Pathology Workup for Early Breast Cancer Diagnosis and Evaluation Neoadjuvant Therapy

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Anatomical Pathology

Optimal Early Breast Cancer Diagnosis and Management

October 26th 2024

For Healthcare professional Only

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Disclaimer

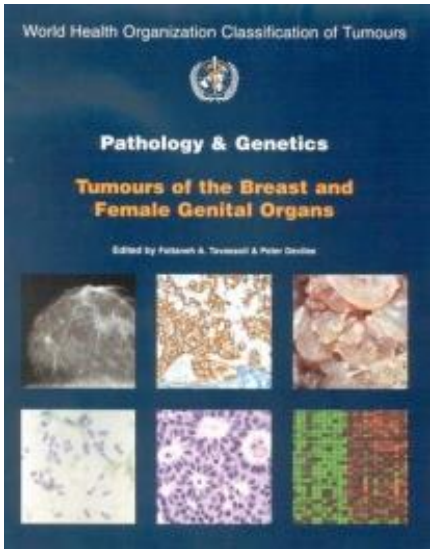
- These educational sessions are conducted for scientific educational purpose, they may contain information relating to products not yet approved by BPOM, or contain information that is not within the current product label.
- These materials are intended only for healthcare professionals

Outline of This Presentation

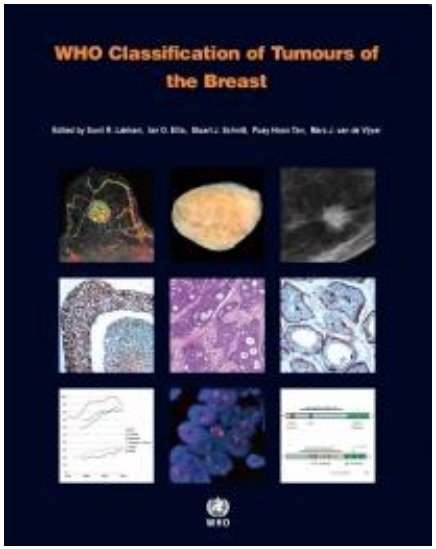
- Epidemiology of breast cancer
- Early breast cancers (EBC) overview
- Biomarkers in breast cancers
- Neoadjuvant therapy
- Pathologic evaluation
- Summary

But first some history …

3rd Edition,
2003
110 pages



4th Edition,
2012
236 pages



5th Edition,
2019
356 pages

Explosion of knowledge!!!
The Explosion of Medical Information

WHO Classification of Breast Tumor (2019)

- Morphological subtypes based on H&E slide
- therapy relevant subtypes (ER and HER2 status)
- Pathologic evaluation post NAC specimens
- Updates in defining and testing HER2
- Tumor-infiltrating lymphocytes (TILs)
- Programmed death-ligand testing 1 (PD-L1) testing

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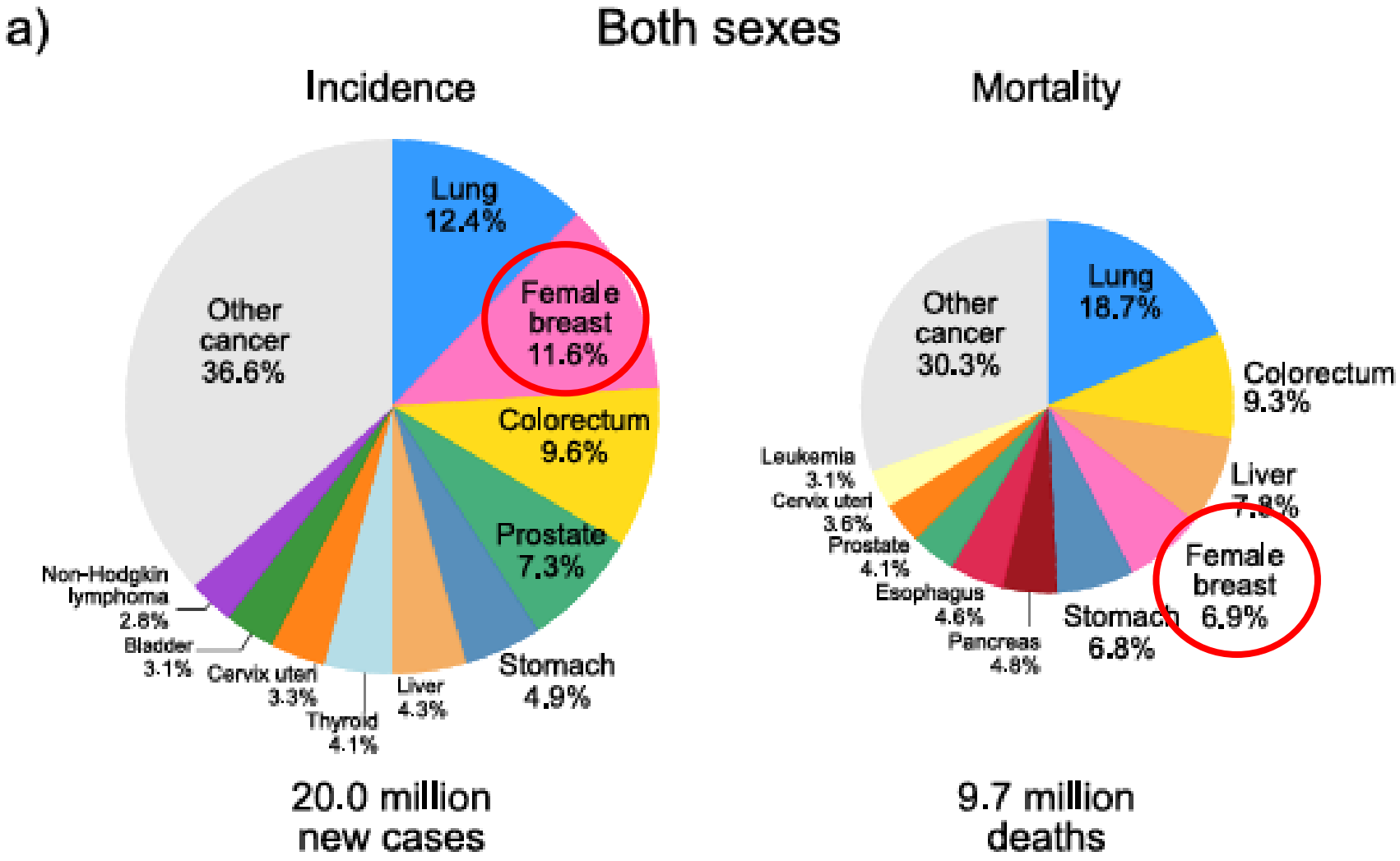
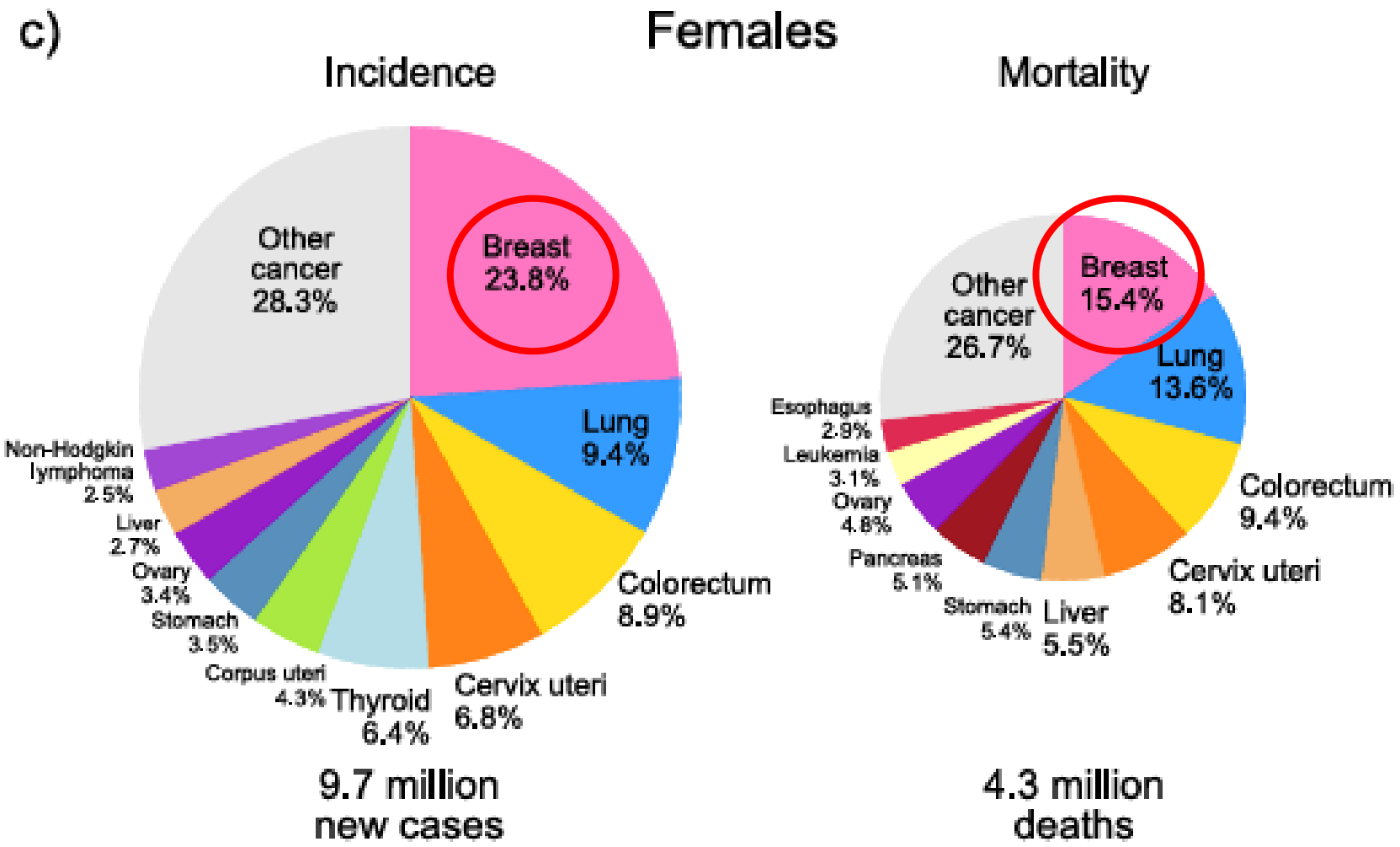
Epidemiology of Breast Cancer



