even if of different types, should be dealt with in a single report.

If multiple tumour sites were present on pre-treatment imaging and/or multiple separate (macroscopically separate) tumour bed sites are present and the invasive carcinoma at these separate sites is distinct by tumour type, grade and/or receptor status then size and cellularity should be recorded for each of the tumours separately to evaluate response (TNM[9,10] stage and RCB).

It can be difficult, if not impossible, on rare occasions to determine whether two adjacent foci represent satellite foci or one lesion. After neoadjuvant therapy, it is common for tumours that on pre-treatment imaging appeared to represent a single tumour to present as scattered foci of residual invasive carcinoma that are separated by areas of fibrosis in the post neoadjuvant therapy resection specimen, due to a heterogenous response to treatment. Union for International Cancer Control (UICC)[9]/(AJCC[10] staging and RCB address this scenario in different ways:

- UICC/AJCC staging considers this scenario as multiple foci irrespective of a pre-treatment finding of multiple foci or a single focus. The pathologist determines and measures the largest focus.
- RCB considers this scenario to be a single focus of scattered residual cancer. RCB considers multifocality only when the foci were clearly separate on pre-treatment imaging or clearly separate on gross examination (see **S3.03 TUMOUR DIMENSIONS**).

S3.02 **Any residual invasive carcinoma must be recorded.**

CS3.02a ICCR

The priority for evaluation of surgical specimens is different after neoadjuvant therapy, with emphasis on accurate identification of the pre-treatment tumour site to enable evaluation of

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tumour response to treatment. Pathologic complete response (pCR), defined as absence of residual invasive disease post neoadjuvant therapy in both the breast and axilla, is associated with improved survival outcomes and forms the primary endpoint for neoadjuvant clinical trials, and identification of residual disease is important to guide future local and systemic adjuvant therapy decisions.[2] Confident localisation of the pre-treatment tumour site and adequate, precise sampling are vital for accurate assessment of pCR.

Residual tumour is often less well defined following treatment, and close clinical-pathological correlation with careful mapping of the pre-treatment tumour site is essential for accurate microscopic assessment of response. It is strongly recommended that a visual record of the sliced specimen is made, and then used as a map of the sections taken to facilitate subsequent histological interpretation and clinical-radiologic-pathologic correlation; this may be in the form of radiographs, photographs, photocopies or drawings. It is helpful to indicate in the pathology report as a non-core element or in the gross description that such a map is available. The map can be stored in the electronic medical record as a specimen image. It may also be helpful to indicate in the report which blocks correspond to the largest cross section of the residual invasive carcinoma. Use of large format 'Mega' blocks may be helpful in this regard.

In cases where there has been an excellent response to therapy there may be no grossly detectable residual tumour present. If there is no visible lesion, then careful palpation of the specimen slices looking for areas of firmness may also assist in identifying the pre-treatment tumour site.

Different types of fiducial markers should be inserted to indicate the site of the tumour prior to treatment; these include metallic clips of different shapes, gel foam clips, carbon pigment, and magnetic or radioactive seeds. Sometimes for large tumours, markers may be placed during the course of therapy when there is evidence of tumour response. If fiducial markers or surgical localisation markers have been inserted, they should be looked for in the surgical specimen. Clips or seeds may be seen macroscopically, but this is not always possible. As fiducial markers are designed to be identifiable on x-ray, specimen x-ray can be helpful to localise the fiducial markers and pre-treatment tumour site. If an intra-operative specimen x-ray has been carried out in the operating theatre the findings should be communicated to the pathologist. The presence of residual microcalcifications that were associated with the tumour pre-treatment may also be a radiographic guide to locating the pre-treatment tumour site. Guidewires or surgical markers (radioactive or magnetic seed or equivalent) may also be placed at the time of surgery to guide excision of the correct area, particularly if breast conservation surgery is attempted. The surgical marker may be placed at the site of the pre-treatment tumour site or residual tumour as identified radiologically, and/or at the site of a fiducial marker placed earlier. The presence of guidewires or surgical markers should be described as part of the gross assessment of the specimen and helps identify the area on which to focus sampling.

Histological changes suggesting tumour was present may be seen at the pre-treatment tumour site after treatment and may include fibrosis, a characteristic pattern of vessels reminiscent of tumour vasculature, myxoid change, and infiltration by macrophages and/or lymphocytes ('microscopic tumour bed'). Sometimes macrophages are abundant and accompanied by extensive necrosis. The site of fiducial marker(s) is usually visible microscopically as they induce a foreign body type reaction which can be seen on histology. The presence of DCIS or calcification microscopically may also act as indicators of the pre-treatment tumour site.

When a small lumpectomy is performed with image guided targeting of the area of concern pre-treatment (the pre-treatment tumour site) then it is reasonable to presume the pre-treatment tumour site has been sampled by sampling the lumpectomy even when only non-specific histologic changes are seen.

All of the above approaches can help identify the location of the tumour pre-treatment (the pre-treatment tumour site); often several or all of them are used at the same time.

If the microscopic tumour bed or marked site are not identified on microscopy, then the specimen should be re-examined and further blocks may need to be taken. On occasion, there may be complete resolution of the tumour and histologic changes at the site may be nonspecific or subtle. In this setting it is worthwhile to make a comment in the report that the likely tumour site has been thoroughly sampled, or if there is uncertainty to indicate the

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uncertainty in the report so appropriate action can be taken. For example, if inadequate clinical information regarding the pre-treatment tumour site has been provided, this should be resolved or conveyed in the report.

S3.03 The maximum dimension of the largest contiguous invasive tumour focus must be recorded.

CS3.03a ICCR

The size of the tumour or of the largest/dominant invasive tumour focus is a key variable required for breast cancer staging and requires accurate assessment to the nearest mm. Histological tumour size is deemed the gold standard but should be correlated with the gross macroscopic size measurement and where possible with the imaging size. Detailed descriptions of how to measure invasive tumour size in specific scenarios, such as when there is extensive DCIS, is provided in the ICCR Invasive carcinoma of the breast dataset.[8]

Determination of tumour dimensions after neoadjuvant therapy can be complicated due to tumour response to treatment and requires documenting the largest cross section of residual tumour with histologic sections. The dimensions of the residual invasive carcinoma are determined initially on gross examination and modified as needed after histologic evaluation. This requires correlating the histologic, macroscopic and imaging findings. Precise mapping with images of the sliced specimen, which can then be used as a map for the sections taken, facilitates subsequent histologic interpretation; this may be in the form of radiographs, photographs, photocopies or drawings. It can be useful to indicate in the report which blocks correspond to the largest cross section of residual tumour.

The final (histologic) tumour dimensions may be smaller or larger than initially suspected on gross evaluation, smaller or larger than the dimensions of the fibrotic (macroscopic or microscopic) tumour bed, smaller or larger than the dimensions on pre-treatment imaging and smaller or larger than the dimensions on Post-treatment imaging.

The approach to defining tumour dimensions in the 8th editions of TNM[9,10] and the RCB (identical to the definitions used in prior TNM editions) can sometimes yield two distinct sets of tumour dimensions (TNM size and RCB area dimensions). Both TNM size and RCB area dimensions are core elements as TNM size is used for TNM[9,10] staging and RCB area dimensions are used to determine RCB.

The size of the largest contiguous invasive tumour focus excluding intervening or adjacent fibrosis is required for breast cancer TNM[9,10] staging and requires accurate assessment to the nearest mm. This measurement can be thought of as a single dimension intended to represent the volume of residual invasive cancer. In instances where it is difficult to determine what to consider the largest contiguous invasive focus, a description explaining how the measurement was determined provides useful documentation (see below). It is helpful to take into account the common growth patterns of breast carcinoma within breast tissue when determining what to consider the largest contiguous focus. For example, invasive lobular carcinoma tends to grow along fibrous tissue and commonly presents with satellite lesions. The satellite lesions would not be included in the TNM size. The growth along fibrous tissue would likely be considered in the TNM size by most observers even with some fibrous tissue between the cells. When residual invasive carcinoma cells are relatively evenly distributed over a fibrotic area then they are probably best considered a single focus. If the distribution of residual invasive carcinoma cells is more uneven it may be better representation to consider separate contiguous foci and to determine which is the largest. If residual invasive carcinoma cells are present in a pattern within normal breast tissue similar to one that is commonly seen in a single focus of invasive breast carcinoma without prior therapy, then they are probably best considered a single focus (ICCR Figure 1). The concept of multifocality within a single tumour bed in the ypT AJCC/UICC stage is different than the concept of multifocality in breast specimens without neoadjuvant treatment as discussed in S3.01a Tumour focality in the Invasive carcinoma of the breast protocol. The considerations discussed in the ICCR Invasive carcinoma of the breast dataset[8] can help inform the interpretation of the post neoadjuvant findings.

For quantification of residual invasive carcinoma using RCB the largest cross sectional area of residual invasive carcinoma including intervening fibrosis is measured in two dimensions. Adjacent fibrosis and adjacent areas with DCIS only are not included in the measurements. In other words, the measurements are from invasive carcinoma cell to invasive carcinoma cell covering the entire extent of the invasive carcinoma within a single (fibrotic) tumour bed site. The measurements may extend beyond the area of fibrosis or be smaller than the area of

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fibrosis. This is the area in which the tumour cellularity is estimated (see **S3.04 TUMOUR CELLULARITY/COMPOSITION**).

In many instances, TNM size and the larger of the two RCB dimensions can be interpreted as the same. When they are different, both should be reported. A description explaining how the measurements were determined provides helpful documentation. For example: "Invasive carcinoma is present as multiple foci with varying cellularity in a single (fibrotic) tumour bed. The largest contiguous focus of invasive carcinoma is … mm (size used for TNM[9,10] staging). The largest cross section of the entire volume containing residual invasive carcinoma within the single residual primary tumour bed measures …mm X …mm (area used to determine RCB)." Adjacent necrosis and mucin without viable invasive carcinoma cells are not included in tumour size measurements for TNM[9,10] staging and RCB.

CS3.03b

It is important for the pathologist to provide the microscopic size. However, where microscopic size measurement is not possible or deemed inaccurate the gross macroscopic, magnetic resonance imaging (MRI), ultrasound, mammographic and clinical tumour size, listed here in priority sequential order, should be used. Consultation with the multidisciplinary team to obtain the imaging and clinical sizes is recommended in such cases.

S3.04 Tumour cellularity must be recorded.

CS3.04a ICCR

Tumour cellularity reduction compared to the pre-treatment biopsy correlates with survival.[11] Tumour cellularity and size after neoadjuvant therapy provide independent prognostic information.[12,13] The reduction in cellularity is often heterogeneous with varying cellularity across the residual invasive carcinoma and with areas of fibrosis without tumour cells separating islands of residual invasive disease. The RCB system addresses this heterogeneity by standardising sampling and estimating the average cellularity across the entire area of residual invasive carcinoma. Combining size and cellularity also dampens the effect of variations due to variable interpretation and sampling (see ICCR Figure 1). Sampling or interpretation may lead to a large tumour with low cellularity or a small tumour with high cellularity.

