

# POST-NEOADJUVANT BREAST PATHOLOGY

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## Current Concepts & Controversies

June 2026

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# Objectives

- Review the role and indications of neoadjuvant therapy (NAT) in breast cancer
- Recognize key post-treatment gross and microscopic changes
- Understand principles of post-NAT pathological assessment and reporting
- Compare AJCC staging with the Residual Cancer Burden (RCB) system

# Article

Human Pathology 162 (2025) 105825



Contents lists available at [ScienceDirect](#)

Human Pathology

journal homepage: [www.elsevier.com/locate/humpath](http://www.elsevier.com/locate/humpath)

Human  
PATHOLOGY

Current concepts and controversies in post-neoadjuvant breast pathology



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## Discussion Points

Pre-treatment Core Biopsy → Neoadjuvant Therapy → Surgery → Gross and Microscopic Evaluation → Adjuvant therapy

# Background

- Neoadjuvant systemic therapy has become standard of care for high-risk early breast cancer
- Pathologic complete response (pCR) = No residual invasive carcinoma in breast or LNs (ypT0/Tis ypN0) → Improved overall survival

# NAT: *What?*

- NACT
  - Various regimes – *Beyond the scope of discussion*
- NET
  - For ER-positive, HER2-negative breast cancers
  - Aromatase inhibitors are preferred, combined with ovarian suppression in premenopausal patients
  - pCR rates are generally low

# NAT: *Why?*

- Allows assessment of tumour response to treatment
  - Response provides prognostic information
- Reduces local disease burden
  - Converts inoperable tumours into surgical candidates
  - Facilitates breast-conserving surgery

# NAT: *Who?*

- Typically for HER2-positive and triple-negative breast cancers that are  $\geq 2$  cm in size ( $\geq$ cT2) or lymph node positive ( $\geq$ cN1)
- However, NAT can be used regardless of hormone receptor or HER2 status if:  
Tumour is large relative to size of breast in patients desiring breast conservation, or if surgery is delayed
- Bulky or matted axillary nodes (cN2, cN3)

# Pre-treatment Biopsy: Pathologist's Role

- Histologic subtype
  - Certain subtypes have favourable prognoses → Systemic therapy is often not indicated
  - *Tubular, cribriform, mucinous, most salivary gland-like CAs, low-grade forms of metaplastic CA*
- Provisional grade
  - NAT can alter tumour cytomorphology and grade
  - Provisional grade on CNB is of uncertain significance in the post-treatment setting
- Prognostic and predictive markers (ER/PR/HER2)
  - Highest pCR rates: HER2-positive breast cancer or TNBC (up to 65%)
  - Lowest pCR rates: ER-positive HER2-negative cancers or when neoadjuvant endocrine therapy is used

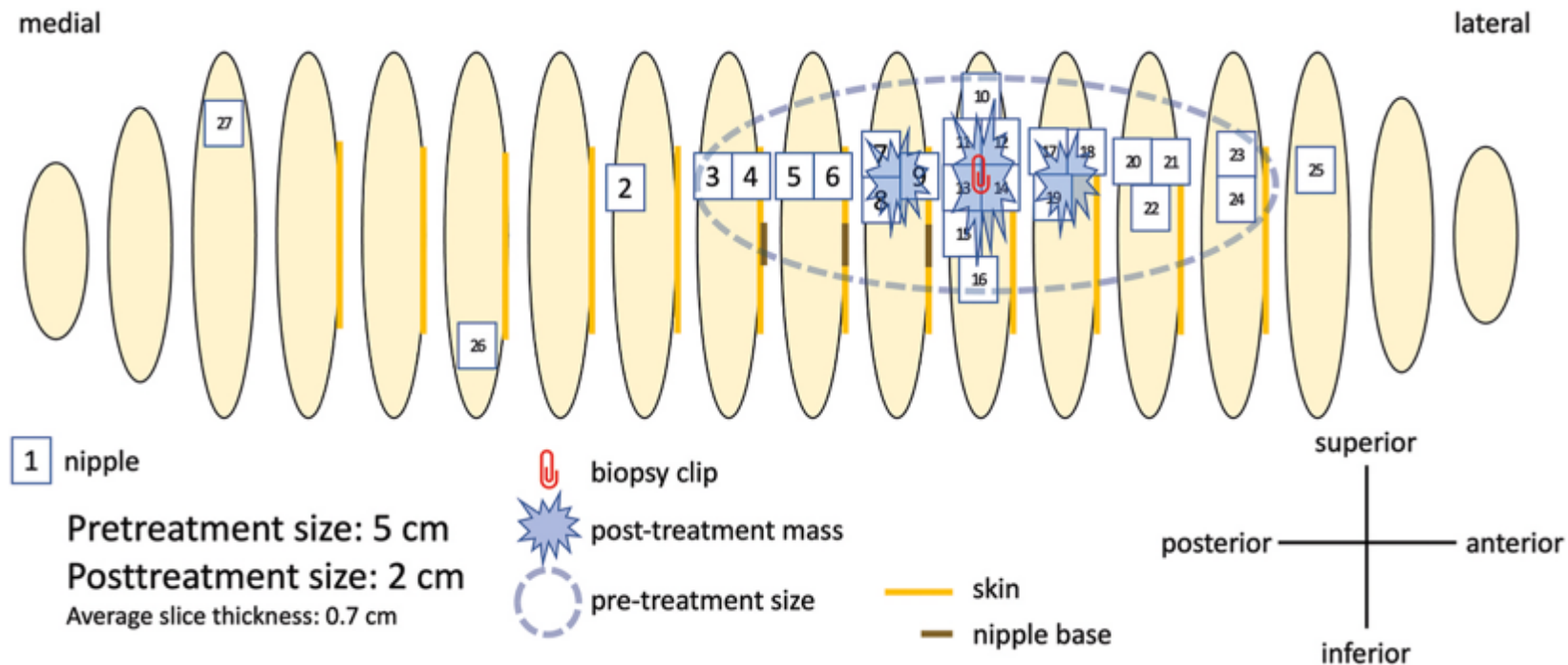
# Intraoperative Consult

- Treatment-related changes complicate the assessment of LN metastases
- Common pitfalls include...
  - Tumour resembling histiocytes
  - Foreign body-type giant cells
  - Lobular carcinoma

# Gross Evaluation

- Integrate clinical information, pre- and post-treatment imaging, biopsy clips / localisation devices
- Pre-treatment tumour size and location guides sampling
- **If tumour is identified:** Sample the residual lesion & surrounding tissue spanning the pre-treatment tumour extent
- **If no tumour is identified:** Sample tumour bed around the original tumour site or where there are biopsy clips
  - Specimen mapping can be helpful