Bray et al. CA Cancer J Clin. 2024;74:229–263

Epidemiology of Breast Cancer

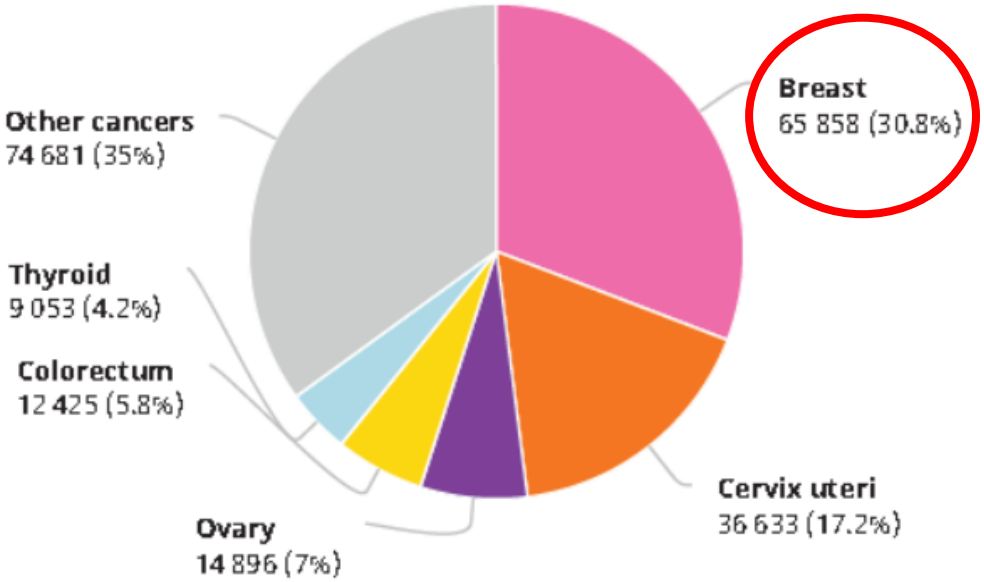


Bray et al. CA Cancer J Clin. 2024;74:229–263

Epidemiology of Breast Cancer

Indonesia

Number of new cases in 2020, females, all ages



360-indonesia-fact-sheets.pdf (iarc.fr)

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Early Breast Cancers (EBC) Overview

- Early breast cancer (Stages I, II, or III) accounts for >90% of all diagnosed breast cancers.
- Most early breast cancer (EBC) cases can be cured by multimodality therapy, although vary by clinical stage and subtype.

- Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LAG, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014; 106.
- S. Loibl, F. André, T. Bachelot, C. H. Barrios, J. Bergh, H. J. Burstein, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, therapy and follow-up. Annals of oncology. 2024

Early Breast Cancers (EBC) Overview

- Nearly 30% of patients EBC will experience breast cancer recurrence.
- Many with distant metastases despite the availability of EBC therapy options with curative intent, including primary surgery, radiation, chemotherapy, and adjuvant endocrine therapy (ET).

- O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist. 2005.
- Sopik V, Sun P, Narod SA. Predictors of time to death after distant recurrence in breast cancer patients. Breast Cancer ResTreat.2019.