The objective of RCB measurement of the residual invasive cancer in the breast is to calculate the invasive cancer cellularity relative to the area containing residual invasive disease. It is typically easier to estimate the cellularity from two steps: 1) the percent of cancer in the area containing residual invasive cancer, then 2) the percent of the cancer component that is in situ (not invasive). The calculator for RCB then calculates the invasive component by area. Alternatively, some pathologists prefer to directly estimate the percent of invasive cancer in the area, and when using the RCB calculator they should enter zero for in situ component (even if there is some). It is recommended that the components of RCB also be reported together in a section of the report, as described in **S3.17 RESIDUAL CANCER BURDEN.**

Residual cancer burden (RCB) is the most validated prognostic factor for describing response to neoadjuvant chemotherapy in any subtype of breast cancer. The RCB standard operating procedure can be downloaded from the RCB calculator website at: http://www.mdanderson.org/ breastcancer_RCB.[14]

There is emerging evidence that post-treatment lymphocytic infiltrate across the residual tumour bed has prognostic significance.[15,16] Post-treatment assessment of the extent of TILs, either in association with residual invasive carcinoma or across the tumour bed when there has been a complete response, can be performed but is optional. The International TILs Working Group maintains a website with instructions and educational materials for assessing TILs in residual breast cancer at: http://www.tilsinbreastcancer.org/.

S3.05 Histological tumour type must be recorded.

CS3.05a ICCR

To ensure consensus and consistency of reporting, it is recommended to use the most recent edition of the World Health Organization (WHO) Classification of Breast Tumours, 5th edition, 2019, nomenclature and definitions for diagnosis and classification of invasive tumour type (Table 1).[17] The ICCR dataset includes 5th edition Corrigenda, September 2020.[18]

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Determination of histologic type is based on routine histologic examination; special stains such as e-cadherin are not required for determining histologic type. Pure special type carcinomas should consist of at least 90% pure pattern. Refer to the ICCR Invasive carcinoma of the breast dataset for more detail.[8]

After neoadjuvant therapy, it may be more difficult to accurately classify the tumour type due to cytopathic changes from treatment. For example, the morphology of an invasive breast carcinoma of no special type (NST) may appear more like that of a lobular carcinoma or a lobular carcinoma may appear more high grade suggesting the possibility of a ductal phenotype.[19] In this instance pre-treatment tumour type should be regarded as more accurate.

The mucin pools of mucinous carcinoma tend to remain even after the invasive carcinoma cells have disappeared following neoadjuvant therapy. Size measurement after neoadjuvant therapy when this picture is present should be from tumour cell to tumour cell not including surrounding mucin. Thorough sampling of mucinous carcinoma with low cellularity after neoadjuvant therapy is needed. Mucin in the absence of viable tumour cells does not preclude classification as pCR.

CS3.05b

As per WHO, for 'mixed IBC-NST and special subtype' cancers, it is recommended to report both cancer types present.

CS3.05c

Encapsulated papillary carcinoma of high nuclear grade is considered as invasive by the WHO [20] and ICCR.[8] We note the evidence base for this position is scant and not definitive in our opinion. As such, given the potentially significant implications for patient management, the RCPA Invasive carcinoma of the breast in the setting of neoadjuvant therapy expert panel's position is that encapsulated papillary carcinoma of high nuclear grade and solid papillary carcinoma of high nuclear grade should still be considered as in situ disease at the discretion of the reporting pathologist, regardless of hormone receptor and HER2 status. For these cases, a comment can be included, referring to the paucity of the evidence base and the need for multidisciplinary discussion.

CS3.05d

Optional reporting of the percentage of the special subtype is at the pathologists' discretion, as it may provide useful data for future research regarding prognostic significance.

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Table 1: Detailed Invasive Tumour Classification based on 2019 World Health Organization classification of breast tumours subsections.[20]

Descriptor	ICD-O codes[a]
Invasive Type for Pure or Mixed (include all types present if >10%)	
Main categories:	
No Special Type	
Invasive breast carcinoma of no special type (see 'a' below)	8500/3
Special Types:	
Invasive lobular carcinoma (see 'b' below)	8520/3
Tubular carcinoma	8211/3
Invasive Cribriform carcinoma	8201/3
Mucinous carcinoma	8480/3
Invasive micropapillary carcinoma	8507/3
Carcinoma with apocrine differentiation	8401/3
Metaplastic carcinoma (see 'c' below)	8575/3
WHO 2019 classification additional sub categories (use 'Other, specify') box):	
a. NST special patterns	
None	8500/3
Present	
medullary	
neuroendocrine differentiation	
pleomorphic	
choriocarcinomatous	
melanocytic features	
oncocytic	8290/3
lipid-rich	8314/3
glycogen-rich	8315/3
clear cell	
sebaceous carcinomas	8410/3
b. Lobular Sub-Type	8520/3
Classical	
Pleomorphic	
Solid	
Alveolar	
Tubulolobular	
Mixed sub-types	
c. Metaplastic carcinoma	8575/3
Low grade adenosquamous carcinoma	
Fibromatosis-like metaplastic carcinoma	
Squamous cell carcinoma	
Spindle cell carcinoma/myoepithelial carcinoma	
Metaplastic carcinoma with mesenchymal differentiation (chondroid, osseous, other types of mesenchymal differentiation)	
Mixed metaplastic carcinoma	
d. Salivary gland-type and other rare tumours	
Mucinous cystadenocarcinoma	8470/3
Acinic cell carcinoma	8550/3
Adenoid cystic carcinoma	8200/3

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Secretory carcinoma	8502/3
Mucoepidermoid carcinoma	8430/3
Polymorphous adenocarcinoma	8525/3
Tall cell carcinoma with reversed polarity	8509/3
e. Invasive papillary carcinomas	
Solid papillary carcinoma - invasive	8509/3
Invasive papillary carcinoma	8503/3
f. Neuroendocrine neoplasms	
Neuroendocrine tumour	8240/3
Neuroendocrine carcinoma	8246/3
g. Epithelial-myoepithelial tumours	
Malignant adenomyoepithelioma	8562/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, Third Edition, second revision (ICD-O-3.2).[21] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Subtype labels are indented. Incorporates all relevant changes from the 5th edition Corrigenda, September 2020.[18]

S3.06 The post-treatment histological tumour grade must be recorded.

CS3.06a ICCR

There is limited evidence that histological grading provides prognostic information after neoadjuvant therapy.[22-24] Post-therapy cytologic changes may be present and alter the grade.

All invasive breast carcinomas should be graded. Although histologic features impacting grading (tubules, nuclear atypia and mitotic rate) may be altered by treatment, grading after neoadjuvant treatment documents the histologic features after neoadjuvant therapy without taking pre-treatment features of the tumour into account. The amount of residual invasive carcinoma remaining may be too small to provide a grade. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) is the recommended method.[25] There are no modifications to the method after neoadjuvant therapy. See CS3.04a Histological tumour grade in the Invasive carcinoma of the breast protocol.

S3.07 Carcinoma in situ and classification of carcinoma in situ must be recorded.

CS3.07a ICCR

The presence of coexisting DCIS (and/or florid or pleomorphic LCIS) is commonplace with invasive carcinomas of the breast and forms part of the overall disease process which requires complete surgical excision to reduce the risk of local recurrence. In the context of extensive surrounding DCIS (and/or florid or pleomorphic LCIS), the total extent of the entire disease process including all invasive tumour foci and associated DCIS should be provided as the whole tumour size. (Note: The whole tumour size is different from the residual invasive carcinoma size used for RCB).

Classification of DCIS with respect to nuclear grade and architecture is dealt with in the companion DCIS, variants of LCIS and low grade lesions dataset.[3] Post-treatment cytologic changes may be present and alter the grade and appearance of the DCIS.

It has been controversial whether residual DCIS after neoadjuvant therapy affects prognosis when residual invasive cancer is not identified.[26] In that circumstance the pathologist should be mindful to consider whether the sampling of tumour bed has been sufficient to exclude invasive disease (particularly important if calcifications were targeted) and to exclude the possibility that the microscopic findings do not represent lymphovascular invasion (LVI). The definition of pCR used may or may not include the absence of DCIS. It is helpful to document the definition of pCR used (ypT0/ypTis ypN0 or ypT0 ypN0). ypTis ypN0 has an excellent prognosis.

S3.08 Tumour extension must be recorded.

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CS3.08a ICCR

Tumour extension to involve overlying skin or underlying skeletal muscle is a variable which influences TNM staging and should be recorded when present. It is recognised that in the context of primary operable breast cancer these phenomena are rare. The majority of cancer resection cases will be confined to the breast with no skin, nipple or underlying skeletal muscle involvement and in this context disease extent classification is deemed non-core.

Satellite skin nodules must be separate from the primary tumour and macroscopically identified to assign a category as T4b. Skin nodules identified only on microscopic examination and in the absence of epidermal ulceration or skin oedema (clinical peau d'orange) do not qualify as T4b. Such tumours should be categorised based on tumour size. 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.

The finding of invasive carcinoma that directly invades into the dermis or epidermis without skin ulceration does not change the pT stage.

The finding of tumour extension into the nipple does not change the pT classification of invasive carcinomas.

Invasion into pectoralis muscle is not considered chest wall invasion, and cancers are not classified as pT4a unless there is invasion deeper than this muscle.

S3.09 Margin status must be recorded.

CS3.09a ICCR

There is an assumption that all breast tissue will be resected in patients undergoing a complete mastectomy and that pathological examination of margins is of limited value. However, there is evidence that margin involvement can increase the risk of local recurrence after mastectomy and modification of the comprehensive margin analysis and reporting recommendations for wide local excision and other similar specimens is adopted for reporting of mastectomy specimens to include a statement of the distance to the closest margin or site of margin involvement.

Assessment of adequacy of excision requires close correlation between the surgical excision procedure and pathological examination. In particular it is essential that the pathologist is made aware of the depth of tissue excised and whether the surgeon has excised all the tissue from the subcutis to the pectoral fascia. Similarly, it has been recognised that involvement of a margin, particularly the posterior margin in a mastectomy specimen, should also be described as this could result in a recommendation for further surgery or radiotherapy.

There remains some controversy regarding the minimum width of uninvolved tissue that defines 'complete' excision, although narrower margins are now more widely accepted as adequate than previously. For this reason, it is recommended that the pathologist reports the measurement to the inked margins of DCIS and invasive carcinoma rather than quoting 'complete' excision or 'not at ink' in histology reports.