# Gross Evaluation



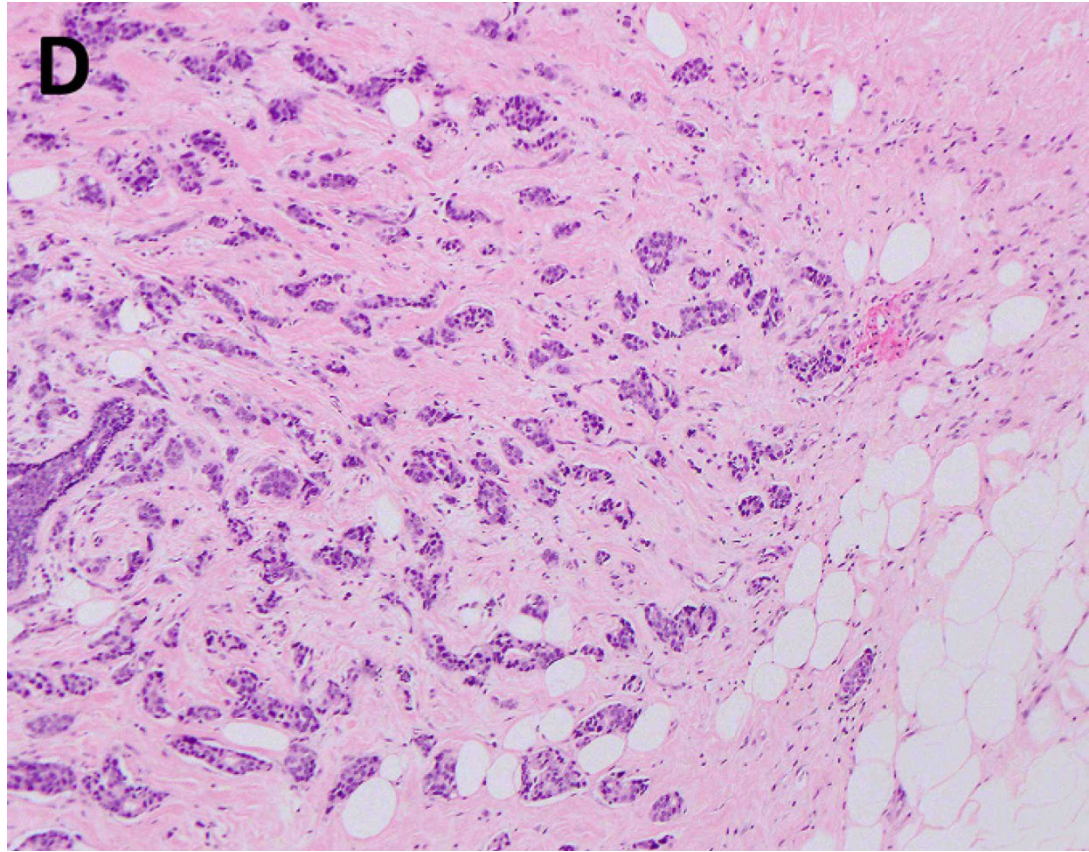
# Microscopic Evaluation

1. Histological alterations (post-treatment changes)
2. Reporting

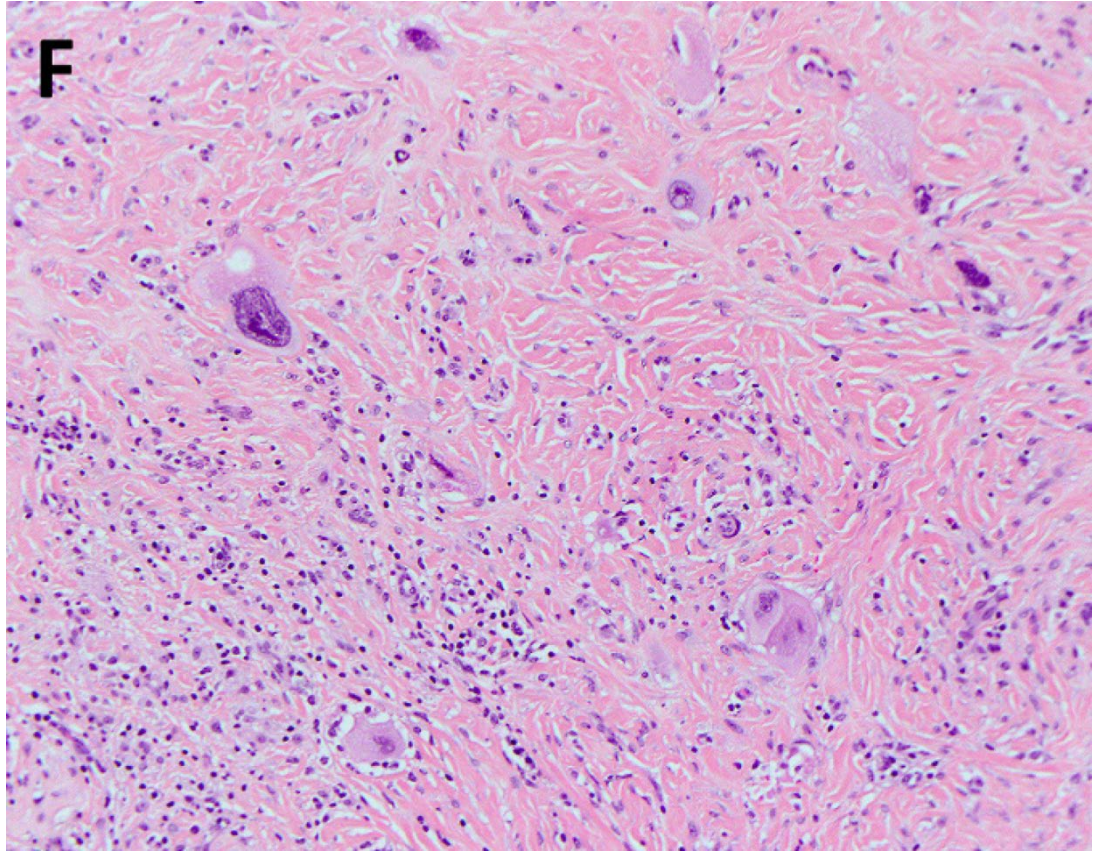
# Post-treatment Changes – Tumour Cells

- **More prominent**
  - Nuclear enlargement, multinucleation, pleomorphism
  - Abundant cytoplasm – Hyper-eosinophilic, vacuolated, cleared
  - NACT tends to increase the tumour cell size
- **More inconspicuous**
  - Cellularity may be reduced
  - Can resemble histiocytes