Early Breast Cancers (EBC) Overview

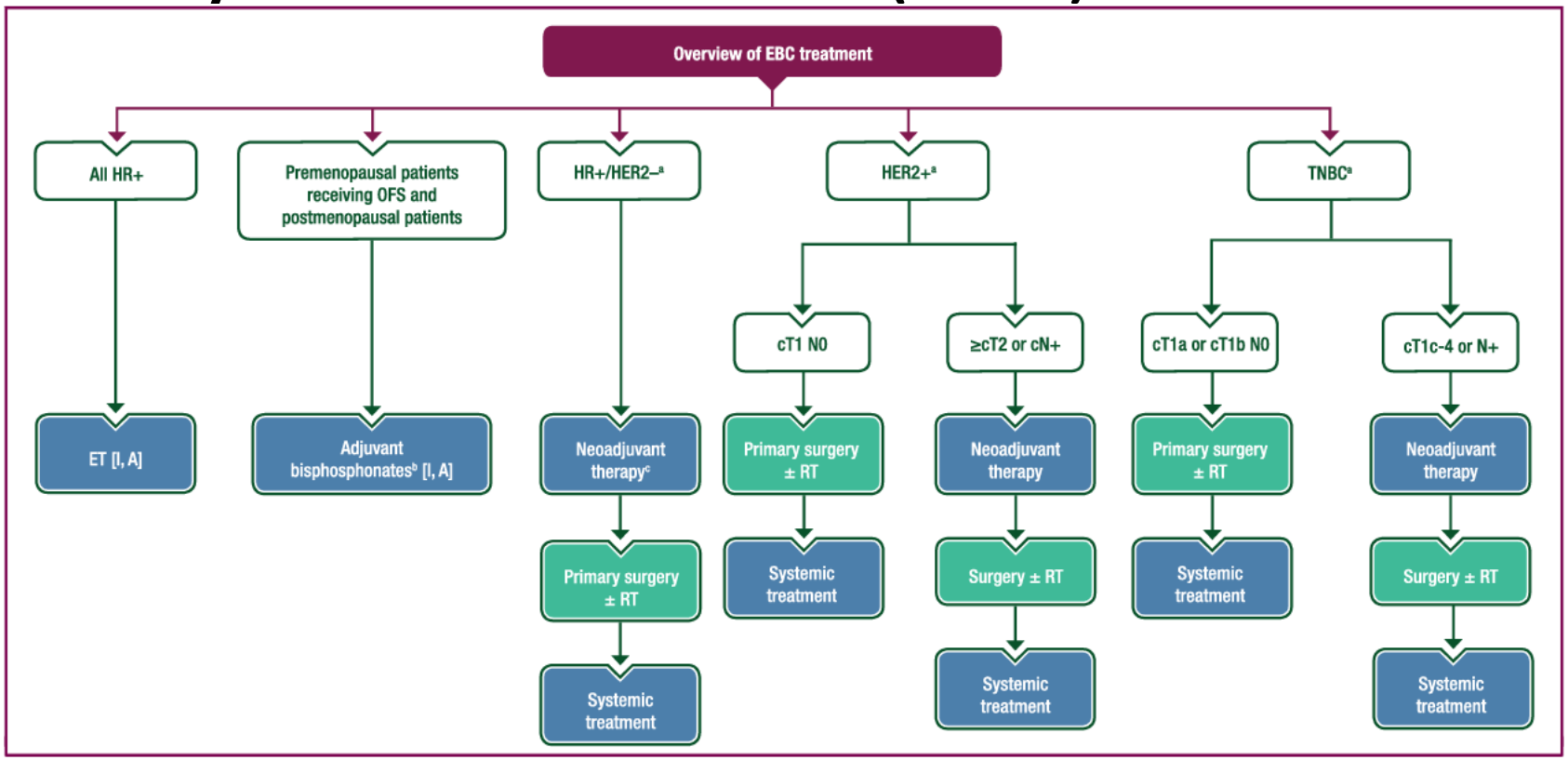

Figure 2. EBC treatment overview.

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.

ALN, axillary lymph node; c, clinical; ChT, chemotherapy; CPG, Clinical Practice Guideline; DCIS, ductal carcinoma *in situ*; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; N, node; OFS, ovarian function suppression; T, tumour; TNBC, triple-negative breast cancer; RT, radiotherapy.

[a]See Figure 3 for management of ALN involvement and Figures 4-7 for systemic therapy according to breast cancer subtype. Recommendations for special situations (elderly patients, male breast cancer and DCIS) are described in the CPG text.

[b]Bisphosphonates are approved for treating bone metastases and osteoporosis and not for prevention of relapse.

[c]If ChT is indicated it may be given in the neoadjuvant setting.

- S. Loibl, F. André, T. Bachelot, C. H. Barrios, J. Bergh, H. J. Burstein, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, therapy and follow-up. Annals of oncology. 2024

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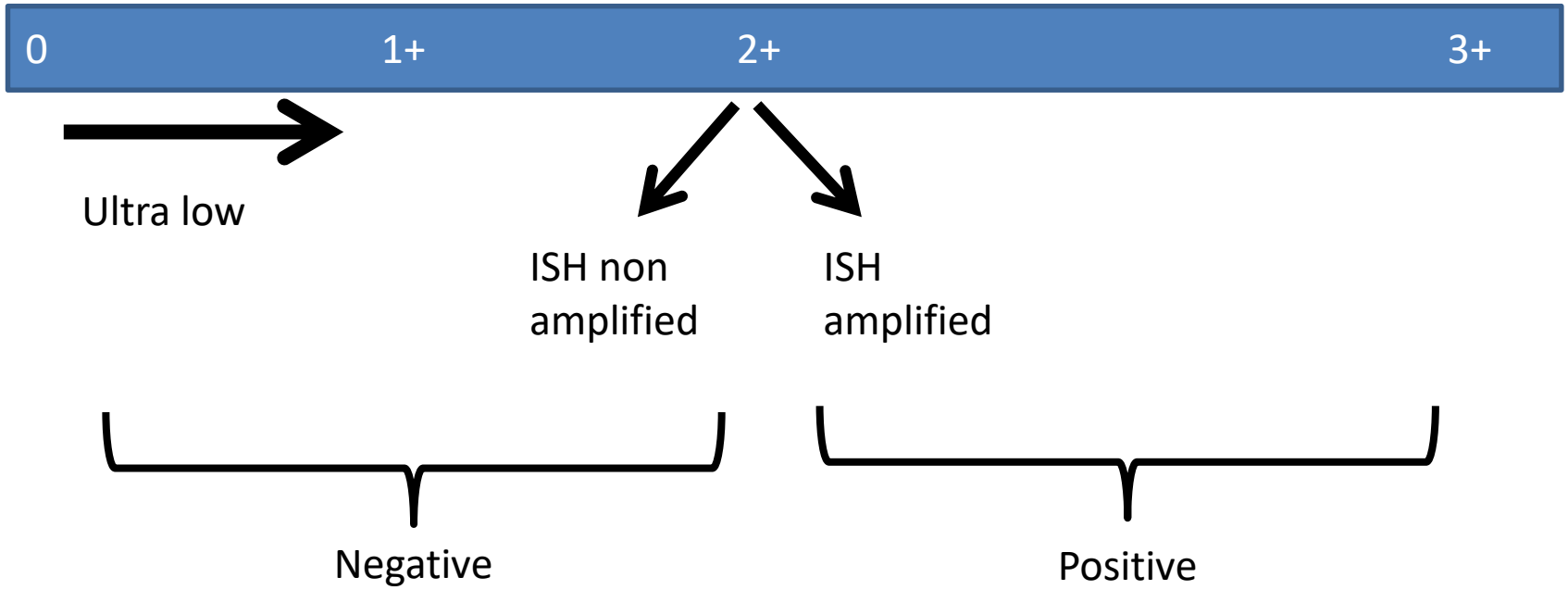
Biomarkers in Breast Cancers

- ER, PR, HER2
- Ki67
- Androgen receptor (AR)
- Neuroendocrine marker
- Surrogate for genetic testings
- Immune checkpoint marker

Biomarkers in Breast Cancers

HER2

- Dichotomous: Negative Positive
- Continuum/ range:



Biomarkers in Breast Cancers

- Molecular staging may impact future therapy decision
- Majority (86%) would not recommend performing ctDNA testing on patients with early-stage breast cancer after surgery in order to assess the risk for recurrence.
- ctDNA will increasingly be implemented in clinical trials but **currently have no role** in the therapy of early-stage breast cancer.
- TILs have been accepted as prognostic markers but may not need to be reported in pathological reports because their role for therapy decisions remains unclear.