Some centres find it helpful to report the approximate extent of margin involvement. The following system is recommended - this is considered a non-core feature:

- Unifocal: one focal area of carcinoma at the margin, <5 mm
- Multifocal: two or more foci of carcinoma at the margin
- Extensive: carcinoma present at the margin over a broad front (≥5 mm).

The presence of microscopically identifiable tumour bed at the margin may be documented in a note in the report and is optional. On a rare occasion if the tumour has a heterogenous pattern of response with scattered invasive carcinoma cells in an area of fibrosis the pathologist may be concerned that a significant amount of residual invasive carcinoma may have been left behind because there is fibrosis at the margin, with fibrosis with scattered invasive carcinoma cells close to the margin and no invasive carcinoma at the margin. However, it is important to remember that surgical resection of the entirety of the tissue involved by the tumour pre-treatment is not necessarily performed after neoadjuvant therapy.

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As such tumour bed that may or may not be identifiable is present at the margin in many specimens after neoadjuvant therapy. The significance of identifiable tumour bed at the margin in the absence of invasive carcinoma at the margin is unclear. Re-excision is usually not performed when identifiable tumour bed is present at the margin in the absence of invasive carcinoma at the margin.

CS3.09b

It may be appropriate to include a statement in the descriptive section of the report where the tumour bed has been frankly transected at the inked surgical margin, as this may impact accurate assessment of cPR.

CS3.09c

The standardised use of a 2 mm margin is associated with low rates of ipsilateral breast tumour recurrence.[27] For each margin <2 mm, specify which margin and margin width.

For optimal clinical communication, it may be helpful to list the nearest involved margin first and so on, with the most distant margin listed last.

CS3.09d

In planning the extent of radiation therapy, radiation oncologists are interested in the margins of the axilla. Histologic assessment of soft tissue margins of tissue resected from the axilla is not standardised and data are not available to guide such assessment. At present, the surgeon's input as to whether gross residual axillary disease is present may have to be used for such treatment planning.

S3.10 The presence or absence of lymphovascular invasion (LVI) must be recorded.

CS3.10a ICCR

The presence of lymphovascular invasion (LVI) is an adverse feature providing independent prognostic information about both local recurrence and survival. Reporting the LVI status for stage IIA and IIB patients who have an axillary lymph node dissection may also influence the use of radiotherapy.

Recognition of LVI may be challenging (see CS3.08a Lymphovascular invasion in primary breast carcinoma in the Invasive carcinoma of the breast protocol).

On occasion, residual invasive carcinoma after neoadjuvant therapy is present as LVI only. This is not considered pCR. This finding should prompt careful re-evaluation of the gross specimen and lymph nodes to ensure appropriate sampling of the correct area and that residual invasive carcinoma or lymph node metastasis was not missed. ypT0 category is assigned with a comment emphasising this is not pCR. For the purposes of calculating the RCB, if there is no other residual invasive cancer, then the extent of the LVI should be estimated in two dimensions and its cellularity estimated relative to this area.

Only LVI identified in breast tissue at the tumour site should be recorded. LVI identified elsewhere, for example in axillary tissue, may be described but not recorded formally as LVI positive. Documenting the presence of dermal LVI is valuable because of its strong association with the clinical findings of inflammatory breast carcinoma. As with LVI only in the breast, LVI at other sites such as dermis or axilla when present without residual invasive carcinoma elsewhere should not be classified as pCR. Perineural invasion should not be recorded as LVI.

CS3.10b

Radiation oncologists are interested in LVI in the axillary fat for their treatment planning. The terms LVI should be reserved for documenting such involvement in the breast tissue. A similar process in the axillary tissue may be described as lymphovascular tumour emboli.

Extensive LVI is important in radiation oncologists' treatment planning.

G3.01 Coexistent pathology should be recorded.

CG3.01a ICCR

In some situations, inclusion of coexisting conditions can be considered beneficial if this supports clinicopathological correlation or patient management. Examples include

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microcalcification detected mammographically and extension into or involvement of a benign lesion such as a sclerosing lesion, papillary lesion or fibroepithelial lesion.

An exhaustive description of all coexisting conditions is not required.

G3.02 The presence or absence of microcalcifications should be recorded.

CG3.02a ICCR

The presence of microcalcifications may help to locate the pre-treatment tumour site with or without the presence of residual invasive carcinoma. Note that calcifications from the original primary cancer usually persist after treatment and should be sampled for microscopic evaluation, but the calcifications may represent the prior DCIS and residual invasive cancer can be present as less obvious tissue density or distortion in the post-treatment breast.

CG3.02b

The presence of site markers in the specimen and the relationship of site markers to the DCIS should also be indicated.

S3.11 The number of lymph nodes examined must be recorded.

CS3.11a ICCR

For axillary staging purpose at least one sentinel node is required in patients who received neoadjuvant treatment and were clinically node negative (cN0) pre-treatment.

In patients with cT1-T2 cN1 disease with clinical and imaging resolution of lymph node positivity after completion of neoadjuvant treatment, based on the results of three separate clinical trials,[28-30] evaluation of at least three sentinel lymph nodes identified with dual tracer technique or removal of the biopsied node as identified by a fiducial marker, is associated with a false negative sentinel lymph node rate of less than 10%.

If a fiducial marker clip has been placed in a biopsied node pre-treatment then it is important for the pathologists to be aware of this at the time of initial sampling of the specimen (sometimes at the frozen section bench) so the pathologist can look for the fiducial marker. Specimen x-ray may help localise the fiducial marker. If an intra-operative specimen x-ray has been carried out in the operating theatre the findings should be communicated to the pathologist. A comment should be made in the pathology report stating whether the fiducial marker was identified and its location (in a sentinel or a non-sentinel node which was positive or negative for carcinoma). Fiducial marker clips or carbon pigment can induce a florid foreign body reaction which can make histological interpretation more difficult, especially if frozen section is performed, and which should not be interpreted as treatment effect.

S3.12 The number of lymph nodes with metastatic carcinoma must be recorded.

G3.03 The number of lymph nodes with macrometastases should be documented.

G3.04 The number of lymph nodes with micrometastases should be documented.

CG3.04a ICCR

The number of lymph nodes containing metastatic carcinoma post neoadjuvant therapy is an important prognostic factor and shows a strong association with disease free and overall survival, independent of the presence of residual tumour in the breast. Any carcinoma cells in the lymph node should be regarded as residual disease. The presence of low burden of residual disease in the lymph nodes (ITCs or micrometastases) represents a very different finding after neoadjuvant therapy than without prior therapy. Both the presence of micro-metastases and of ITCs has significant prognostic implications.

The number of micrometastatic lymph nodes is added to the number of macrometastatic lymph nodes, provided that there is at least one lymph node with macrometastasis to derive the pN category.

If no macrometastasis is present, the number of micrometastatic lymph nodes (provided there is at least one) does not alter the pN1mi category but may still reflect prognostic information.

The number of lymph nodes with metastatic carcinoma excluding ITCs is used for ypN classification (see **PATHOLOGICAL STAGING**).

S3.13 The number of lymph nodes with isolated tumour cells (ICTs) must be recorded.

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CS3.13a ICCR

Isolated tumour cell (ITC) clusters are single tumour cells or small clusters of carcinoma spanning less than or equal to 0.2 mm in greatest dimension or adding to less than or equal to 200 cells in a single histological cross section. ITCs can be detected by routine H&E stains or IHC but should be verified in H&E-stained slides. Currently ITCs are not classified as metastatic deposits for the purposes of staging. If only ITCs are identified in lymph nodes, the ypN classification is ypN0(i+).

Post neoadjuvant chemotherapy ITCs can occur in two contexts. There can be scattered single cells lying within a background of post-treatment changes such as fibrosis suggestive of previous gross metastatic disease that has partially responded to therapy, or there can be scattered single cells or small clusters within lymph node parenchyma with no evidence of treatment related changes. Both these scenarios represent residual viable tumour that is treatment resistant, and in the post neoadjuvant setting, the presence of ITCs (ypN0(i+) category) excludes pCR.

In contrast to the adjuvant setting, it is currently advised that presence of ITCs in sentinel lymph nodes post neoadjuvant therapy should result in further axillary treatment with either completion axillary dissection or axillary radiotherapy. In the SN FNAC trial, when nodes containing ITCs were regarded as node positive, the false negative rate for sentinel lymph node biopsy fell from 13% to 8%.[29]

According to CAP guidelines, nodes containing only ITCs are excluded from the total positive node count for purposes of ypN classification but should be included in the total number of nodes evaluated.[31]

For calculation of the RCB lymph nodes with ITCs post-neoadjuvant chemotherapy, with or without treatment related changes, are regarded as node positive and included in the number of lymph nodes with metastatic carcinoma. Lymph nodes with ITCs are also regarded as positive in some national guidelines, for example RCPath guidelines.[32]

S3.14 The size of the largest metastasis must be recorded.

CS3.14a ICCR

The size of the largest metastasis is a strong predictor of disease free and overall survival post neoadjuvant chemotherapy,[33] and it is one of the variables used to calculate the RCB.[13]

Measuring the size of the largest metastatic deposit can be very challenging post neoadjuvant chemotherapy. The measurement of residual carcinoma in the post neoadjuvant therapy setting is a subject of debate and varies in different classification systems. According to the AJCC 8th edition Staging System, only the size of the largest contiguous focus of residual carcinoma present in the lymph nodes is used for lymph node classification.[10] Treatment-induced fibrosis between adjacent foci of residual carcinoma is not included in the size measurement.[31,34,35] In other regions such as the United Kingdom, Ireland, Australasian and South-East Asian countries, the size includes foci of residual viable carcinoma with intervening treatment-induced stromal fibrosis. This second measurement (largest metastatic extent measured from tumour cell to tumour cell including intervening fibrosis and extracapsular extension 'RCB size', 'largest lymph node metastasis') is also the measurement used to determine RCB (see ICCR Figure 2).

If there are clearly separate foci within a node with intervening nodal tissue, then these should be measured as distinct foci and the largest single focus used as the size of the largest metastatic deposit.

S3.15 The presence of extranodal extension must be recorded.

CS3.15a ICCR

Extranodal extension (ENE) may be grossly visible (matted lymph nodes) but is most often a microscopic finding. In studies which looked at the effect of ENE on prognosis and overall nodal burden when ENE was present only in sentinel lymph nodes, ENE was only included as a qualitative variable i.e., present or absent.[36-38] There is no firm evidence to recommend further quantifying ENE at this stage.

Extranodal extension (ENE) is included in the size of the largest lymph node metastasis for the purpose of calculating RCB.