# Post-treatment Changes – Tumour



Reduced cellularity

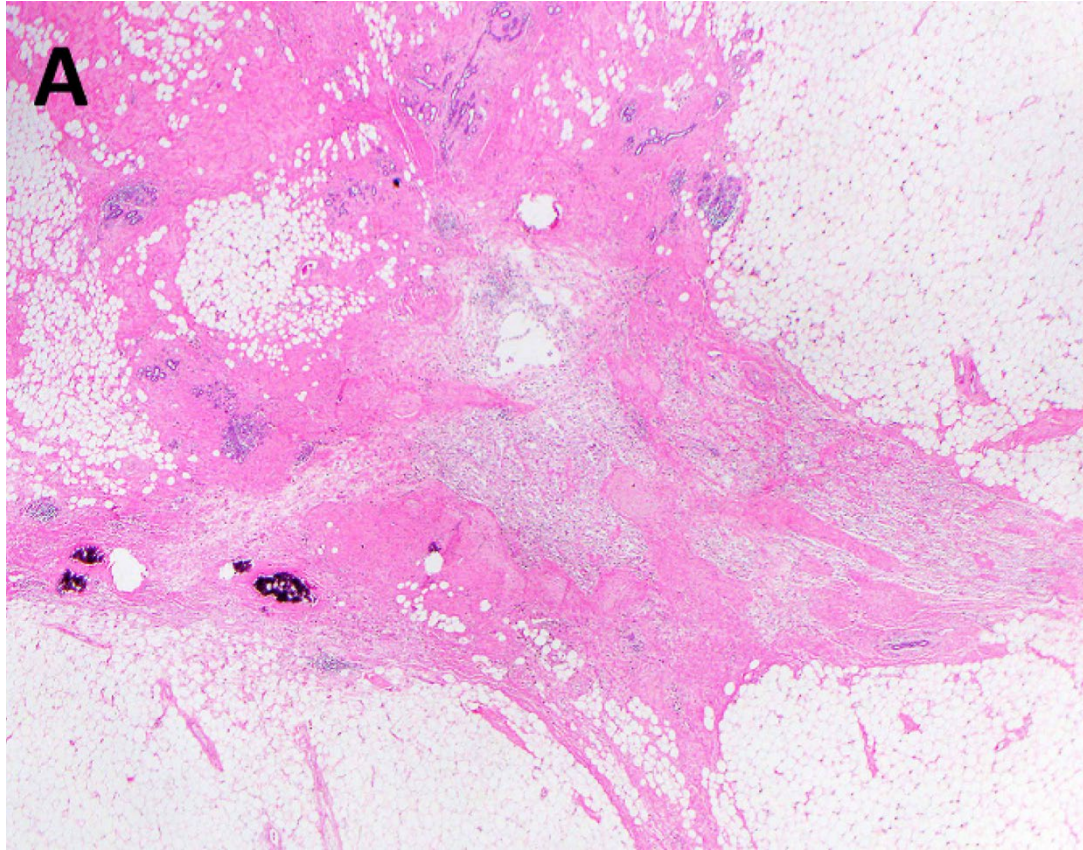


Low cellularity; prominent tumour cells

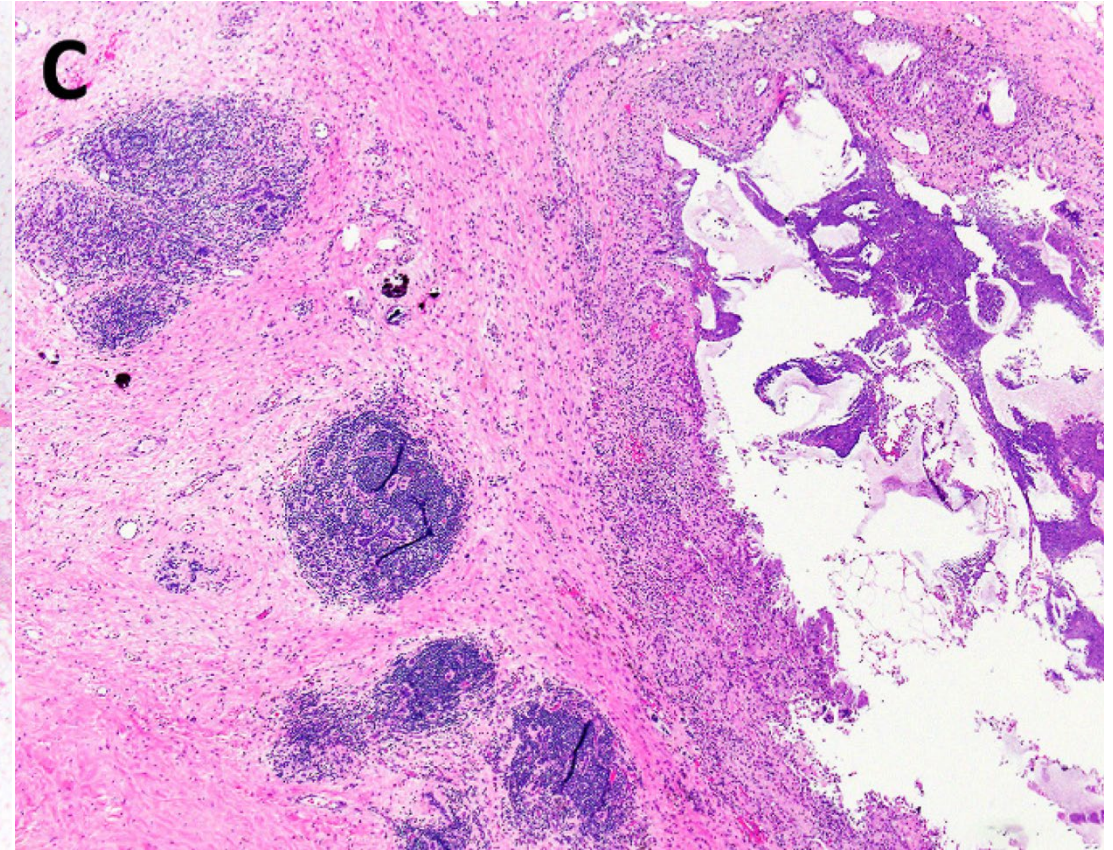
# Post-treatment Changes – Stroma

- Fibrosis
- Edema / myxoid change
- Extensive necrosis
- Haemosiderin deposition
- Chronic inflammation, foamy / haemosiderin-laden macrophages, multinucleated giant cells
- Calcifications
- Paucity of benign breast epithelial elements
- Increased vasculature
- Stromal retraction artifact around tumour can simulate LVI