- Consensus Discussion on Optimization of Primary Breast Cancer therapy. Breast Care. 2023;18:213–222

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Neoadjuvant Therapy

- Downstaging:
  - Convert non-operable tumor to operable
  - Convert mastectomy to breast conserving surgery
  - Convert axillary dissection to SLN bx
- Monitor treatment response and tailor subsequent locoregional and systemic therapy
  - pCR patients may not benefit for further regional therapy (adjuvant radiotherapy)
  - Poor response patients can be identified and entered into trials of novel targeted agents

- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018.

Neoadjuvant Therapy

- More likely to eradicate micrometastatic disease than chemotherapy delayed after surgery
- Conversely (by delaying surgery), increase the risk of metastatic spread for chemoresistant tumor
- Pathological complete response (pCR) has become primary end point.

- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018.
- Provenzano E, Bossuyt V, Viale G, Cameron D, Badve S, Denkert C, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. Modern Pathology. 2015.

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Pathologic Evaluation

- Careful pathologic evaluation is essential.
- Clinical examination and imaging studies are not sensitive and specific to evaluate response.
  - Patients with complete clinical/imaging response may have residual cancer on histologic evaluation
  - Clinical/imaging residual mass maybe due to therapy related changes rather than residual cancer.

- Provenzano E, Bossuyt V, Viale G, Cameron D, Badve S, Denkert C, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. Modern Pathology. 2015.
- Lanjewar S, Patil P, Fineberg S. Pathologic reporting practices for breast cancer specimens after neoadjuvant chemotherapy—a survey of pathologists in academic institutions across the United States. Modern Pathology. 2020.

Pathologic Evaluation

Special challenges in evaluation of post neoadjuvant systemic therapy (NAC) breast specimens:

- Specimen handling
- Histologic evaluation
- Classification of tumor response and reporting
- Biomarker evaluation

Pathologic Evaluation

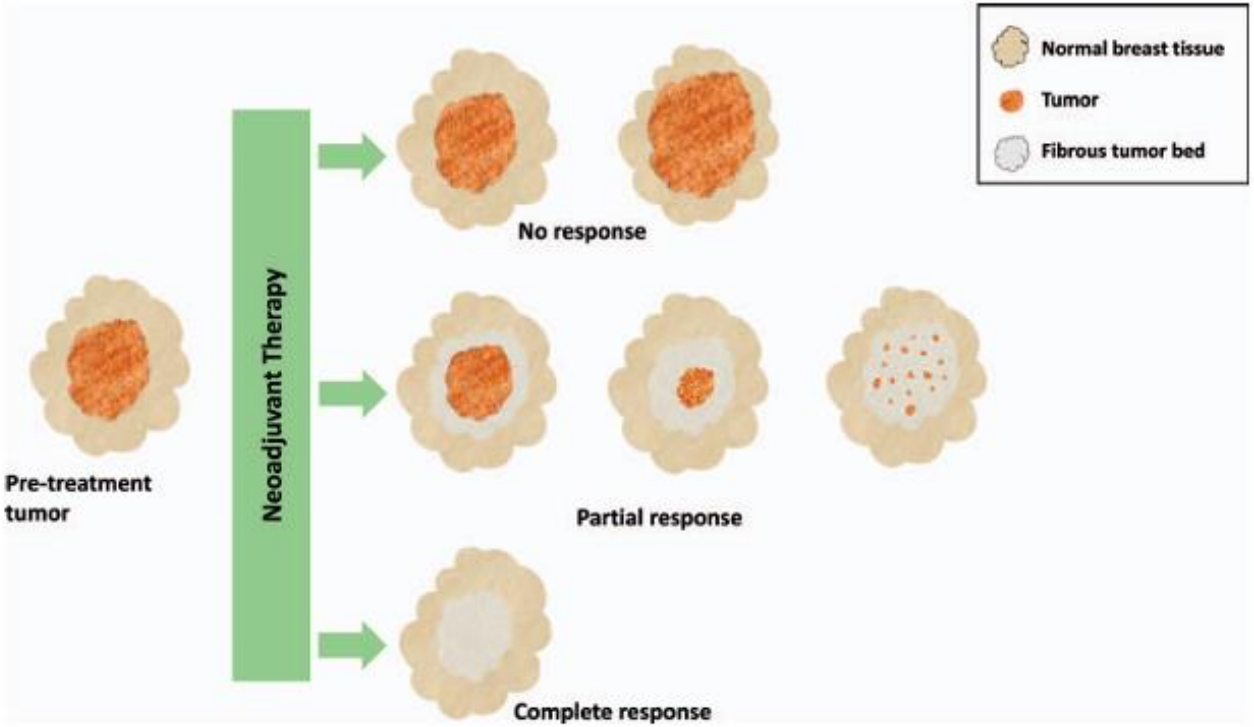
Specimen handling:

- Time from tissue acquisition to fixation should be as short as possible
- Fixed in 10% NBF for 6-72 hours
- Cytology specimens must be fixed in formalin
- Samples should be sliced at 5- to 10-mm intervals after appropriate gross inspection and margins designation
- Sections should ideally not be used for HER2 testing if cut >6 weeks earlier
- It is strongly recommended that an image of the sliced specimen be recorded (radiograph, photograph, photocopy, or drawing) and then used as a map for the sections taken

- Wolff AC, et al. J Clin Oncol. 2018;36:2105–22. 2. Wolff AC, et al. J Clin Oncol. 2023;167:993–1000.
- Sahoo S, Krings G, Chen YY, Carter JM, Chen B, Guo H, et al. Standardizing Pathologic Evaluation of Breast Carcinoma After Neoadjuvant Chemotherapy. Arch Pathol Lab Med. 2023.

Pathologic Evaluation

Figure 1. *Schematic diagram demonstrates the different types of treatment responses seen in breast carcinomas after neoadjuvant chemotherapy.*



- Provenzano E, Bossuyt V, Viale G, Cameron D, Badve S, Denkert C, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. Modern Pathology. 2015.
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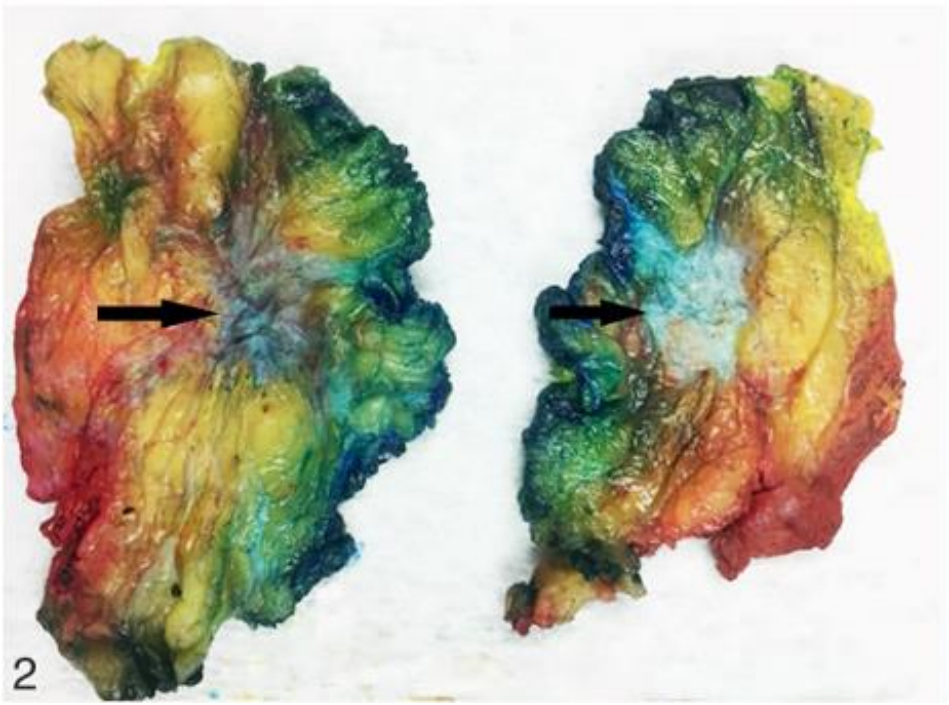
Pathologic Evaluation