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CS3.015b

The presence of ENE has prognostic significance,[39,40] but the size does not.[40,41] The method of measurement of extent of ENE varies,[42] with evidence for measuring the circumferential extent, perpendicular extent or simply the largest extent measuring into the fat as equally valid. Due to the current lack of standardisation of the method of measurement, the RCPA neoadjuvant breast expert panel recommend the presence of ENE should be reported as standard, but reporting the extent of ENE is optional.

G3.05 The presence of a treatment effect should be documented.

CG3.05a ICCR

Treatment effect is best reported separately for lymph nodes with residual carcinoma (A) and for lymph nodes without residual carcinoma (B).

Treatment effect is defined as areas of scarring, hyalinization, necrosis, mucoid or myxoid change in the lymph node (akin to tumour bed in the breast specimen), and/or the presence/absence of cellular alterations in the residual carcinoma attributable to the neoadjuvant treatment. Reporting of treatment effect in lymph nodes is strongly encouraged, as it may act as an indicator of the extent of lymph node involvement before neoadjuvant treatment, and of the tumour response to treatment. However, interpretation of fibrosis in nodes can be very subjective, and areas of fibrosis may be seen in lymph nodes in the adjuvant setting. Caution must be taken not to over interpret biopsy site changes and small amounts of fibrosis, particularly capsular fibrosis, as evidence of previous metastatic disease. If there is variable response between nodes then this should be commented on in the report. The number of lymph nodes showing changes suggestive of treatment effect without the presence of residual tumour cells may be an indicator of pre-treatment nodal burden, and may be used in decision making regarding the need for adjuvant radiotherapy.

S3.16 Pathologic complete response (pCR) must be recorded.

CS3.16a ICCR

Pathologic complete response (pCR) is now defined as no invasive disease in the breast (ypT0/ypTis or ypT0) and no disease in all sampled lymph nodes (ypN0). An international effort tried to standardise the definition and aspects of clinical practice and pathologic evaluation that impact the determination of pCR.[43,44] Fiducial marker placement to mark the primary tumour site prior to initiating therapy is very important. To improve the accuracy of sentinel lymph node biopsy the placement of a clip in involved lymph nodes is also recommended. Appropriate handling of the pathology specimen is critical (see **Background: ICCR General information - Specimen handling post neoadjuvant treatment** section). Directed sampling with identification of the tumour site is needed to accurately determine the pCR status.

Absence of disease in all sampled lymph nodes, including absence of ITCs, is required for pCR. LVI only associated with the primary tumour or elsewhere (for example, dermal LVI or in the axilla) is not considered pCR. The presence of in situ carcinoma, lobular neoplasia, necrotic tumour and mucin in the absence of viable disease do not preclude classification as pCR.

It is unclear if residual DCIS after neoadjuvant therapy affects prognosis. The definition of pCR used may or may not include the absence of DCIS. It is helpful to document the definition of pCR used (ypT0/ypTis ypN0 or ypT0 ypN0). ypTis ypN0 has an excellent prognosis.

CS3.16b

The consensus of the RCPA neoadjuvant breast expert panel is that the local definition of pCR does *not* include in situ carcinoma and only refers to invasive disease.

S3.17 Residual cancer burden (RCB) must be recorded.

CS3.17a ICCR

Multivariable response predictors combine individual prognostic elements. The RCB index combines residual carcinoma in the breast (tumour size and cellularity) and in the lymph nodes (number of lymph nodes with carcinoma and extent of largest lymph node metastasis)

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into a single continuous RCB score that can be divided into RCB class 0 corresponding to pCR, RCB I minimal residual disease, RCB II moderate residual disease, and RCB III extensive residual disease. After neoadjuvant chemotherapy (with anti-HER2 therapy when applicable) the RCB score and classes are prognostic overall, within AJCC anatomic stage groups[10] and within breast cancer subtypes (triple negative, hormone receptor (HR)+ HER2-, HR+ HER2+, and HR- HER2+). RCB was originally described in 2007.[13] A standard operating procedure (SOP), teaching materials and a calculator are freely available at: http://www.mdanderson.org/breastcancer_RCB.[14] RCB is widely used in a variety of settings and is reproducible.[13,45,46] A recent pooled meta-analysis including over 5,000 patients confirmed that RCB score and classes were independently and strongly prognostic in all breast cancer subtypes.[47] The AJCC 8th edition Staging System[10] recommends adding additional descriptions to staging, such as the number of foci, total area of involvement, RCB, etc. AJCC stage and RCB provide complementary information.

Residual cancer burden (RCB) score and class can be included in the pathology report. For best results it is important to follow the SOP including appropriate sampling of the tumour bed and to use uniform definitions for the elements as explained in the SOP and this dataset. It is preferable if the pathologist interpreting the RCB can also report the calculated result. It is also helpful to provide the core elements used to calculate RCB when RCB class and score are reported. If the RCB score is not calculated, then the required information should be provided and formatted in the report such that any member of the clinical team reading the report would exactly enter the correct information and obtain the correct result from the calculator, as this facilitates calculation of RCB at a later date by the clinical team or when access to the online calculator is not available at the site of reporting.

Combining the core prognostic elements from the surgical specimen into a single score with corresponding prognosis improves reproducibility by dampening the effects of variable results of individual elements due to differences in interpretation or sampling (for example, if there are multiple foci of invasive carcinoma in an area of fibrosis this would give a large tumour with low cellularity if they are interpreted as a single tumour or a small tumour with high cellularity if only the largest individual focus is assessed (see ICCR Figure 1, **TUMOUR DIMENSIONS**)), and facilitates interpretation, comparisons, and clinical decisions. Other factors such as pre-treatment burden of disease and tumour biology may also be important predictors of prognosis in a given situation.

When multiple separate lesions are present the one with the greatest burden of residual disease determines RCB. This is often the largest lesion. It is useful to also calculate the RCB score for the smaller lesions if they are more cellular and may yield a higher RCB score. If the separate invasive carcinomas are distinct by tumour type, grade and/or receptor status then RCB should be reported for each. For example, after neoadjuvant therapy with chemotherapy and anti-HER2 therapy in a patient with a synchronous HER2 positive tumour and HR positive HER2 negative tumour response in both tumours is expected to be different. RCB is expected to be prognostic in both tumours. In particular, the response in the HER2 positive tumour will determine the need to escalate subsequent therapy.

Residual cancer burden (RCB) cannot be reliably calculated if the positive lymph nodes were removed prior to neoadjuvant therapy as the number of lymph nodes with carcinoma and the extent of the largest lymph node metastasis are needed. Areas of fibrosis and extracapsular extension are included in the measurement. The 'RCB size of the largest lymph node metastasis' may be different from the size used to determine AJCC[10] N categories. For ITCs, a number <1 can be entered for the extent of the largest lymph node metastasis. The number of involved nodes used to calculate RCB includes the number of lymph nodes with macrometastases, micrometastases and ITCs. Involved internal mammary lymph nodes are included in the lymph node count to calculate RCB.

At this time, pathology response endpoints following neoadjuvant endocrine therapy are insufficiently validated to be considered as core elements. The Preoperative Endocrine Prognostic Index (PEPI) is recommended as a non-core element when reporting response from neoadjuvant endocrine therapy. PEPI has not been extensively validated for prognosis, but the results to date with PEPI are promising and it combines parameters that have known prognostic information: tumour size, involved nodes, proliferative suppression, and persistence of ER positive status of the residual invasive cancer.

Residual cancer burden (RCB) and yp stage (UICC[9]/AJCC[10] TNM) were not designed for prognosis after neoadjuvant endocrine therapy, and their prognostic value has not been

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demonstrated in this setting. It is already clear that patients with ER positive disease who achieve a low RCB or ypStage from chemotherapy-based treatment will have an excellent prognosis with adjuvant endocrine therapy. However, it remains unproven whether achieving that same response with neoadjuvant endocrine therapy would impart the same excellent prognosis with continued adjuvant endocrine therapy as there are currently no data. The elements to determine RCB and the RCB score can still be used to describe the findings in the surgical specimen post neoadjuvant endocrine therapy, but it would be prudent to add a note to the report that the prognostic value of RCB score and class has not been demonstrated in the setting of neoadjuvant endocrine therapy.

There are insufficient data to support specific prognostic tools as core elements for other types of neoadjuvant therapy. However, the elements in this dataset are reasonable to describe the pathological findings in these more unusual or investigational treatment settings.

CS3.17b

RCB is not appropriate to use in the context of neoadjuvant endocrine therapy. The PEPI score is more appropriate and may be reported for these patients if required.

G3.06 Other microscopic comments should be recorded.

CG3.06a

Any additional relevant microscopic comments should be recorded.

CG3.06b

(Nirmala to draft/edit): The presence of lymphovascular invasion in the axilla should be reported. The presence of tumour blebs can be an indication of replaced lymph nodes. Lymph emboli within the afferent and efferent lymphatics may be confused with perinodal lymphatics.

ANCILLARY STUDIES

G4.01 Post-treatment estrogen receptor (ER) status can be reported for cases of invasive breast carcinoma.

CG4.01a ICCR

Hormone receptor status should be performed on pre-treatment core biopsy. Depending on the resources available it may be repeated after neoadjuvant therapy, although routine retesting of receptor status in residual disease is not currently advocated. Repeat testing can be considered if abundant residual disease is present in the breast or lymph nodes. Repeat testing is also indicated if tumour foci show morphology suggesting a different breast cancer subtype than was present in the pre-treatment core biopsy.

Change in estrogen (ER) status post neoadjuvant chemotherapy has been reported in up to 47% of patients, with a meta-analysis identifying a change in ER status in 13-18% of cases.[48,49] This can be from positive to negative, or negative to positive. The significance of a change in ER status for survival outcomes and clinical management is less certain. Some series have suggested improved survival outcomes with endocrine therapy in patients that revert from ER negative to ER positive disease.[50]

If the PEPI is being measured for response to neoadjuvant endocrine therapy, then ER immunohistochemistry (IHC) and Ki-67 IHC of the residual primary tumour need to be performed and recorded.[51,52]

When a tumour is negative but no internal control cells are present, the pathologist must exercise judgment as to whether the assay can be interpreted as a true negative. If there is doubt, then a recommendation to repeat on another block or specimen that contains internal controls should be made.

'Cannot be determined' is used when any issue prevents reliable interpretation of the result. This can include suboptimal specimen handling, presence of artefacts (crush or edge artefacts) making interpretation difficult, or if the analytical testing procedure failed.

See also CS4.01a Estrogen receptor in the Invasive carcinoma of the breast protocol.

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G4.02 Post-treatment progesterone receptor (PR) status can be reported for cases of invasive breast carcinoma.

CG4.02a ICCR

Change in progesterone receptor (PR) status post neoadjuvant chemotherapy is seen more frequently than changes in ER status, perhaps reflecting changes in ER signalling, with a meta-analysis identifying a change in PR status in 26-32% of cases.[48,49] This can be from positive to negative, or negative to positive. The significance of a change in PR status for survival outcomes and clinical management is even less certain than for ER.