# Post-treatment Changes – Stroma

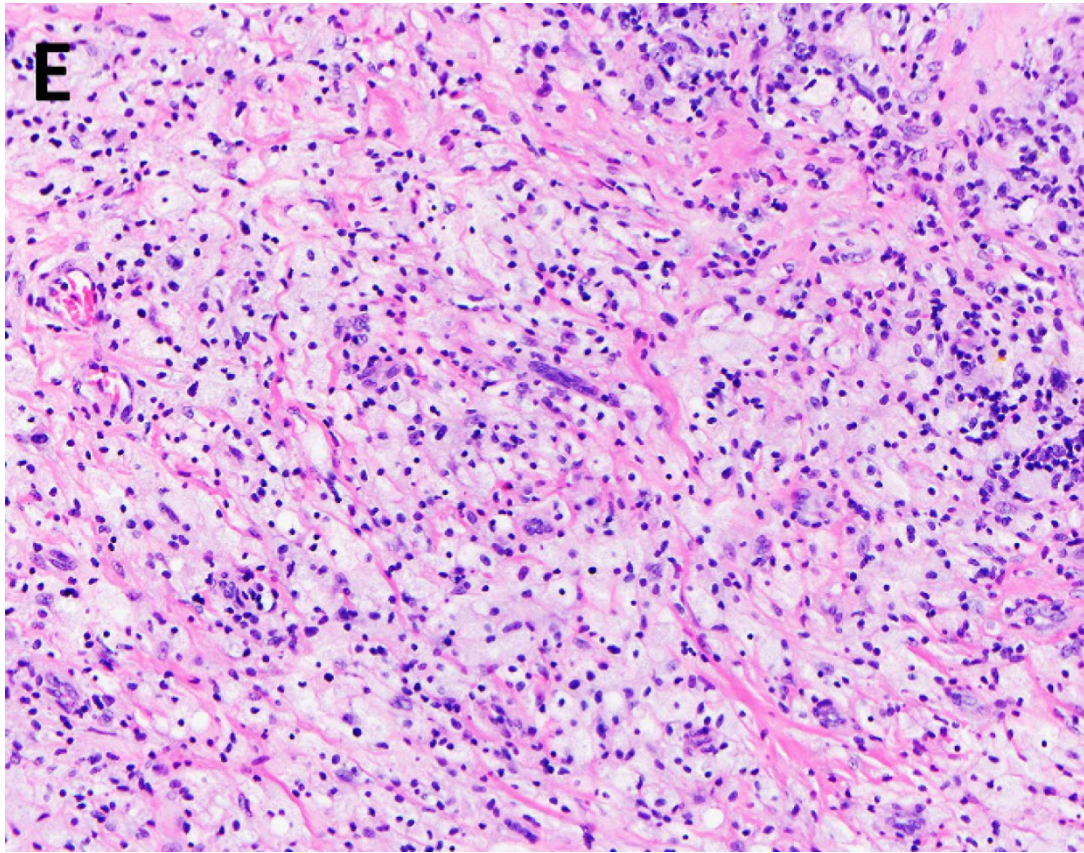


Fibrosis, histiocytes, calcifications

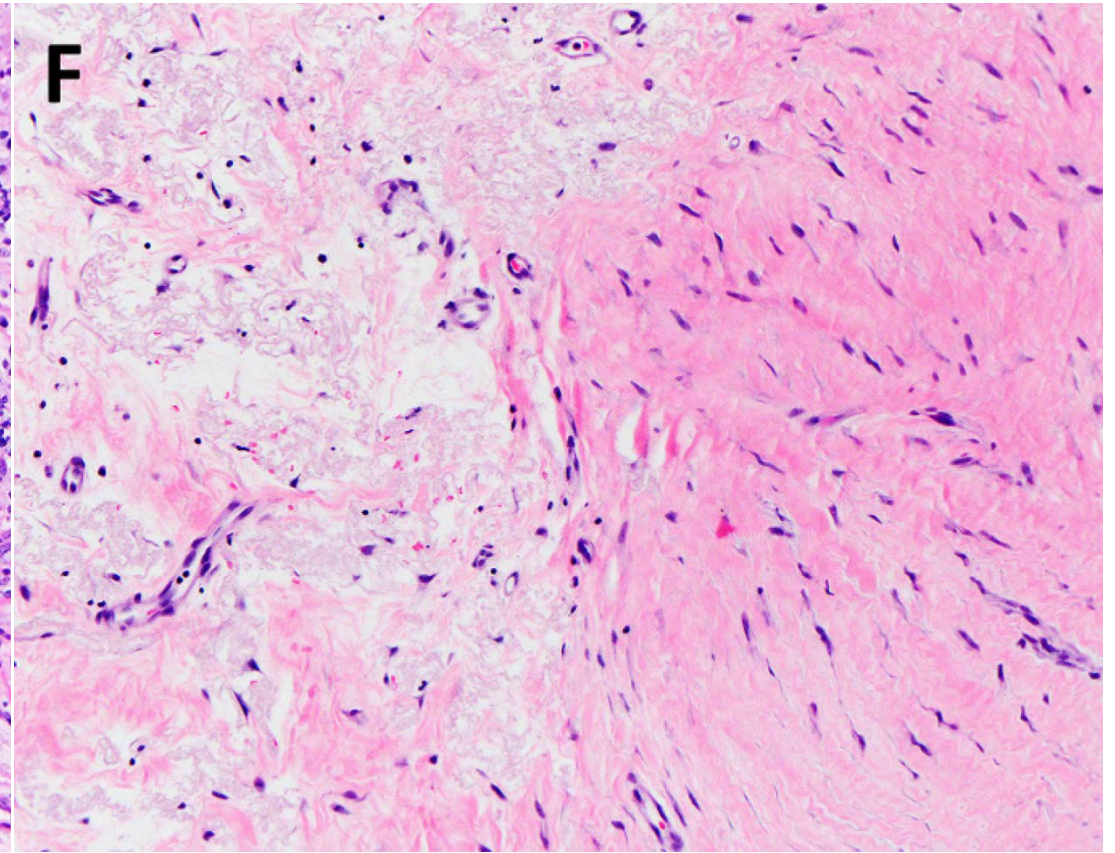


Lymphocytes; biopsy site changes

# Post-treatment Changes – Stroma



Lymphohistiocytic infiltrate



Fibrosis, myxoid change

# Reporting

- Histological subtype
- Repeat grading
- **CAP:** Checklist is not required if no cancer is present in the specimen

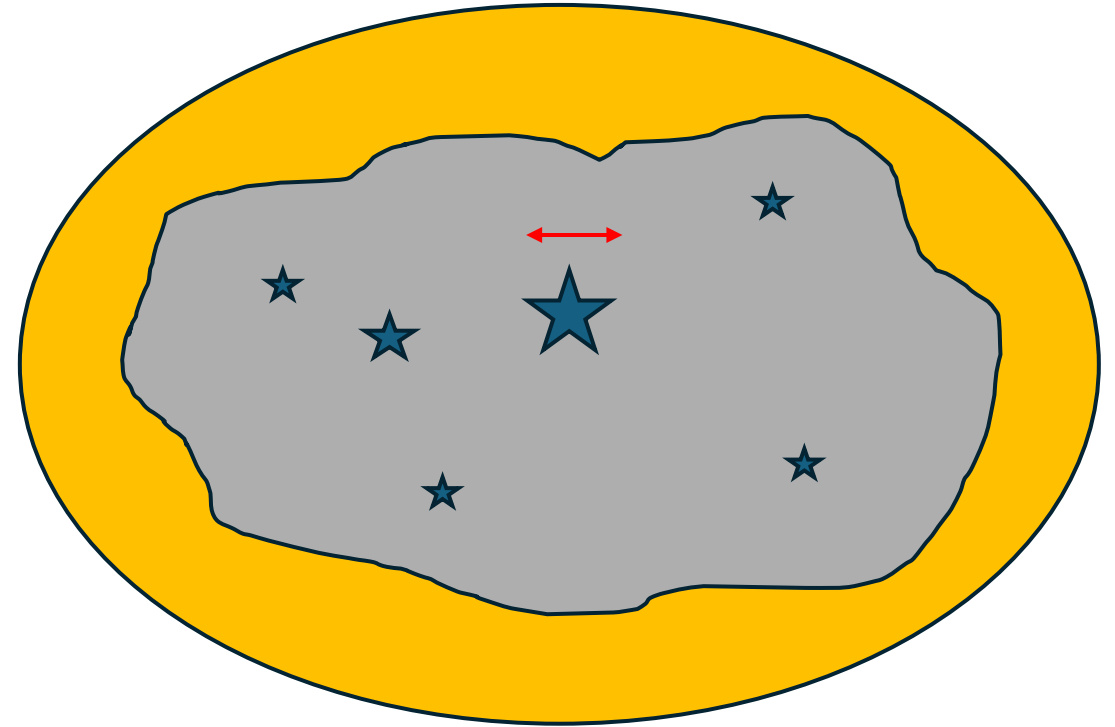
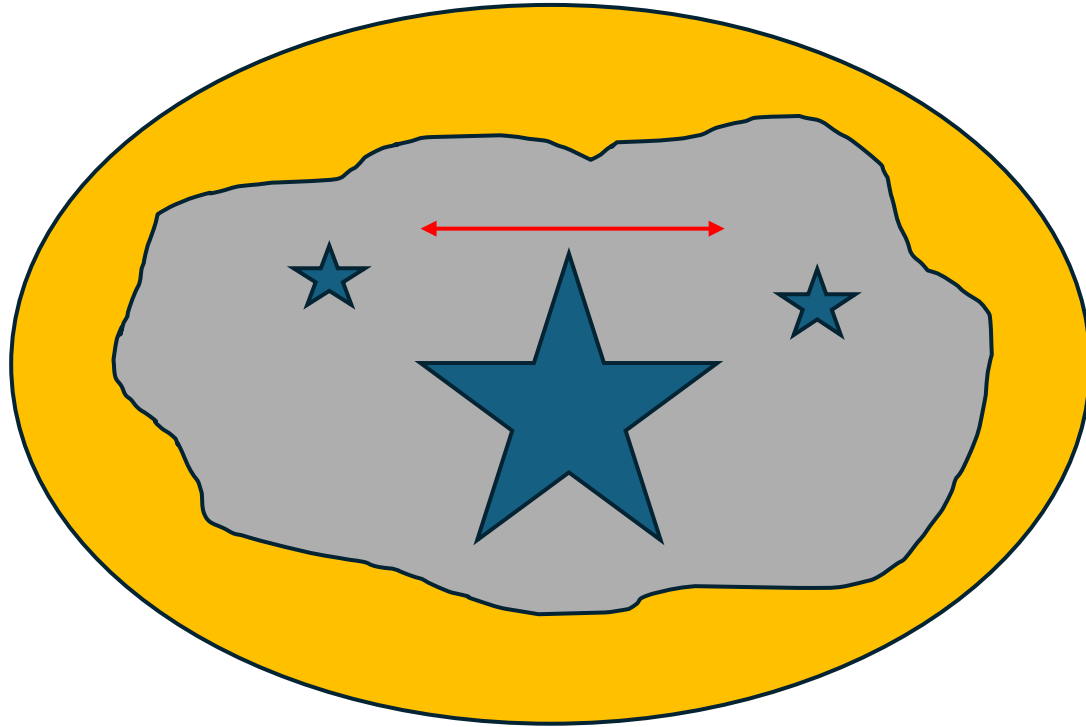
# Reporting

- Most widely used systems for reporting the extent of residual breast cancer
  - AJCC
  - Residual Cancer Burden (RCB)

# AJCC (8<sup>th</sup> Ed)

- pCR = No residual carcinoma
- ypT & ypN categories
  - Size of largest contiguous focus of invasive carcinoma excluding intervening treatment-related fibrosis
  - “Contiguous” is defined as cells that are touching each other with no fibrosis in between; much inter- and intra-observer variability
- “m” modifier indicates multiple foci of invasive disease (non-contiguous)
  - **Practical challenge:** Treatment response with reduced tumour cellularity can result in multiple small foci / dispersed single cells of residual carcinoma within a larger tumour bed
  - *Offered solution: Use RCB or report distance over which tumour foci extend, the number of tumor foci present, or the number of slides/blocks in which tumour appears*

# AJCC



?