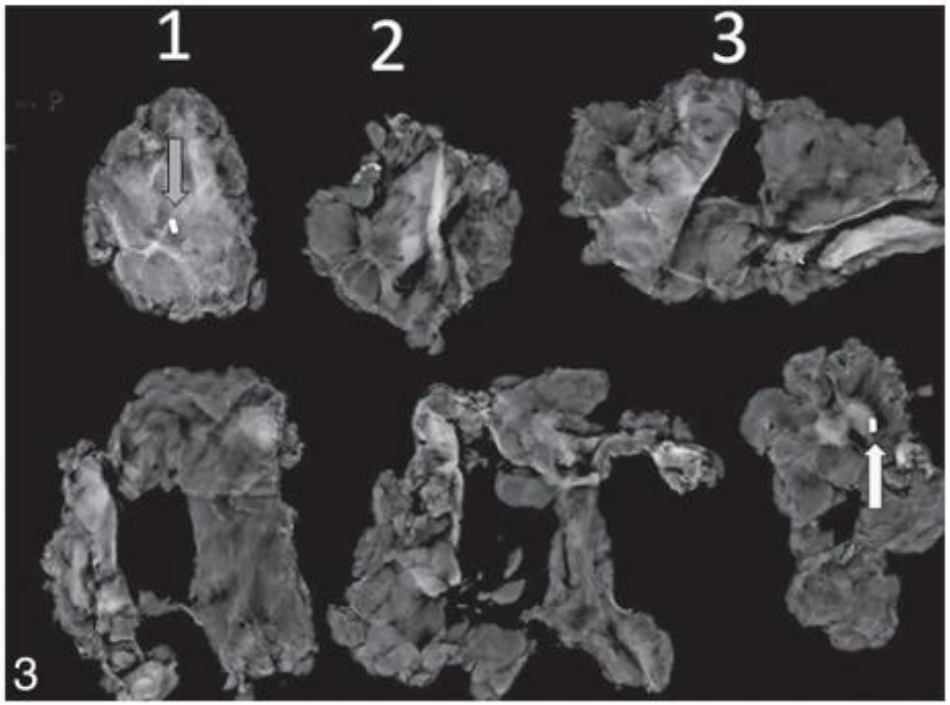
- One of the most critical steps in accurately evaluate response to NAC is the macroscopic assessment of the specimen.
- Residual tumor is usually less well defined and softer than untreated tumor, making it more difficult to detect grossly.
- Therefore, careful mapping and more extensive sampling is required for histopathologic study.

Pathologic Evaluation

- Relatively easy to identify residual tumor when there is minimal or no response to NAC.
- The general term fibrous tumor bed or tumor bed area refers to the grossly or radiologically identifiable area of breast parenchyma where the tumor was located before initiation of systemic therapy.

Pathologic Evaluation





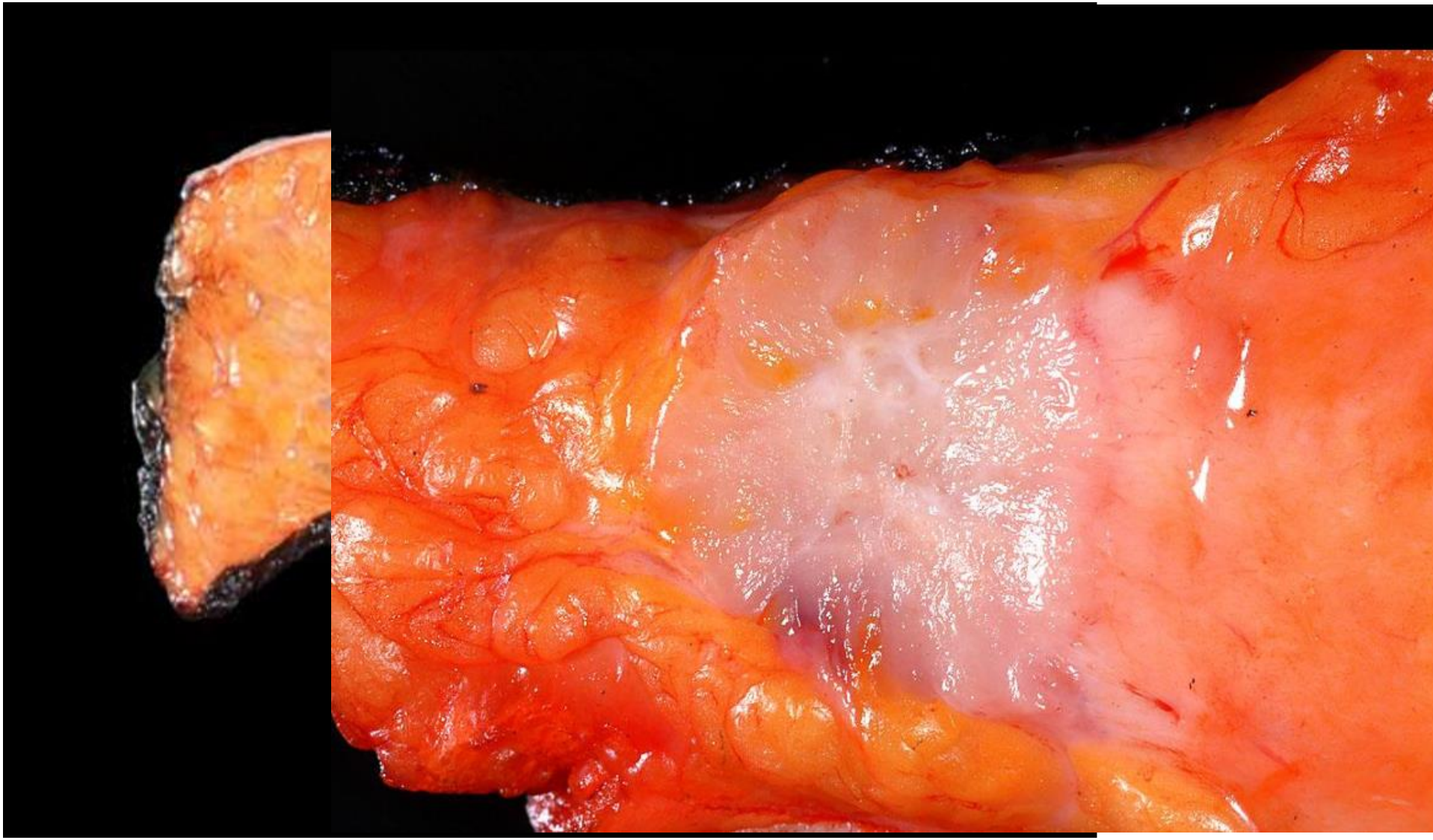
- Figure 2. Grossly identifiable fibrous tumor bed after neoadjuvant chemotherapy (arrows).
- Figure 3. Specimen radiograph of a partial mastectomy with 2 separate tumors and corresponding biopsy clips (arrows).