When a tumour is negative but no internal control cells are present, the pathologist must exercise judgment as to whether the assay can be interpreted as a true negative. If there is doubt, then a recommendation to repeat on another block or specimen that contains internal controls should be made.

'Cannot be determined' is used when any issue prevents reliable interpretation of the result. This can include suboptimal specimen handling, presence of artefacts (crush or edge artefacts) making interpretation difficult, or if the analytical testing procedure failed.

See also **POST-TREATMENT ESTROGEN RECEPTOR** and CS4.01a Estrogen receptor and CS4.02a Progesterone receptor in the Invasive carcinoma of the breast protocol.

G4.03 Post-treatment HER2 status can be reported for invasive breast cancer.

CG4.03a ICCR

HER2 status should be performed on pre-treatment core biopsy. Depending on the resources available it may be repeated after neoadjuvant therapy, although routine retesting of receptor status in residual disease is not currently advocated. Repeat testing can be considered if abundant residual disease is present in the breast or lymph nodes. Repeat testing is also indicated if tumour foci show morphology suggesting a different breast cancer subtype than was present in the pre-treatment core biopsy.

Changes in HER2 status are less frequent than changes in hormone receptor status. A large population-based series from Japan identified a change in HER2 status on IHC in 20% of cases, but only 8% showed a change with HER2 FISH.[53] Conversion from HER2 positive to HER2 negative status is more common than negative to positive. Persistence of a HER2 negative clone post neoadjuvant therapy with chemotherapy plus HER2 targeted agents occurs in approximately one third of cases and is associated with worse survival outcomes.[54]

'Cannot be determined' is used when any issue prevents reliable interpretation of the result. This can include suboptimal specimen handling, presence of artefacts (crush or edge artefacts) making interpretation difficult, or if the analytical testing procedure failed.

See also S4.03a HER2 in the Invasive carcinoma of the breast protocol.

CG4.03b

In Australia, IHC 2+ and 3+ cases require ISH assessment to determine amplification and thus eligibility for anti-HER2 therapies.

Also, in Australia, the Medicare Benefits Schedule (MBS) requires evidence of *HER2* ISH amplification to qualify for subsidised access to HER2 agents. The RCPA-endorsed position,[55] published in 2020 after extensive review by a multidisciplinary RCPA Invasive breast expert committee, is that IHC 3+ cases should NOT be reported as positive, but rather HER2 reporting should be deferred until the ISH results are also available and an integrated final report, inclusive of IHC and ISH findings can be issued. The turnaround time for ISH reporting is only one extra day in many laboratories, such that most pathologists tend to simply state in a preliminary report that 'HER2 assessment is proceeding' if ISH is being performed. They do not state the IHC results in the preliminary report and issue a final report with the complete findings and interpretation of results.

In New Zealand access to HER2 targeted therapy is available on the basis of either a IHC 3+ score, or amplification, as per ASCO CAP guidelines.[5] For NZ cases where ISH is being used, to avoid misunderstandings, it is recommended that the results of tests be made available in one final report that integrates IHC and ISH results.

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G4.04 Any other post-treatment ancillary studies should be recorded.

CG4.04a ICCR

Primary tumour

The results of any additional ancillary studies such as multigene test results when performed are recommended to be included or added subsequently to the pathology report to ensure a record of all assays performed on the case in a single comprehensive report.

The information on Ki-67 expression after therapy is distinct from the information on the core biopsy. Suppression of proliferation has been shown to be associated with response to neoadjuvant chemotherapy and improved survival.[56,57]

A decrease in Ki-67 following two weeks of neoadjuvant endocrine therapy has been associated with endocrine responsiveness and improved survival in window studies of anti-estrogen therapy.[52,58,59] Decreased Ki-67 occurs in most tumours treated with a cdk4/6 inhibitor of cell cycle entry in combination with neoadjuvant endocrine therapy, and currently there is uncertainty about what that means.

If the PEPI index is being measured for response to neoadjuvant endocrine therapy, then ER IHC and Ki-67 IHC of the residual primary tumour need to be performed and recorded.[51,52]

See also CG4.01 Ancillary studies in the Invasive carcinoma of the breast protocol for additional information on Ki-67 proliferation index.

Lymph nodes

Immunohistochemistry (IHC)

The routine use of keratin IHC assays to evaluate lymph nodes obtained post neoadjuvant treatment with no evidence of carcinoma in haematoxylin and eosin (H&E)-stained sections is not routinely recommended. However, keratin IHC can be useful to evaluate suspicious cells identified in H&E-stained sections. The identification of tumour cells in lymph nodes obtained post neoadjuvant treatment using IHC for keratins was not associated with significantly worse prognosis in a retrospective study.[60] Tumour cells should be classified in the same way regardless of the method of detection with or without IHC.

Refer to ICCR dataset for full commentary.

CG4.04b

For patients being treated with neoadjuvant endocrine therapy, a fall in Ki-67 levels two weeks after the start of therapy is a useful biomarker of likely response.[61]

While the US-based ASCO and National Comprehensive Cancer Network (NCCN) do not advocate routine Ki-67 reporting,[62] the St Gallen Guidelines[63] and the WHO,[20] serving regions with less ready access to multiparameter gene testing, note its value.

Interest in Ki-67 evaluation is expected to increase in response to the MonarchE study results.[64] Even though Ki-67 index was prognostic, but not predictive of response, patients with Ki-67 positive cancers drew a larger benefit from treatment.[64] In 2021 the United States Food and Drug Administration (FDA) approved Abemaciclib for “HR positive, HER2 negative, node positive early breast cancer at high risk of recurrence AND a Ki-67 score ≥20%, as determined by ‘an FDA approved test’”.[65] At present the only such companion diagnostic is Ki-67 IHC MIB-1 PharmDx (Dako Omnis), to be evaluated under the following conditions:

- Using the EnVision FLEX visualisation system on Dako Omnis
- Using the Ki-67 PharmDx score
- Reported positive for Ki-67 if ≥ 20% nuclear staining of any intensity

At present the Ki-67 PharmDx platform is not available in Australasia. The RCPA Invasive Carcinoma of the Breast expert panel notes that system refers to scoring Ki-67 expression across the entire slide. The correlative studies needed to assess other antibodies, assays and platforms for this purpose are ongoing. At present the results of other Ki-67 evaluation platforms cannot be assumed to be equivalent to the specific companion diagnostic used in the MonarchE study,[64] but this study is expected to focus demand for more routine Ki-67 assessment.

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In the meantime, it may be helpful to report the antibody, platform and scoring system (global, hotspot or other method) used for Ki-67 evaluation.

CG4.04c

Immunotherapy, using monoclonal antibodies to PD1/PDL1 or CTLA-4, potentiates antitumour host immune response.[66] At present, triple negative breast cancer (TNBC) is the focus of breast immunotherapy trials. The IMPassion 130 trial found that immunohistochemical expression of the SP142 PDL1 antibody on >1% of immune cells was predictive of significantly better survival for women with locally advanced or metastatic TNBC, treated with Atezolizumab in addition to nab-paclitaxel.[67]

The Keynote-522 Trial,[68] based the evaluation of PDL1 on the 22C3 PharmDX antibody and used the CPS score of ≥1 to stratify responses to Pembrolizumab based therapy. PDL1 status was not predictive of response in this trial but was prognostic.

Immunotherapy for subsets of breast cancer patients is in clinical use and under active investigation. Oncologists are likely to continue to be interested in this biomarker.

PDL1 IHC evaluation can be performed in discussion with the medical oncologist. The assay used and the scoring algorithm are specific to each trial and are NOT interchangeable.

CG4.04d

The Luminal androgen receptor (LAR) subtype is one of the four stable subtypes of TNBC, as per the revised TNBC type-4 classification.[69,70]

The LAR subtype accounts for 20–40% of TNBCs. It is characterised by a luminal-like pattern of gene expression, reduced sensitivity to neoadjuvant chemotherapy and elevated expression of the androgen receptor (AR).[71]

These cancers may be responsive to anti-androgen strategies.

If AR is evaluated, it may be reported using the parameters of the Allred score, including the proportion score and the average intensity.

Moving forward, a better biomarker for the selection of patients suitable for treatment with AR inhibitors is a major unmet need. However, at present there is interest among treating medical oncologists in the evaluation of AR in TNBC.

CG4.04e

Information regarding the results of multigene assessments, *PIK3CA* mutations, mismatch repair protein expression assessment, tumour mutation burden index, PDL1 assessment and *NTRK* assessment, if performed, may be reported in this section.

PATHOLOGICAL STAGING INFORMATION

S5.01 Pathological staging must be recorded.

CS5.01a ICCR

The Tumour Node Metastasis (TNM) system of the UICC is recommended.[9] In the UICC TNM Staging System,[9] breast cancer staging can be done for primary untreated disease, breast cancer treated with primary systemic therapies or in the recurrent setting. To distinguish between these, the symbols of categorisation are added before the tumour and nodal categories. For uniform use, the order of these categories is advised to be y – r – p or c (if none of these latter two are given, this is synonymous with c).

Pathologic Classification

Classification of T, N, and M by pathology examination of a post-treatment specimen is denoted by use of a lower case 'yp' prefix (ypT, ypN, ypM).

Pathological T (ypT): Histological assessment of the primary tumour (pT) generally is based on the largest contiguous invasive tumour focus without intervening areas of fibrosis (see **TUMOUR DIMENSIONS** section for methodology details). These dimensions may be different than the dimensions used for RCB.

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The suffix ‘m’ indicates the presence of multiple primary tumours (see **TUMOUR FOCALITY**) in a single site and is recorded in parentheses, e.g., ypT(m) NM.

Breast cancer staging involves the inclusion of the nodal status according to the ypN categories as defined above. Nodal stage post neoadjuvant therapy has been shown to correlate with survival outcomes, and is important for cancer registry purposes to monitor the population demographics of breast cancer.

The number of lymph nodes with metastases for UICC[9]/AJCC[10] staging includes the number of lymph nodes with macrometastases and with micrometastases provided one macrometastasis is present. The number of lymph nodes with metastases used for UICC[9]/AJCC[10] staging may be different than the number used to calculate RCB as for calculating the RCB the number of lymph nodes with ITCs and micrometastases are also included regardless of the presence of a lymph node with macrometastases.

S5.02 **The year of publication and edition of the cancer staging system used in S5.02 must be included in the report.**

CS5.02a

This is especially important when a new edition staging system has recently been published.