-  Breast tissue
-  Fibrosis
-  Residual Tumour

# RCB

- Parameters
  - Breast
    - Size of tumour bed (includes post-treatment fibrosis)
    - Tumour cellularity (%) within tumour bed
    - % of tumour that is DCIS (*to be subtracted*)
  - Lymph node
    - Number of involved lymph nodes
    - Largest lymph node deposit (includes post-treatment fibrosis)
- Use online calculator
- **CAP guidelines:** RCB is not validated or designed for **neoadjuvant endocrine treatment** → RCB Score should not be reported



Estimates volume of tumour

# Residual Cancer Burden Calculator

\*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

Primary Tumor Bed Area:

(mm) X (mm)

Overall Cancer Cellularity (as percentage of area):

(%)

Percentage of Cancer That Is *in situ* Disease:

(%)

(2) Lymph Nodes

Number of Positive Lymph Nodes:

Diameter of Largest Metastasis:

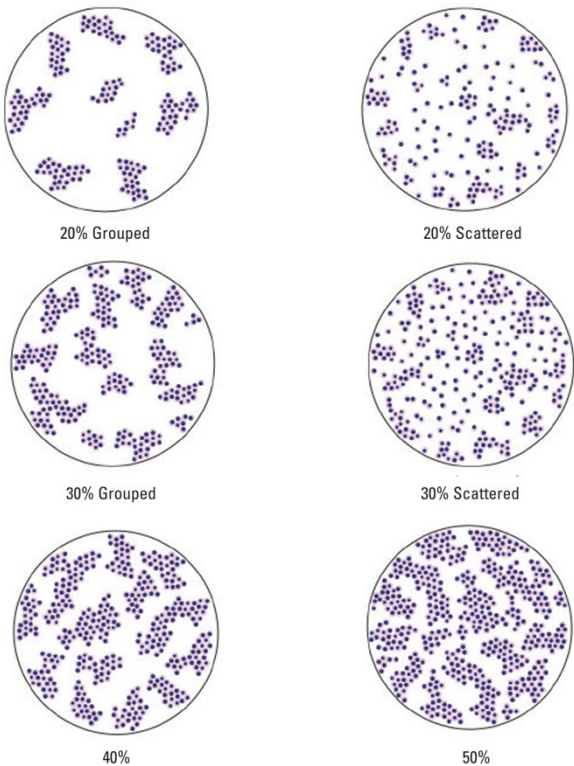
(mm)

Reset

Calculate

Residual Cancer Burden:

Residual Cancer Burden Class:



# RCB

|                               |                      |
|-------------------------------|----------------------|
| Residual Cancer Burden:       | <input type="text"/> |
| Residual Cancer Burden Class: | <input type="text"/> |

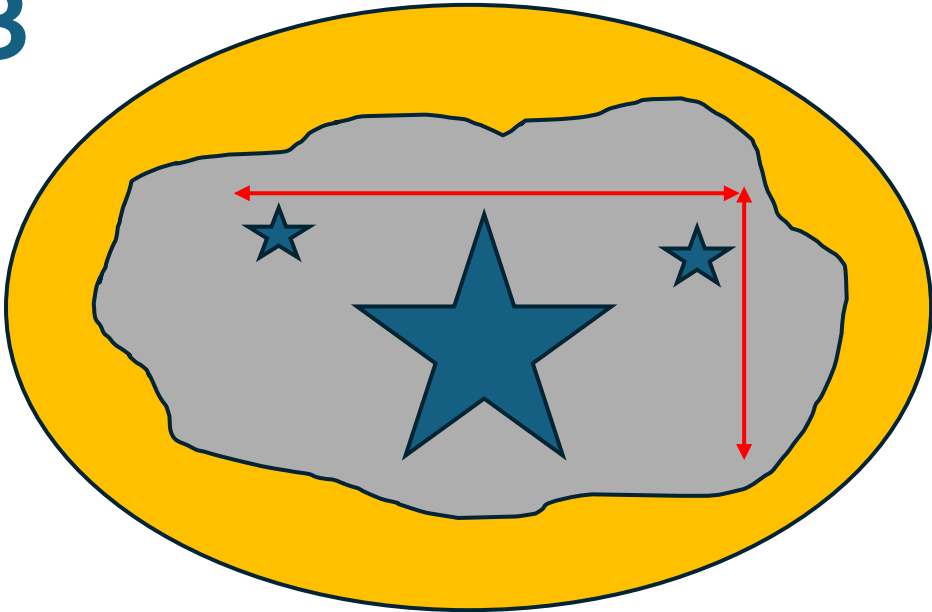
- RCB scores are classified into classes: *0, I, II, III*
  - *RCB-0* = No residual invasive carcinoma in the breast or lymph nodes *or* residual DCIS only with negative lymph nodes

| RCB Class | Cut-offs    |
|-----------|-------------|
| 0 (PCR)   | 0           |
| I         | 0 – 1.36    |
| II        | 1.37 – 3.28 |
| III       | >3.28       |

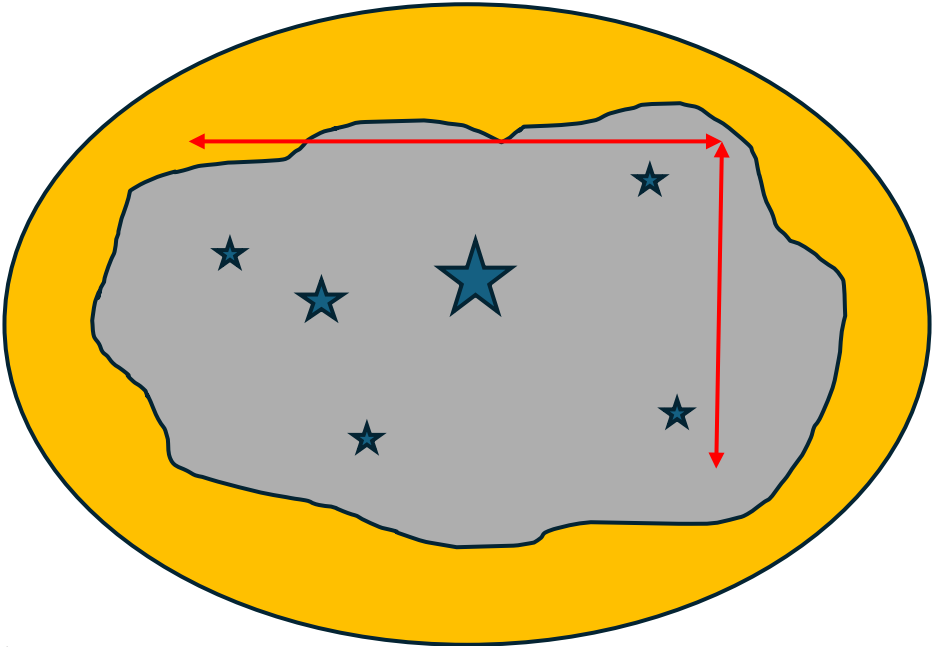


Worse outcomes across all receptor subtypes and treatment regimens

# RCB

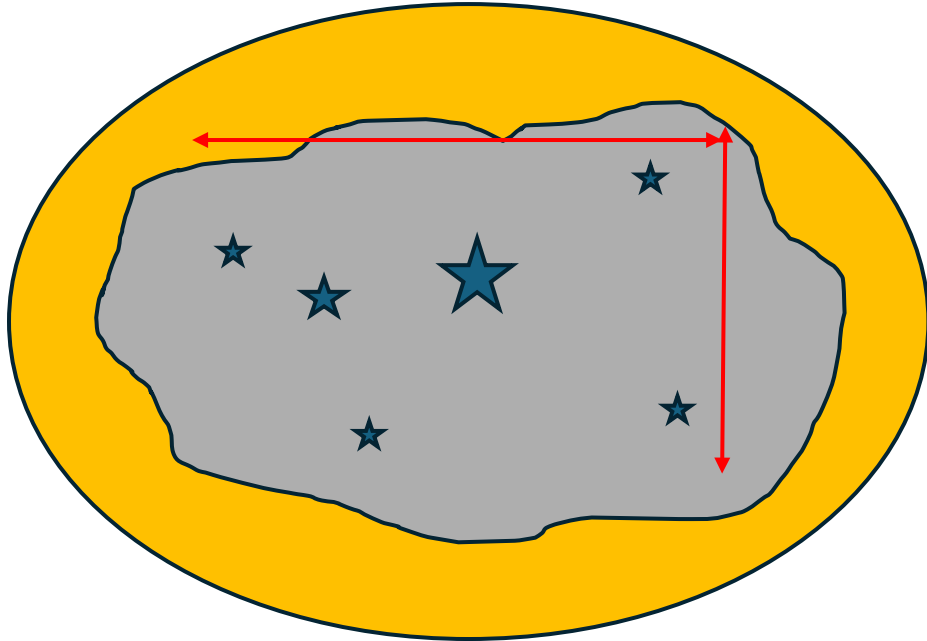


|                                                      |                   |
|------------------------------------------------------|-------------------|
| (1) Primary Tumor Bed                                |                   |
| Primary Tumor Bed Area:                              | 30 (mm) X 15 (mm) |
| Overall Cancer Cellularity (as percentage of area):  | 40 (%)            |
| Percentage of Cancer That Is <i>in situ</i> Disease: | 0 (%)             |
| (2) Lymph Nodes                                      |                   |
| Number of Positive Lymph Nodes:                      | 0                 |
| Diameter of Largest Metastasis:                      | 0 (mm)            |
| <div>Reset Calculate</div>                           |                   |
| Residual Cancer Burden:                              | 2.014             |
| Residual Cancer Burden Class:                        | RCB-II            |