- Provenzano E, Bossuyt V, Viale G, Cameron D, Badve S, Denkert C, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. Modern Pathology. 2015.
- Sahoo S, Krings G, Chen YY, Carter JM, Chen B, Guo H, et al. Standardizing Pathologic Evaluation of Breast Carcinoma After Neoadjuvant Chemotherapy. Arch Pathol Lab Med. 2023.

Pathologic Evaluation

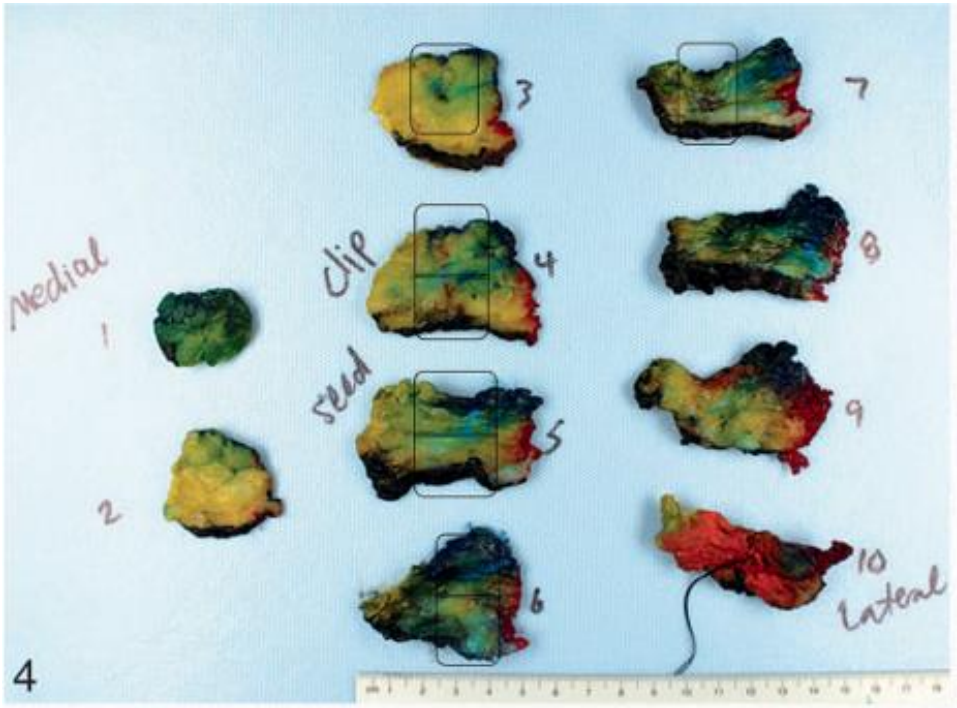
- Identification of tumor bed is essential
- Failure to identify tumor bed or not sample the right area can result in erroneous classification of pCR