DIAGNOSTIC OVERVIEW

S6.01 **Diagnostic summary**

CS6.01a

The ‘Diagnostic summary’ section of the final formatted report should include:

- Specimen laterality
- Tumour site
- Tumour focality
- Residual tumour dimensions (largest)
- Histological tumour type
- Post-treatment histological tumour grade
- Carcinoma in situ
- Tumour extension
- Margin status
- Lymphovascular invasion
- Pathological staging
- Residual cancer burden class and score

G6.01 Overarching comment

CG6.01a

A field for free text or narrative in which the reporting pathologist can give overarching case comment should be provided.

This field may be used, for example, to:

- list any relevant ancillary tests
- document any noteworthy adverse gross and/or histological features
- express any diagnostic subtlety or nuance that is beyond synoptic capture
- document further consultation or results still pending.

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iv. Background

ICCR – General information

There has been an increase in the use of neoadjuvant chemotherapy in recent times that has been driven by greater access to effective treatments, desire for breast conservation, and most recently clinical desire to learn prognostic information from the response of a patient's disease to the treatment given which may increasingly guide further therapy. The recommended prognostic tools are multivariable, and so combine individual data elements from pathology evaluation. Certainly, it is now core information for there to be accurate determination of whether pCR has been achieved and to provide accurate prognostic information if there is residual disease. To this end, the RCB method is the most validated prognostic tool for patients with residual disease after neoadjuvant chemotherapy-based treatments for any subtype of breast cancer. Results from a multinational pooled analysis of RCB in over 5,000 subjects were recently reported[72] and have now established sufficient level of evidence to include reporting of RCB as core elements in addition to UICC[9]/AJCC[10] ypTNM stage.

Neoadjuvant endocrine therapy is sometimes given instead of chemotherapy, but pCR is a rare outcome. A brief pre-operative exposure to endocrine therapy (for example, because of a delay in surgery) is not considered neoadjuvant therapy. At this time, pathology response endpoints following neoadjuvant endocrine therapy are insufficiently validated to be considered as core elements, but the PEPI is recommended as a non-core element when reporting response from neoadjuvant endocrine therapy. PEPI has limited validation for prognosis and combines parameters that have known prognostic information: tumour size, involved nodes, proliferative suppression, and persistence of ER positive status of the residual invasive cancer. Although there are insufficient data to support specific prognostic tools as core elements for neoadjuvant endocrine therapy when combined with other targeted therapy, immunotherapy, radiotherapy, or other novel treatments, it is reasonable to use this dataset to document pathology information that would be relevant for any type of neoadjuvant therapy, even if investigational treatment. Biological indicators might be differently affected by molecular treatments; however the estimation of extent and pathology of residual disease is generally relevant.

Data entered into this dataset represent the findings in the surgical specimen after neoadjuvant therapy. To emphasise this, the modifier 'post-treatment' is added to several elements (Histological tumour grade, ER, PR, HER2 and Ancillary studies). When no residual invasive carcinoma is present then the remaining elements pertaining to residual invasive carcinoma (Tumour dimensions, Tumour cellularity/composition, Histological tumour type, Post-treatment histological tumour grade, Tumour extension, Margin status, Post-treatment ER, Post-treatment PR, Post-treatment HER2 and Post-treatment ancillary studies) are removed from the report. These elements should not be populated with information from the prior core biopsy.

Specimen handling post neoadjuvant treatment

The objective is to document the extent of residual invasive carcinoma or accurately confirm complete response. Because residual carcinoma may be indistinct, we use all the knowledge available to us from imaging, radiological clips, markers, gross appearance and palpation to guide sampling for histology. Therefore, it is important to have a visual map of the sections of the gross specimen so that the extent of histologically confirmed invasive residual carcinoma can be measured in the resected specimen. The grossly fibrotic lesion may or may not represent the extent of the residual invasive carcinoma, but it is the extent of residual invasive carcinoma that is the most important to measure.

Detailed specimen handling as described previously,[43,73-75] with close correlation with radiological findings, accurate macroscopic description and precise block designation is vital for reliable identification of the **pre-treatment tumour site*** and assessment of tumour response post neoadjuvant therapy. Precise mapping of the specimen with intelligent block selection guided by close radiological-pathological correlation is preferable to exhaustive sampling. It is strongly recommended that an image of the sliced specimen is recorded, and then used as a map for the sections taken to facilitate subsequent histological interpretation; this may be in the form of radiographs, photographs, photocopies or drawings. The pathologist should evaluate the extent of residual primary cancer in two stages: 1) macroscopic tumour bed as the extent of possible disease based on informed evaluation of the pre-treatment tumour site(s) and any other suspicious areas, and 2) the extent of disease that is confirmed to be cancer after careful sampling for histopathology review and mapping of those findings to the original specimen.

In cases where there has been an excellent response to therapy, there may be no grossly detectable residual tumour present. If there is no visible lesion, then careful palpation of the specimen slices looking for areas of firmness may assist in identifying the tumour bed. Ideally, a fiducial marker (clip or equivalent) will have been placed in the tumour at the time of diagnosis, even in patients who will undergo a mastectomy. The fiducial marker may be identified macroscopically, but if not found on gross examination specimen x-ray can be used to localise the site. The presence of microcalcifications may also help identify the tumour bed on x-ray.

Tumours may show a heterogeneous response to therapy, with patchy distribution of residual islands of tumour cells dispersed across the entire tumour bed. Hence, even if there is a discrete visible lesion present after chemotherapy,

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sampling needs to extend beyond this to encompass the area occupied by the tumour on pre-treatment imaging. This often requires more extensive block taking than in the adjuvant setting. A maximum of 25 blocks across the tumour bed, including five blocks to span the maximum tumour dimension, should be sufficient to document pCR.[43] If the tumour bed or clip site is not present in the sections, the specimen needs to be re-examined in conjunction with the imaging and further blocks may need to be taken.

* The term '*tumour bed*' in post-treatment breast specimens is often used in different ways to describe the area where cancer was and may still be. To avoid confusion, in this document the term 'pre-treatment tumour site' is used to refer to the location of the tumour pre-treatment. The terms 'macroscopic tumour bed' and 'microscopic tumour bed' are explained below. The RCB website[14] uses the terms 'residual tumour bed' and 'primary tumour bed' interchangeably to refer to the area involved by residual invasive carcinoma as measured initially from the macroscopic findings and modified by the microscopic findings (see **RESIDUAL INVASIVE CARCINOMA**).

- 'Macroscopic tumour bed' also often referred to as 'tumour bed': Macroscopically identifiable area post-treatment at the pre-treatment tumour site. Macroscopic findings usually fibrosis may be present at the pre-treatment tumour site. Grossly identifiable residual invasive carcinoma may or may not be present in the macroscopic tumour bed. The boundaries of the macroscopic tumour bed are often not distinct and therefore measurements of the macroscopic tumour bed are often subjective. Alternatively, anywhere in the volume covered by the tumour pre-treatment may be considered the 'macroscopic tumour bed' regardless of the presence of a macroscopic lesion.
- 'Microscopic tumour bed': Microscopically identifiable area post-treatment at the pre-treatment tumour site. Histologic changes such as fibrosis, a characteristic pattern of vessels reminiscent of tumour vasculature, myxoid change, and infiltration by macrophages and/or lymphocytes (sometimes abundant and accompanied by extensive necrosis), suggesting that there was a tumour in this e location pre-treatment, may be present at the pre-treatment tumour site. It may be difficult to differentiate these histologic changes from breast tissue that was never involved by tumour and defining the exact boundaries of this area is nearly impossible, and it should not be measured. Alternatively, anywhere in the volume covered by the tumour pre-treatment may be considered the 'microscopic tumour bed' regardless of the presence of histologic changes. Residual invasive carcinoma may or may not be present in the microscopic tumour bed.
- 'Residual tumour bed' or 'Primary tumour bed' (RCB website calculator): The area in the breast involved by residual invasive carcinoma as measured initially from the macroscopic findings and modified by the microscopic findings.

Macroscopically occult residual invasive carcinoma identified microscopically may extend beyond the macroscopic tumour bed. Residual invasive carcinoma may also extend beyond the area of breast tissue showing the background histologic stromal changes suggesting that there was a tumour in the location pre-treatment (see ICCR Figure 1, **TUMOUR DIMENSIONS**).

Histologic changes related to systemic therapy can be seen in breast tissue (usually in the form of enlarged cells with vacuolated cytoplasm and smudgy nuclear atypia) at the pre-treatment tumour site in the 'microscopic tumour bed' as well as away from the pre-treatment tumour site.

The following table is provided for reference and may be used as needed.

Reporting in table format is not required, and the same information may be provided as indicated in the reporting guide.

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Table 1A ICCR: 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			

Breast cancer - Demographics in Australasia

Breast cancer is the most common invasive cancer among Australian women.

Breast cancer is one of the leading causes of cancer-related death in Australian women. However, owing to earlier detection by screening mammography and improved treatment, survival from breast cancer has been improving.[76] Australia's death rate from breast cancer is similar to those of Canada and the United States of America, and lower than for Western Europe.[77]

Best Practice Procedures for Australasia

Providing an accurate understanding of the distinct pathological features enables treatment protocols to be tailored to tumour characteristics based on the latest evidence. Correlation of the pre-operative clinical findings with those of imaging, percutaneous biopsy and surgical histopathology is a vital part of the multidisciplinary assessment process and is fundamental to the effective management of breast cancer and quality care of the patient.

Ideally, pathology data regarding the diagnosis and receptor profile is available at the time of the patients' initial medical appointments, so a tailored treatment plan may be discussed and organised to suite each persons' specific cancer. Neoadjuvant therapy is now commonly used for triple negative and HER2 positive breast cancers and during the COVID-19 pandemic, neoadjuvant endocrine therapy (NAET) was used to control the disease while managing delays in surgery.[78]

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Appendix 1 - Exemplar Request Information Sheet

Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy Structured Reporting Exemplar Request Information Sheet (1st Edition, 2023)

Includes the International Collaboration on Cancer Reporting (ICCR) dataset content.
Royal College of Pathologists of Australasia (RCPA) content is boxed in red *

DEMOGRAPHIC INFORMATION

Family name | Given name(s) | **ACCESSION NUMBER**

Date of birth (DD – MM – YYYY) | Patient address | Date of request (DD – MM – YYYY)

Sex: ○ Male ○ Female ○ Intersex/indeterminate

Ethnicity: ○ Unknown ○ Aboriginal/Torres Strait Islander (AU) ○ Māori (NZ) ○ Other ethnicity:

COPY TO DOCTORS

PRINCIPAL CLINICIAN

Requesting doctor - name and contact details

Patient health identifiers (e.g. MRN, IHI or NHI)

Mandatory fields (standards) are in **bold** (e.g., **S1.03 ACCESSION NUMBER**).
Optional fields (guidelines) are in grey (e.g., G1.01 COPY TO DOCTORS).