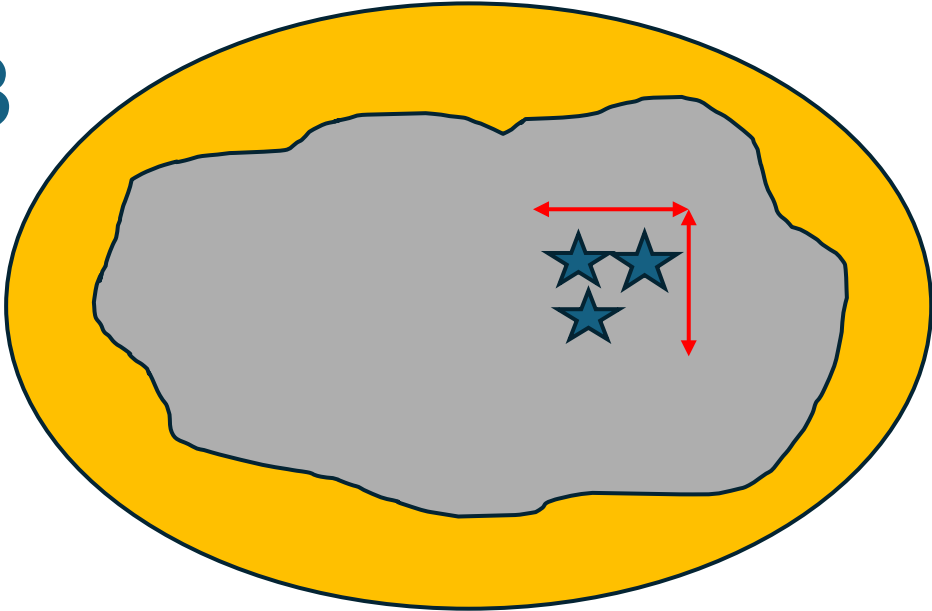
|                                                      |                   |
|------------------------------------------------------|-------------------|
| (1) Primary Tumor Bed                                |                   |
| Primary Tumor Bed Area:                              | 30 (mm) X 15 (mm) |
| Overall Cancer Cellularity (as percentage of area):  | 15 (%)            |
| Percentage of Cancer That Is <i>in situ</i> Disease: | 0 (%)             |
| (2) Lymph Nodes                                      |                   |
| Number of Positive Lymph Nodes:                      | 0                 |
| Diameter of Largest Metastasis:                      | 0 (mm)            |
| <div>Reset Calculate</div>                           |                   |
| Residual Cancer Burden:                              | 1.704             |
| Residual Cancer Burden Class:                        | RCB-II            |

# RCB – Highly weighted towards LN status



|                                                                               |                                                                             |
|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| <i>(1) Primary Tumor Bed</i>                                                  |                                                                             |
| Primary Tumor Bed Area:                                                       | <input type="text" value="30"/> (mm) X <input type="text" value="15"/> (mm) |
| Overall Cancer Cellularity (as percentage of area):                           | <input type="text" value="15"/> (%)                                         |
| Percentage of Cancer That Is <i>in situ</i> Disease:                          | <input type="text" value="0"/> (%)                                          |
| <i>(2) Lymph Nodes</i>                                                        |                                                                             |
| Number of Positive Lymph Nodes:                                               | <input type="text" value="3"/>                                              |
| Diameter of Largest Metastasis:                                               | <input type="text" value="7"/> (mm)                                         |
| <input type="button" value="Reset"/> <input type="button" value="Calculate"/> |                                                                             |
| Residual Cancer Burden:                                                       | <input type="text" value="3.31"/>                                           |
| Residual Cancer Burden Class:                                                 | <input type="text" value="RCB-III"/>                                        |

# RCB



(1) Primary Tumor Bed

Primary Tumor Bed Area:

10

(mm)

X

10

(mm)

Overall Cancer Cellularity (as percentage of area):

80

(%)

Percentage of Cancer That Is *in situ* Disease:

0

(%)

(2) Lymph Nodes

Number of Positive Lymph Nodes:

0

Diameter of Largest Metastasis:

0

(mm)

Reset

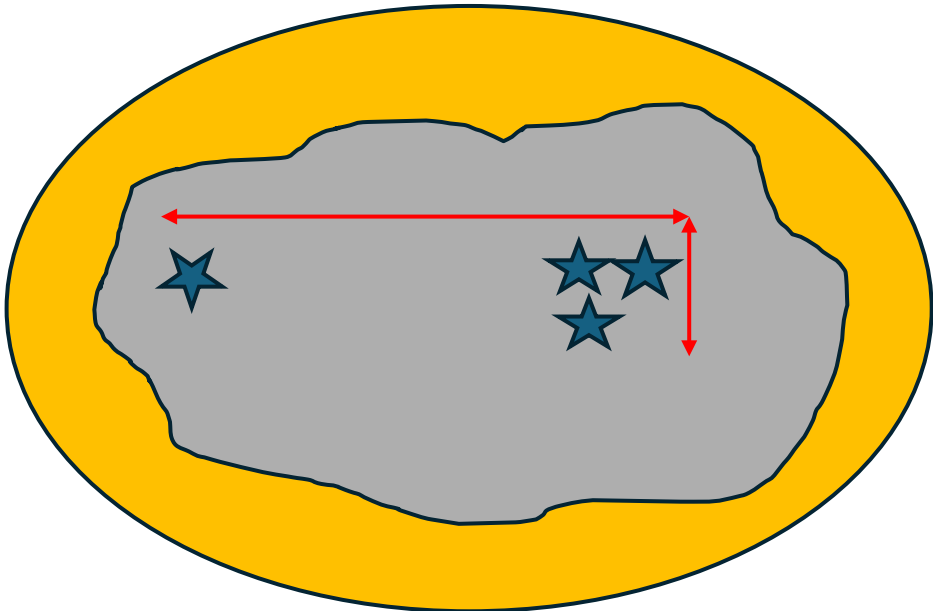
Calculate

Residual Cancer Burden:

1.994

Residual Cancer Burden Class:

RCB-II



(1) Primary Tumor Bed

Primary Tumor Bed Area

Largest Dimension 1 × Largest Dimension 2

40

(mm)

×

10

(mm)

Overall Cancer Cellularity (as percentage of area)

20

(%)

Percentage of Cancer That Is *in situ* Disease

0

(%)

(2) Lymph Nodes

Number of Positive Lymph Nodes

0

(%)

Diameter of Largest Metastasis

0

(mm)