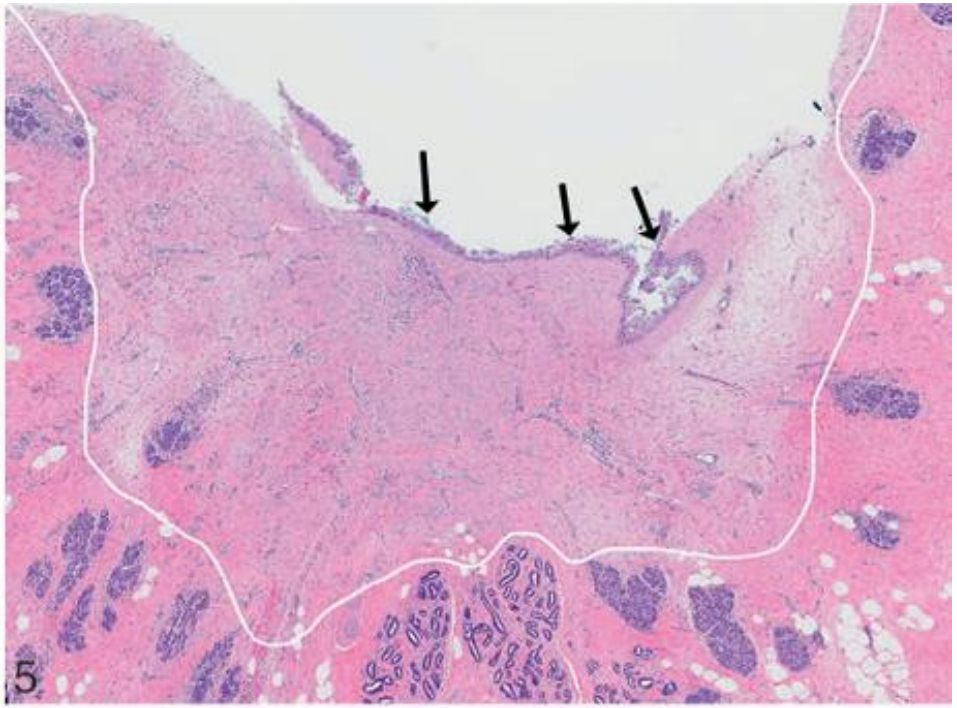
Pathologic Evaluation



- Courtesy of Prof. A. A. Sahin , MD. The 59th IAP Thailand Annual Meeting. 2019

Pathologic Evaluation

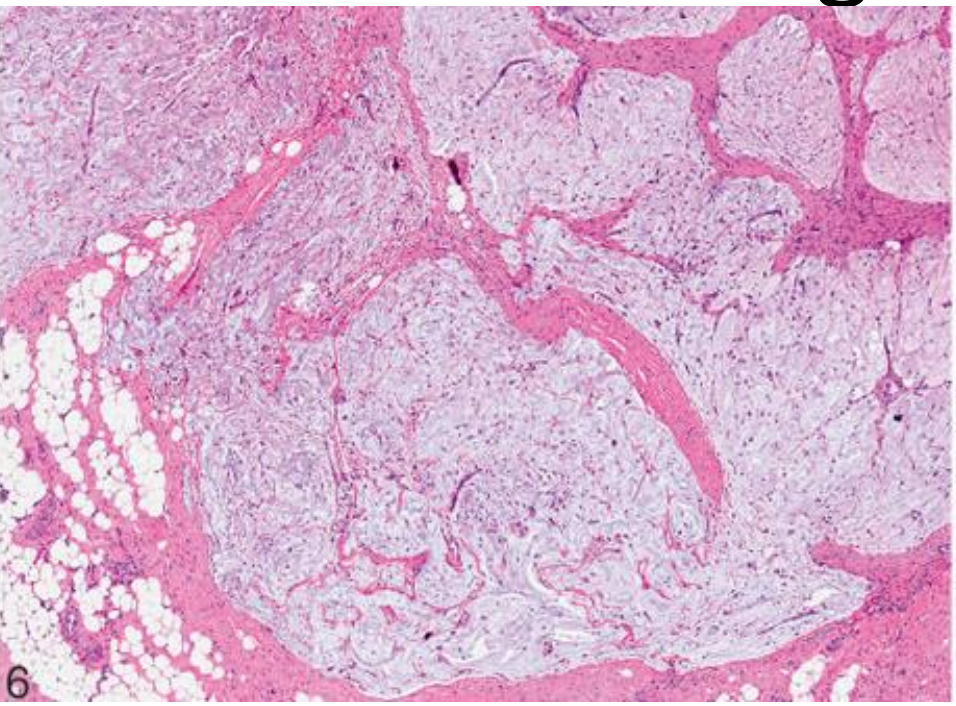


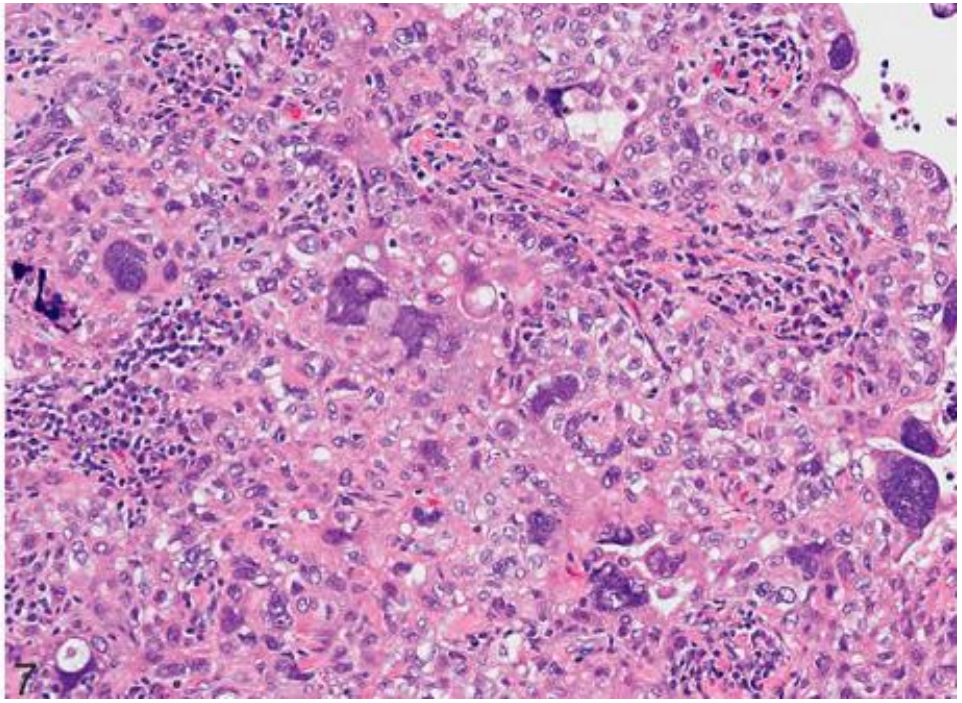


- Figure 4. A posttreatment partial mastectomy specimen serially sectioned and annotated to show the origin of sections in relation to the biopsy clip and radioactive seed used for localization of the tumor bed.
- Figure 5. Low-power appearance of a tumor bed (outlined) characterized by pale vascularized stroma without glandular structures, surrounded by normal breast lobules. The arrows indicate the presence of prior core biopsy site lined by macrophages (HE, X20).

- Sahoo S, Krings G, Chen YY, Carter JM, Chen B, Guo H, et al. Standardizing Pathologic Evaluation of Breast Carcinoma After Neoadjuvant Chemotherapy. Arch Pathol Lab Med. 2023.