☐ Indicates multi-select ○ Indicates single select

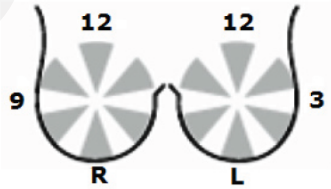
CLINICAL INFORMATION (provided from request form)

OR

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

Neoadjuvant treatment(s) (select all that apply)

☐ Chemotherapy ☐ Hormonal therapy
☐ Immune therapy ☐ Anti-HER2 targeted therapy
☐ Other, *specify* ☐ Radiation therapy



Pre-treatment tumour characteristics

Laterality	
Site(s) and # of tumours	
Date of diagnosis	
Imaging size at diagnosis	
Cancer subtype	
Hormone receptor and HER2 status	

RCPA Neoadjuvant Breast Structured Reporting - Exemplar Request Information Sheet (1st Edition 2023)

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

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

Result: ◯ Positive ◯ Negative

Method of localisation (e.g., clip, carbon, hook wire, radioactive pellets, magnetic seeds)

Number of fiducial markers (e.g., clips) placed

Location of nodes and clips

Other clinical information, *specify*

OPERATIVE PROCEDURE - BREAST

- ◯ Excision (less than total mastectomy)
  - ◯ Therapeutic wide local excision
  - ◯ Re-excision
- ◯ Total mastectomy
  - ◯ Simple mastectomy
  - ◯ Nipple-sparing mastectomy
  - ◯ Skin-sparing mastectomy
- ◯ Additional specimens, *specify*

OPERATIVE PROCEDURE - AXILLA (select all that apply)

- ☐ Sentinel lymph node biopsy
- ☐ Targeted axillary clearance
- ☐ Other non-sentinel lymph node biopsy
- ☐ Axillary lymph node dissection
  - ☐ Level I
  - ☐ Level II
  - ☐ Level III
- ☐ Axillary lymph node level III, excision
- ☐ Other regional lymph node(s) biopsy, *specify*
- ☐ Other, *specify*

COLD ISCHAEMIC TIME AND TIME IN FIXATIVE

- ◯ Compliant with RCPA guidelines
- ◯ Other, *specify*

RCPA Neoadjuvant Breast Structured Reporting - Exemplar Request Information Sheet (1st Edition 2023)

The above Exemplar Request Information Sheet is also published to the RCPA website.

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Appendix 2 - Exemplar Histopathology Report

BLOGGS, Fatima Y.
C/O Paradise Close
Wreck Bay Resort
Nar Nar Goon East, 3181

Female

DOB 1/7/1982
MRN M1196785

Lab Ref: **23/P11744**
Referred: 30/3/2022

Copy to: Dr N.G.Chappie
Rainforest Cancer Centre.

Referred by: Dr V. Brown
Suite 3, AJC Medical Centre,

NEOADJUVANT BREAST CANCER - STRUCTURED REPORT

DIAGNOSTIC SUMMARY: Residual tumour post neoadjuvant chemotherapy with clear surgical margins and negative sentinel lymph nodes

CLINICAL

Clinical information: R breast 2 o'clock 4cm FN 21 mm residual Ca (30mm pre-NACT). R breast WLE + SLNBx

Operative procedure - Breast: Wide local excision

Operative procedure - Axilla: Sentinel node biopsy

Cold ischaemic time and fixation: Within RCPA and ASCO-CAP guidelines

MACROSCOPIC

Specimen laterality: Right

Specimen dimensions: 80 mm (mediolateral), 65mm (anteroposterior),
55 mm (superoinferior)

Specimen weight: 117g

Specimen details: Differential inking: superior margin inked blue, inferior black, posterior orange and anterior green. The specimen is serially sectioned from medial to lateral into thirteen slices. Slice one and slice thirteen each measure 15 mm in thickness. The remaining slices each measure 5 mm in thickness.

Tumour site: The cut surface shows a well circumscribed green soft necrotic lesion spanning slices five to eleven measuring 35 mm anterior to posterior, 32 mm medial to lateral and 25 mm superior to inferior. The lesion lies greater than 10 mm from all margins.

Nature and site of all blocks: (Block A - cruciate section slice 1, B to E - slice 3, F to K - slice 5 flipped, L to Q - slice 8 with wing clip, R to U - slice 10, V to X - slice 12, Y - cruciate sections slice 13)

Other macroscopic comments: A wing clip is identified in slice eight.

MICROSCOPIC

Tumour focality: Unifocal

Residual invasive carcinoma: Present

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Tumour bed dimensions:	33 mm x 24 mm
Size of largest contiguous focus:	33 mm
Tumour cellularity/composition:	40% invasive only
Histological tumour type:	NST
Post-treatment histological tumour grade:	3
Carcinoma in situ:	Not identified, Necrosis not identified
Tumour extension into skin:	Skin is present and uninvolved
Tumour extension into nipple:	Nipple tissue is not present
Tumour extension into skeletal muscle/chest wall:	Skeletal muscle is free of carcinoma
Margin status:	Not involved, all margins >10 mm
Lymphovascular invasion:	Not identified
Coexistent pathology:	None identified
Microcalcifications:	Not identified
Number of sentinel lymph nodes examined:	4
No. of non-sentinel lymph nodes examined	0
No. of nodes with metastatic carcinoma:	0
Evidence of fiducial marker:	Not applicable
Number of lymph nodes with metastatic carcinoma:	0
Number of lymph nodes with ITCs:	0
Treatment effect:	Not identified
Pathologic complete response (pCR):	Residual invasive cancer – Not pCR
Residual cancer burden (RCB):	Average invasive cancer cellularity in RCB area 40%, 2.114 (Residual Cancer Burden Class-II)

ANCILLARY STUDIES

Post-treatment ER/PR/HER2:	Not performed
Post-treatment ancillary studies:	Not performed
Representative blocks for ancillary studies:	1G

PATHOLOGICAL STAGING INFORMATION

Pathological staging:	**ypT2, yp N0, M0 (ypIIA)**
Year and edition of staging system:	**2018 (8th Edition)**

Reported by A/Prof N. Pathmanathan (21/10/23)

The above Exemplar Histopathology Report is also published to the RCPA website.

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Appendix 3 - Practice Audits

Structured reporting for invasive carcinomas of the breast presents an ideal opportunity to perform practice audits. This is because structured pathology reports are more likely to produce consistent data on the expected range of positive findings.

The following parameters may be helpful for practice audit and cross practice correlation:

- Distribution of pathologic complete response rates

- Distribution of grades for symptomatic breast cancers
    - ER positive/HER2 negative on pre-treatment core
    - ER positive/HER2 positive on pre-treatment core
    - Triple Negative on pre-treatment core

- Distribution of pathologic complete response rates
    - All tumours

- Distribution of RCB class for individual pathologists
    - ER positive/HER2 negative on pre-treatment core
    - ER positive/HER2 positive on pre-treatment core
    - Triple Negative on pre-treatment core

- Distribution of grades for symptomatic cancers – individual pathologists
    - ER positive/HER2 negative on pre-treatment core
    - ER positive/HER2 positive on pre-treatment core
    - Triple Negative on pre-treatment core

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Appendix 4 - Definitions

The following definitions describe general or technical terms used in the Royal College of Pathologists of Australasia (RCPA) structured pathology reporting of cancer protocols. Readers should take particular note of the definitions for 'standard', 'guideline' and 'commentary', because these form the basis of RCPA protocols.

Ancillary study An ancillary study or finding is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.

Clinical information Patient information required to inform pathological assessment, usually provided with the specimen request form, also referred to as 'pre-test information.'

Commentary Commentary is text, diagrams or photographs that clarify the standards (see below) and guidelines (see below), provide examples and help with interpretation, where necessary (not every standard or guideline has commentary).

Commentary is used to:

- define the way an item should be reported, to foster reproducibility.
- explain why an item is included (e.g., how does the item assist with clinical management or prognosis of the specific cancer).
- cite published evidence in support of the standard or guideline.
- state any exceptions to a standard or guideline.

In the RCPA protocols, commentary is prefixed with 'CS' (for commentary on a standard) or 'CG' (for commentary on a guideline), numbered to be consistent with the relevant standard or guideline, and with sequential alphabetic lettering within each set of commentaries (e.g., CS1.01a, CG2.05b).

Demographic information Patient demographic information allows for the identification of a patient, as well as patient data categorisation for the purpose of statistical analysis and epidemiology.

Diagnostic summary Pathology reports for cancers contain a summary of diagnostic findings most relevant to making treatment decisions. This can be listed at the top or the bottom of the histopathology report.

Form Designed to provide a checklist of the protocol elements, with response values and spaces for notes.

General commentary General commentary is text that is not associated with a specific standard or guideline. It is used:

- to provide a brief introduction to a chapter, if necessary.
- for items that are not standards or guidelines but are included in the protocol as items of potential importance, for which there is currently insufficient evidence to recommend their inclusion. (Note: in future reviews of protocols, such items may be reclassified as either standards or guidelines, in line with diagnostic and prognostic advances, following evidentiary review).

Guideline Guidelines are recommendations; they are not mandatory, as indicated by the use of the word 'should'. Guidelines cover items that are unanimously agreed should be included in the protocol but are not supported by the National Health and Medical Research Council (NHMRC) level III-2 evidence.[79] These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Guidelines include key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, block identification key, may be included as either required or recommended elements by

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	consensus of the expert committee. Such findings are essential from a clinical governance perspective, because they provide a clear, evidentiary decision-making trail. Guidelines are not used for research items. In RCPA protocols, guidelines are prefixed with 'G' and numbered consecutively within each chapter (e.g., G1.10).
Macroscopic findings	Measurements, or assessment of a biopsy specimen made by the unaided eye.
Microscopic findings	In RCPA protocols, the term 'microscopic findings' refers to histo-morphological assessment.
Predictive factor	A *predictive factor* is a measurement that is associated with response or lack of response to a particular therapy.
Prognostic factor	A *prognostic factor* is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy. It can be thought of as a measure of the natural history of the disease.
Provisional staging	Pathological stage is optimally assigned in a multidisciplinary setting. The pathologist can provide relevant information for determining stage prior to the multidisciplinary team meeting, to assist with clinical decision making.
Standard	Standards are mandatory, as indicated by the use of the term 'must'. Standards are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the NHMRC levels of evidence[79] document). In rare circumstances, where level III-2 evidence is not available an element may be made a Standard where there is unanimous agreement in the expert committee. An appropriate staging system e.g., Pathological Tumour-node-metastasis (TNM) staging would normally be included as a required element. These elements must be recorded and at the discretion of the pathologist included in the pathology report according to the needs of the recipient of the report. The summation of all standards represents the minimum dataset for the cancer. In RCPA protocols, standards are prefixed with 'S' and numbered consecutively within each chapter (e.g., S1.02).
Structured report	A report format which utilises standard headings, definitions and nomenclature with required information.
Synoptic report	A structured report in condensed form (as a synopsis or precis).
Synthesis	Synthesis is the process in which two or more pre-existing elements are combined, resulting in the formation of something new. The Oxford dictionary defines synthesis as 'the combination of components or elements to form a connected whole'. In the context of structured pathology reporting, synthesis represents the integration and interpretation of information from two or more modalities to derive new information.