Reset

Calculate

Results

Residual Cancer Burden

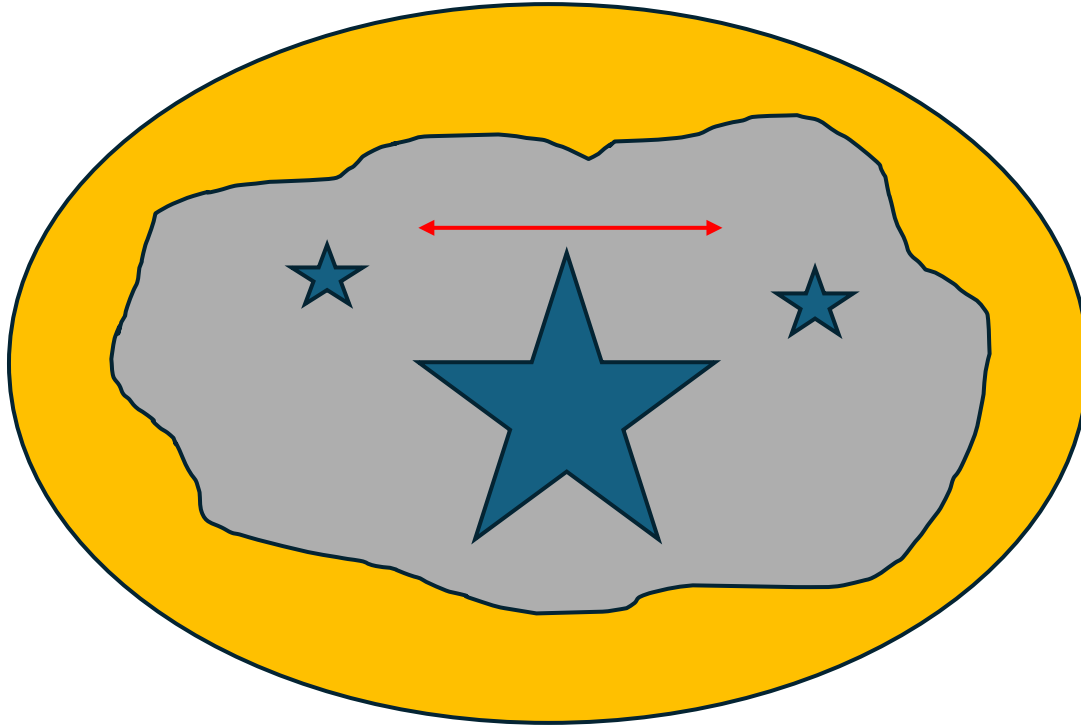
1.772

Residual Cancer Burden Class

RCB-II

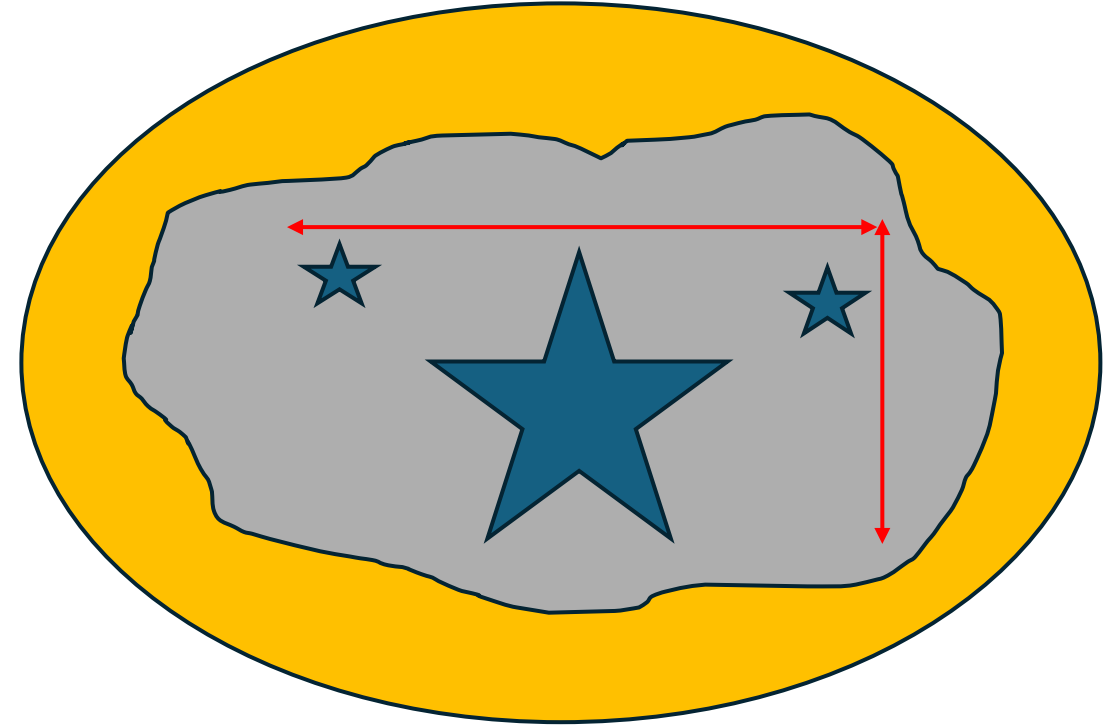
Pathweb, Department of Pathology, NUHS

# Summary – AJCC vs. RCB



**AJCC**

Largest contiguous focus excl. fibrosis



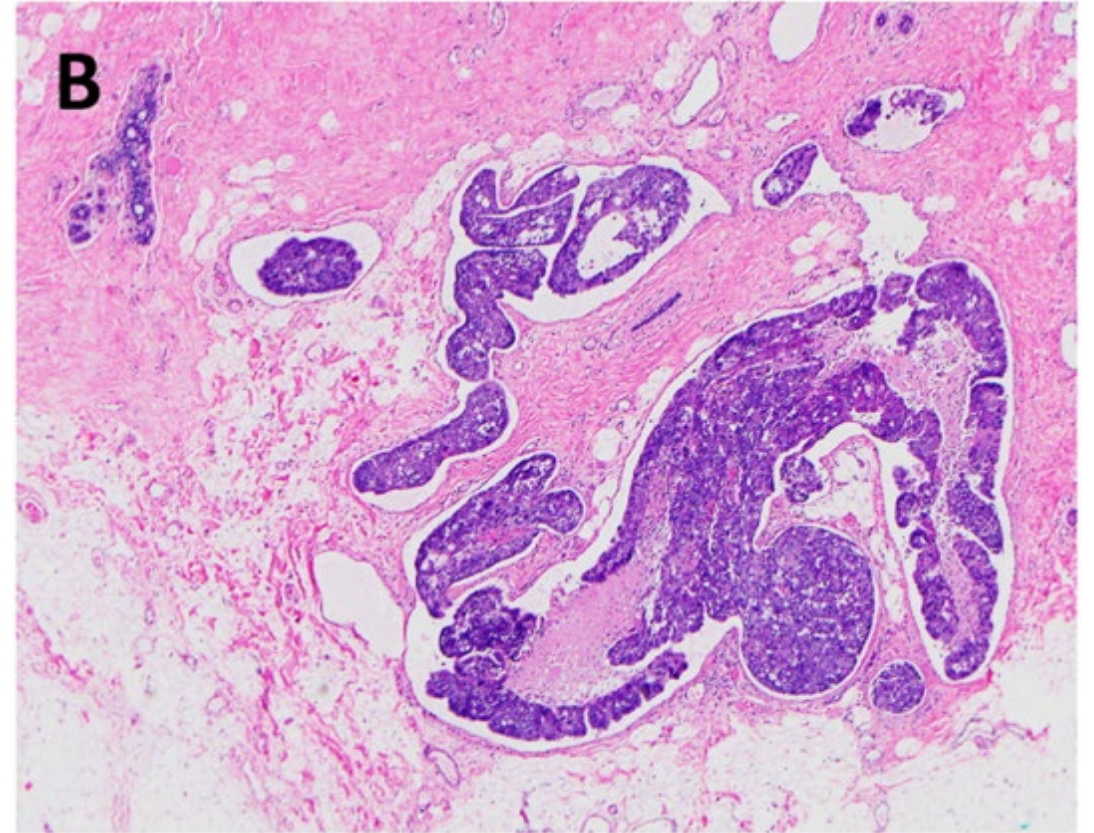
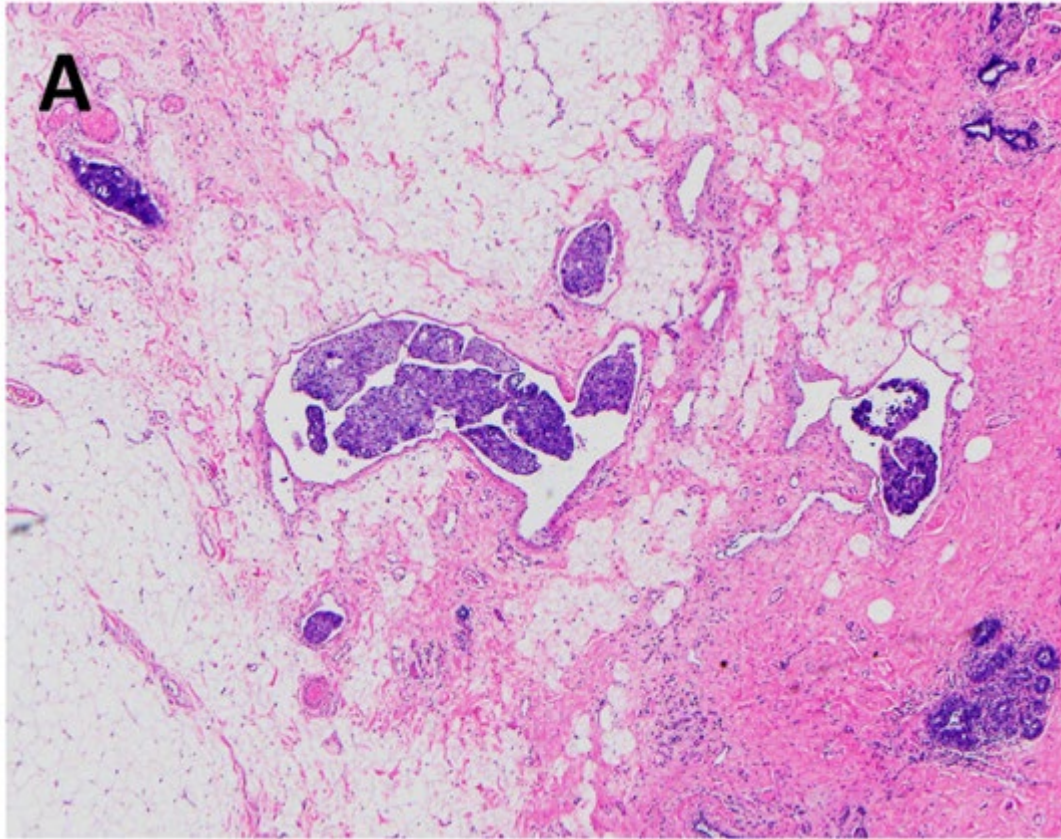
**RCB**

- Tumour bed incl. fibrosis
- % of residual tumour

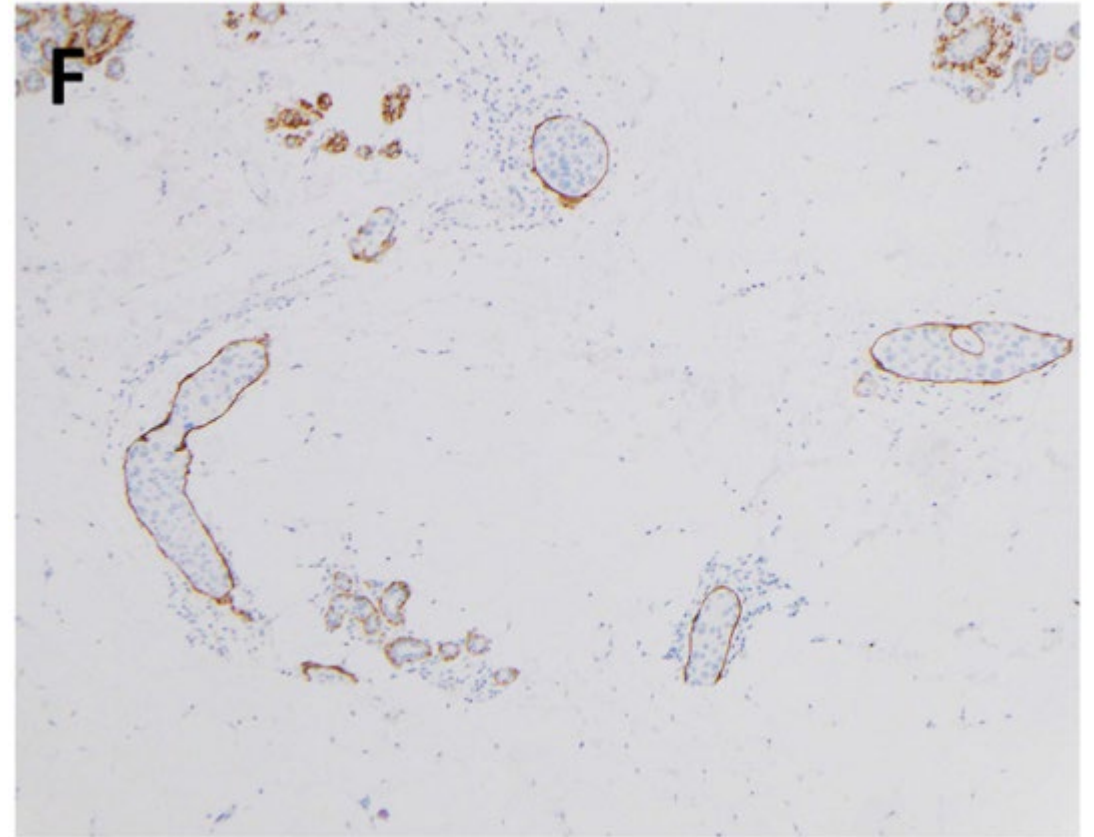
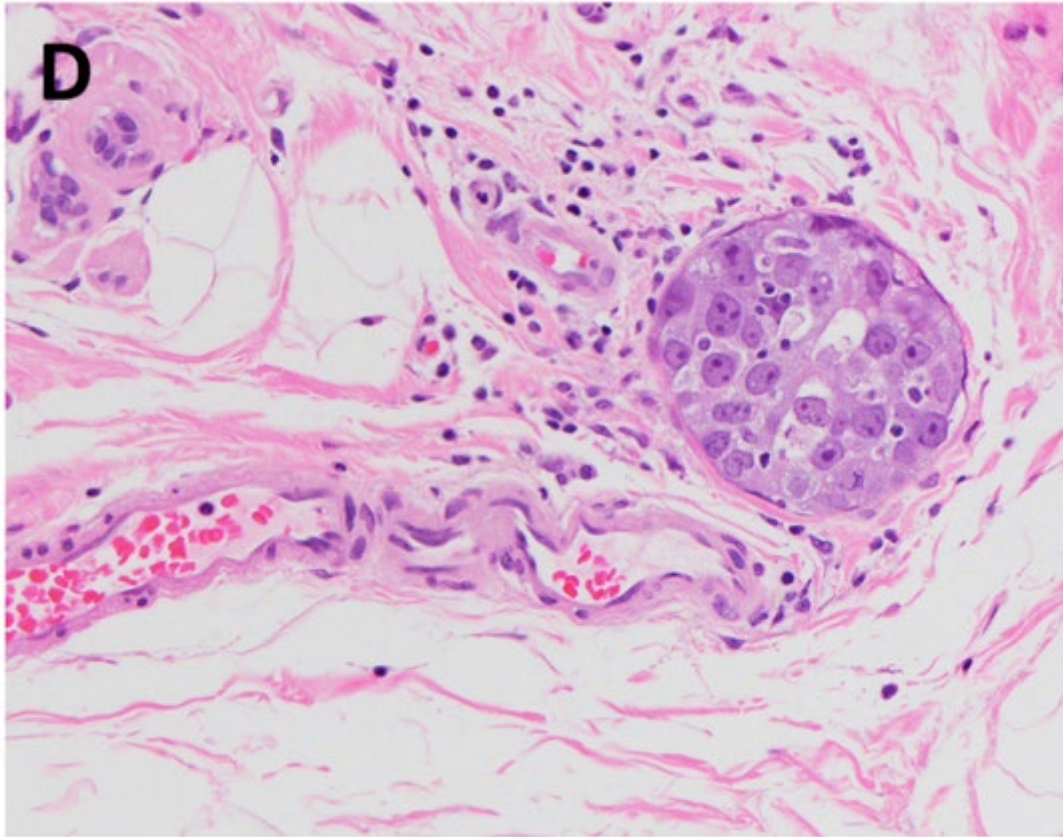
# LVI only

- Dilated spaces containing tumour can be recognised on H&E
- Mimics residual DCIS
  - Important distinction since DCIS is considered pCR
  - D2-40 & myoepithelial markers can help to distinguish

# LVI only



# LVI only



D2-40

# Breast markers after NACT

- Most tumours retain the same (pre-treatment) ER/PR/HER2 profile
- Sometimes discordant
  - Most common is PR (+) → (−)
  - HER2 (+) → (−); especially after neoadjuvant trastuzumab therapy

# Breast markers after NACT

- No widely accepted consensus on when to repeat biomarker testing after NAT
- NUH: Not repeated unless requested
- **Suggested practice (CAP)** – Repeat testing if...
  - Initially negative (or low-positive) biomarkers
  - Tumour has different histologic appearance

# Take-home Messages

- Accurate post-NAT assessment requires correlation with clinical, imaging, and gross findings
- Treatment-related changes can significantly alter tumour morphology and create diagnostic pitfalls
- AJCC and RCB assess residual disease differently and provide complementary information
- Lymph node status remains a major determinant of prognosis and residual disease burden
- Recommendations are evolving with developing research in the field