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Appendix 5 – Implementation

This appendix provides additional information regarding how the protocol can be implemented in routine pathology practice. Some of the elements described in the protocol will be routinely collected by non-pathologists initially, as part of systematic laboratory procedures to populate the histopathology report.

Reports should incorporate a structured format using standardised headings (e.g., Clinical Information, Macroscopic, Microscopic, Ancillary studies etc). Lengthy narrative style reports lacking any headings or structure, and where critical standard information is difficult to find within slabs of text, is not compliant with SPRC. Free text can be utilised as part of the SPRC format, especially for providing nuance for borderline or difficult cases.

Each protocol includes a reporting proforma and checklist. These outline the elements to be reported and the value lists to be used to record the responses. Elements are categorised as standards or guidelines.

Standards are the mandatory or required minimum for reporting of the specific cancer. All standards must be included in the report. Guidelines are optional and those which are deemed not applicable do not need to be included report. The standard or guideline numbers which appear in the protocol (e.g., S2.03) do not need to be included in the report.

The element names (e.g., Tumour site, Perineural invasion etc) and value list responses (e.g., Positive, Not identified etc) should be used in the report as per the relevant protocol proforma. Formatting in regard to font, spacing, tabulation and sequencing are at the discretion of the laboratory/pathologist.

Additional items for local use may be added to the report.

Demographic information

- Accurate and complete demographic information is critical in the histopathology report. The patient's demographic information is entered or updated during accessioning of the specimen. Laboratory information management systems typically automatically include the demographic information into the report. In this case, it does not need to be repeated within the histopathology report by the pathologist.

Clinical information

- Clinical information is collected by the clinical team and essential information required to inform pathological assessment is often provided with the pathology request form accompanying the specimen.
- This information is typically recorded by staff during accessioning of the specimen or at the point of macroscopic cut-up.

Macroscopic information

- Macroscopic findings are documented during the cut-up procedure or specimen preparation for sectioning. Dictation templates for the reporting of macroscopic data have been published in the Macroscopic Cut-Up Manual.

Microscopic information

- Microscopic findings or the histo-morphological assessment is reported by the pathologist after all key information and slides are provided.

Ancillary studies

- Ancillary findings are reported by the pathologist after initial review of the specimen and once the pathologist is satisfied that the ancillary test meets the relevant quality controls (e.g., when internal or external controls are satisfactory). Subsequent rounds of ancillary tests may be required.

Pathological staging information

- Pathologists report the pathological staging information according to each specimen and the information available. Clinical stage groupings should not be included when there is incomplete information.

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Diagnostic overview

- The diagnostic summary and/or overarching comment is reported by the pathologist according to the needs of each diagnostic case.

Subsequent follow up reports

It is not uncommon for a patient to undergo more than one resection of a cancer; for instance, if the initial margins are involved, or if it recurs following original resection, or for metastases (such as brain metastases). A full structured report may not be appropriate in these cases although the standards relevant to the additional resection need to be included (e.g., completeness of excision). For these cases, reference can be made to the prior structured report.

Compliance at Level 3

In describing the implementation of SPRC in Ontario, Canada, Srigley et al described a spectrum of reporting from traditional narrative reports with no prescribed content or format (Level 1), to fully conformant, structured and encoded information (Level 6).[80]

This approach has been further developed for the Australasian context by the SPRC Project and is described in the RCPA Position Statement on Implementation of Structured Pathology Reporting of Cancer[81] and in the Levels of Structured Pathology Reporting of Cancer infographic.

Compliance at Level 3 will improve the completeness, conciseness, conformity and clarity of cancer reports and requires only that cancer report content complies with the available SPRC published protocols and that a structured or synoptic format is used (though not necessarily using advanced data entry tools). Level 3 is 'entry level' compliance which can be achieved using a simple word processor or text editor and is the simplest form of implementation that does not require investment in new technology.

Therefore, compliance at Level 3 is considered achievable by all and in Australia, the National Pathology Accreditation Advisory Council (NPAAC) considers this to be the minimum level of compliance for reporting of cancers for which published protocols exist.[82]

The implementation of structured reporting at Level 3 provides an excellent foundation for further progress to Level 6. In the course of implementing to Level 3, it is expected that some software-capable organisations will find it easier and more effective to implement at higher levels with the added benefits gained.

A simple Implementation guide and NPAAC compliance FAQs document has been developed to provide guidance to laboratories implementing SPRC to Level 3.

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Appendix 6 – Pre-analytical

This appendix describes the information that should be collected before the pathology test. Some of this information can be provided on generic pathology request forms; any additional information required specifically for reporting may be provided by the clinician on a separate request information sheet. Example request information sheets are also available. Elements which are in bold text are those which pathologists consider to be required information. Those in non-bold text are recommended.

Also included in this appendix are the procedures that are recommended before handover of specimens to the laboratory.

Patient information

S1.01 Adequate demographic and request information must be provided with the specimen.

- Items relevant to cancer reporting protocols include:
    - patient name
    - date of birth
    - sex
    - identification and contact details of requesting doctor
    - date of request
- The patient's ethnicity should be recorded, if known. In particular whether the patient identifies as Aboriginal and/or Torres Strait islander in Australia or Māori in New Zealand. This is in support of a government initiative to monitor the health of those who identify as indigenous, particularly in relation to cancer.
- The patient's health identifiers should be provided.
- The patient's health identifiers may include the patient's Medical Record Number as well as a national health number such as a patient's Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (New Zealand).

Clinical information

S1.02 All clinical information as documented on the request form must be recorded verbatim.

- The request information may be recorded as a single text (narrative) field or it may be recorded atomically.
- Any relevant patient or family history should be provided.
- Any additional relevant information should be recorded.
    - A free text field should be completed by the referring doctor to communicate anything that is not addressed by the above points, such as previous cancers, risk factors, investigations, treatments and family history.

S1.03 The pathology accession number of the specimen must be recorded.

S1.04 The principal clinician involved in the patient's care and responsible for investigating the patient must be recorded.

CS1.04a

The principal clinician should provide key information regarding the clinical presentation of the patient. Follow up may be required with the principal clinician for a number of reasons:

- The clinical assessment and staging may be incomplete at the time of biopsy.

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- The pathology request is often authored by the clinician performing the surgical excision/biopsy rather than the clinician who is investigating and managing the patient.
- The identity of this clinician is often not indicated on the pathology request form

In practice therefore, it is important in such cases that the reporting pathologist should be able to communicate with the managing clinician for clarification.

CS1.04b

The Australian Healthcare identifiers i.e., Healthcare Provider Identifier - Individual (HPI-I) and Healthcare Provider Identifier - Organisation (HPI-O) should be included, where possible, to identify the principal clinician involved in the patient's care.

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Appendix 7 – Specimen Handling and Macroscopic Guidelines

Tissue banking

- Pathologists may be asked to provide tissue samples from fresh specimens for tissue banking or research purposes. The decision to provide tissue should only be made if the pathologist is sure that the diagnostic process including the measurement of maximum depth of invasion and other important parameters that influence patient prognosis and management will not be compromised. As a safeguard, research use of the tissue samples may be put on hold until the diagnostic process is complete.
- If tissue is sampled for banking or research then this should be done in consultation with a pathologist and recorded in the report. It is good practice to specify a paraffin block that is ideal for future ancillary testing or research purposes, if possible.

Specimen imaging

- Detailed fixation and specimen handling instructions are available from the RCPA online Cut-up Manual:

  https://www.rcpa.edu.au/Manuals/Macroscopic-Cut-Up-Manual
- Images of the gross specimen showing the overall conformation of the tumour and showing the relation of the tumour to the resection margins, are desirable, and useful for multidisciplinary meetings.

Specimen handling

- **The specimen must be handled in a systematic and thorough fashion to ensure completeness and accuracy of pathological data.**
  - Specimen reception: Specimens are best received without delay either fresh or in formalin. This allows optimal orientation and sampling of non-fixed tissue e.g., tumour bank, research. Where receipt of fresh specimen is impractical, the specimen should be sent in an adequate volume of formalin (approximately 10 times greater than the tissue volume) depending on local approach.[83]
  - The opened, cleaned specimen should be fixed, at least overnight, in an adequate volume of formalin. Despite the pressure by clinicians on the pathologist for rapid turnaround, adequate fixation and processing of specimens is highly important. Full fixation facilitates obtaining thin transverse slices through the tumour and it has also been shown to increase lymph node yield. Slices can be made into appropriate tissue to aid fixation. The entire specimen should then be placed in an adequate amount of formalin for complete fixation.
  - In addition, the experience of the person cutting up and reporting the specimen, is probably an important determinant of quality pathology, however further studies in this area are warranted.
  - Hormone receptor assays can be performed on paraffin-embedded biopsy material (including excised tissue), cytological smears or cell-block preparations.
  - Published evidence is inconsistent as to which type of specimen yields the most accurate results for hormone receptor assays. Some studies favour excision biopsies,[84,85] while others suggest that core biopsies might provide more reliable hormone receptor estimations than excision biopsies or mastectomies.[86] Institutions that have established protocols for carrying out receptor staining on core biopsy specimens may do so, ensuring that there is representative tumour present with optimal fixation. In acknowledgement of the central importance of hormone receptor status on patient management, when the excision specimen is hormone receptor (ER and PR) negative, laboratories may wish to repeat the hormone receptor assessment on the specimen and also to check the hormone receptors on the core biopsy sample in order to confirm the original findings. In the same vein, if hormone receptor assessment has been undertaken on core biopsies and has been found to be negative, this assessment should be repeated on the resection specimen to avoid a false negative result. Core biopsies must be assessed for biomarkers when the patient is a candidate for neoadjuvant chemotherapy or there are severe fixation and processing issues with the excised specimen.

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- Hormone receptor assays can be performed on cytologic specimens.[87]
- Fixation for 24 hours will achieve optimal results for both small samples (e.g., core biopsies) and larger samples (e.g., excision biopsy), because formalin fixation is a time-dependent chemical reaction which proceeds at a similar rate in both cases. Short fixation times (e.g., <6–8 hours) are likely to compromise hormone receptor assay results.[85]
- Hormone receptor staining may be compromised by fixation in hot formalin or fixatives other than 10% neutral buffered formalin.
- Immunoreactivity may also be impaired by prolonged formalin fixation (possibly only extreme fixation times),[85,88] but this risk is rarely relevant, given clinical imperatives for rapid reporting.

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Appendix 8 – Copyright and Disclaimer

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