Pathologic Evaluation

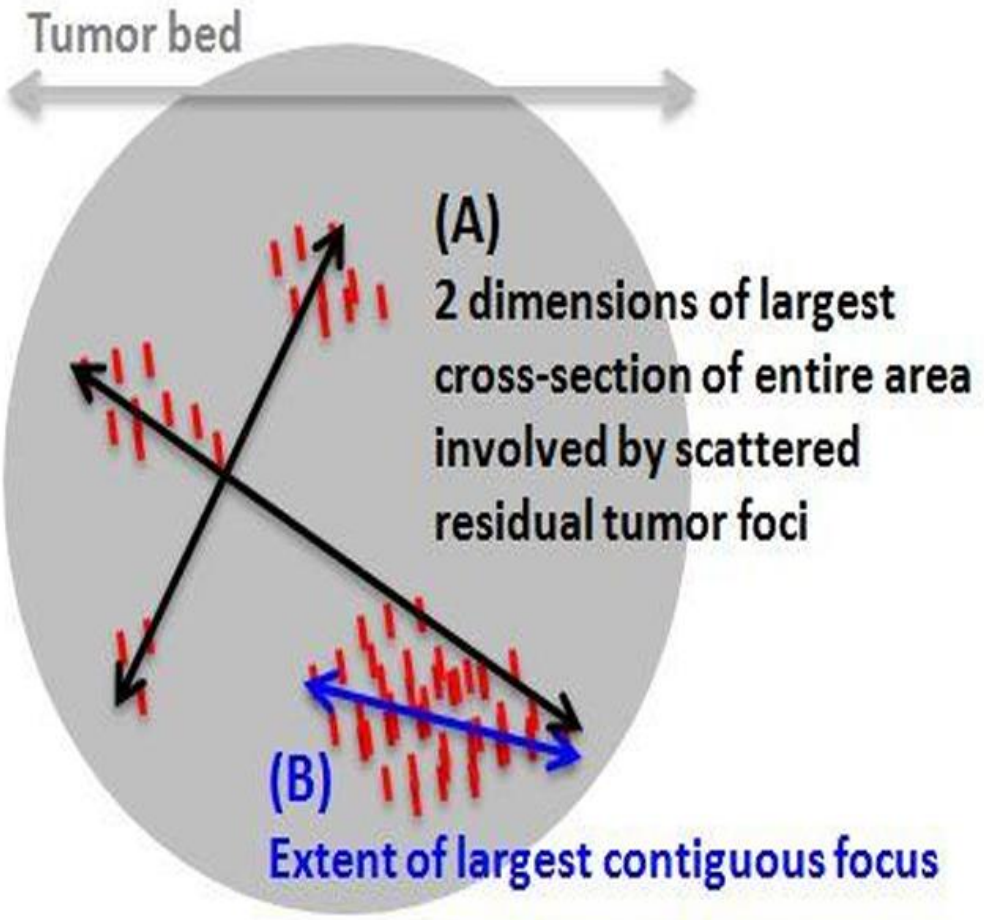


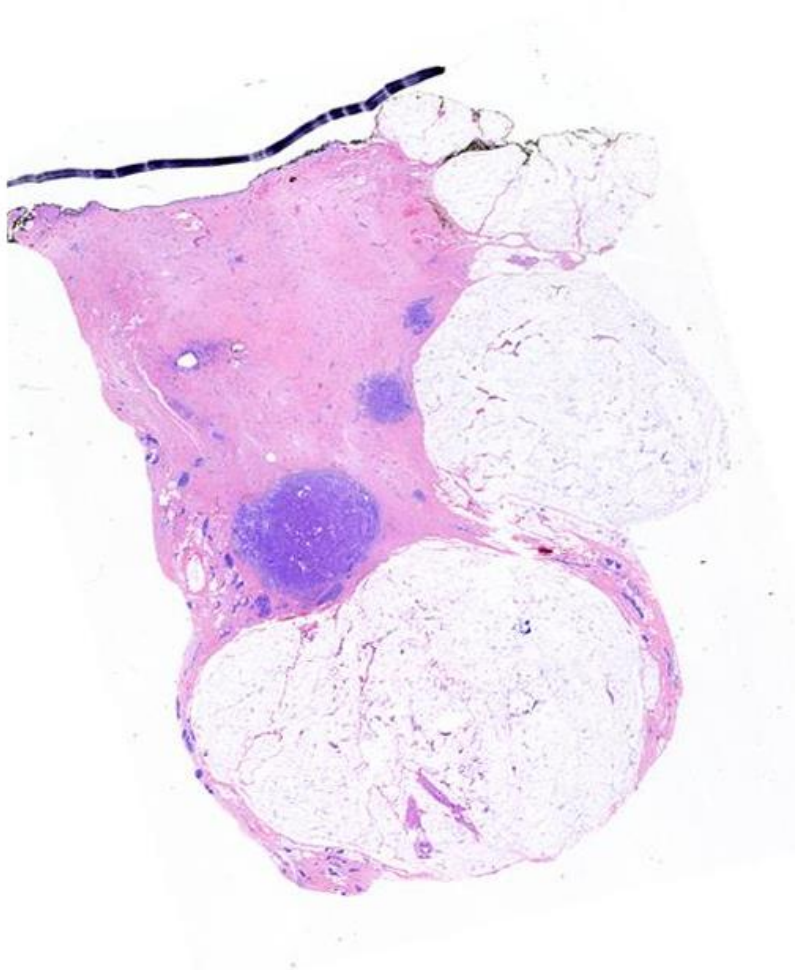


- Figure 6. Tumor bed of a high-grade mucinous carcinoma with complete response to neoadjuvant chemotherapy reveals only extracellular mucin without tumor cells (HE, X40).
- Figure 7. Cellular changes in residual tumor after chemotherapy demonstrate pleomorphic and bizarre nuclei but inconspicuous mitoses (HE, X100).

- Sahoo S, Krings G, Chen YY, Carter JM, Chen B, Guo H, et al. Standardizing Pathologic Evaluation of Breast Carcinoma After Neoadjuvant Chemotherapy. Arch Pathol Lab Med. 2023.

Pathologic Evaluation





Measuring tumor size post NAC

- Provenzano E, Bossuyt V, Viale G, Cameron D, Badve S, Denkert C, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. Modern Pathology. 2015.

Pathologic Evaluation

Classification Systems to Evaluate Response to NAC:

- National Surgical Adjuvant Breast and Bowel Project B18 trial (NSABP-B18)
- Miller and Payne system (MPS)
- Chevallier's classification
- Sataloff's classification
- Residual cancer burden (RCB)
- Pinder
- AJCC

Pathologic Evaluation

	pCR
NSABP B-18	Breast only
Miller and Payne	Breast only
Chevallier's	Breast and LN
Sataloff's	Breast and LN
RCB	Breast and LN
Pinder	Breast and LN
AJCC	Breast and LN

Pathologic Evaluation

Residual Cancer Burden (RCB):

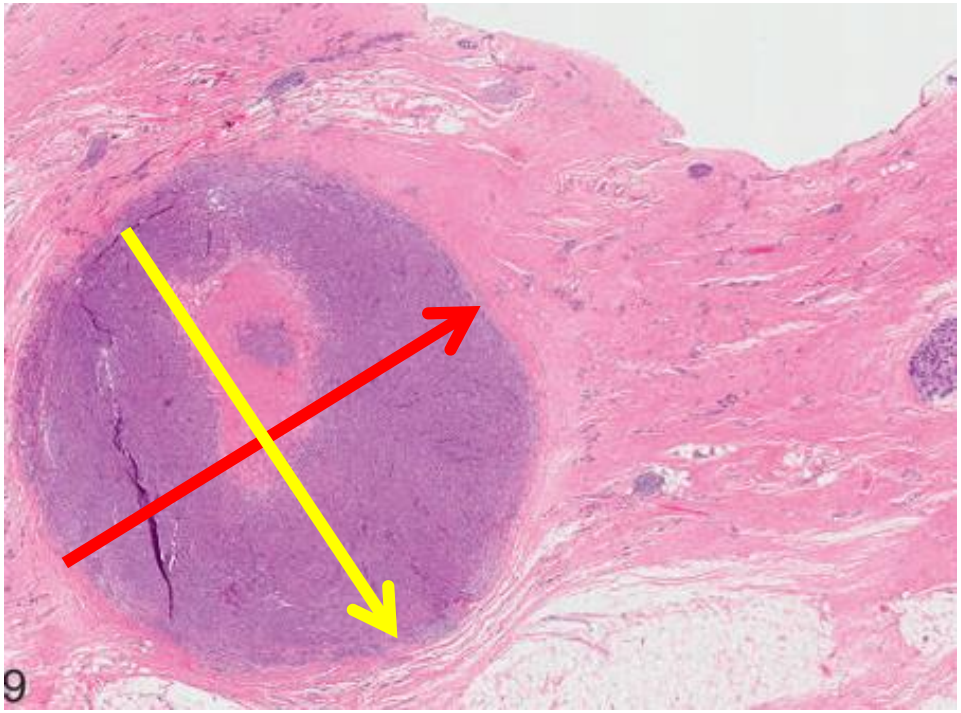
- Uses cellularity of post-treatment residual invasive carcinoma over the tumor bed, the presence of lymph node metastasis, and the size of the largest lymph node metastasis
  - RCB-0 No carcinoma in breast or lymph nodes (pCR)
  - RCB-I Partial response
  - RCB-II Partial response
  - RCB-III Chemoresistant

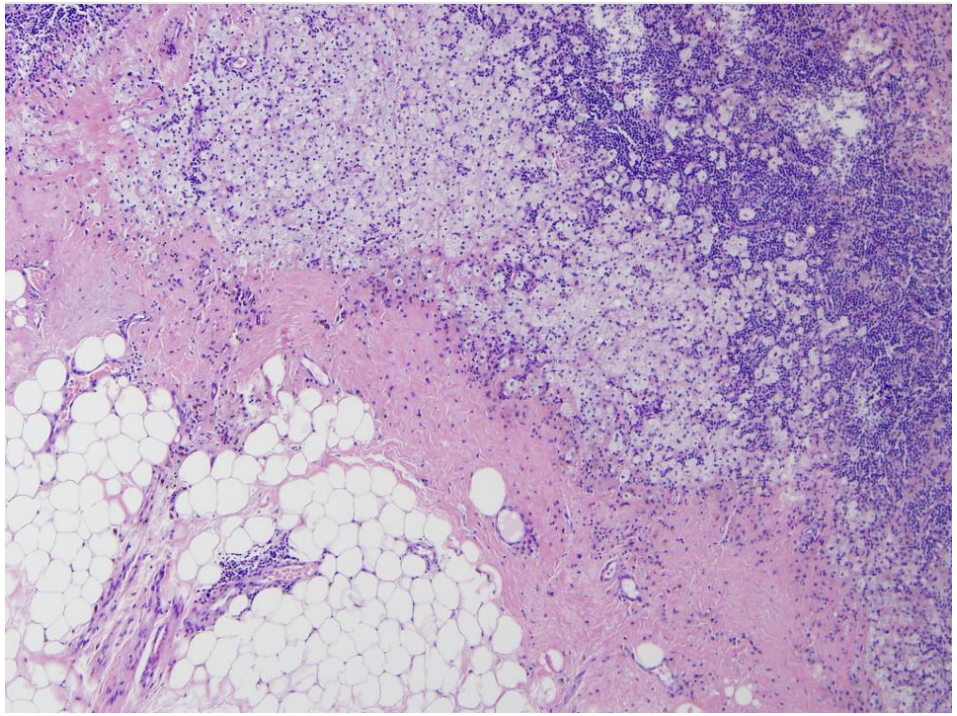
Pathologic Evaluation

Residual Cancer Burden Calculator

1. Primary tumor bed
   - Primary tumor bed : …… mm X ….. mm
   - Overall cancer cellularity : …… %
   - Percentage of DCIS : …… %
2. Lymph nodes
   - Number of positive lymph nodes: ……
   - Diameter of largest metastasis : …..

Pathologic Evaluation



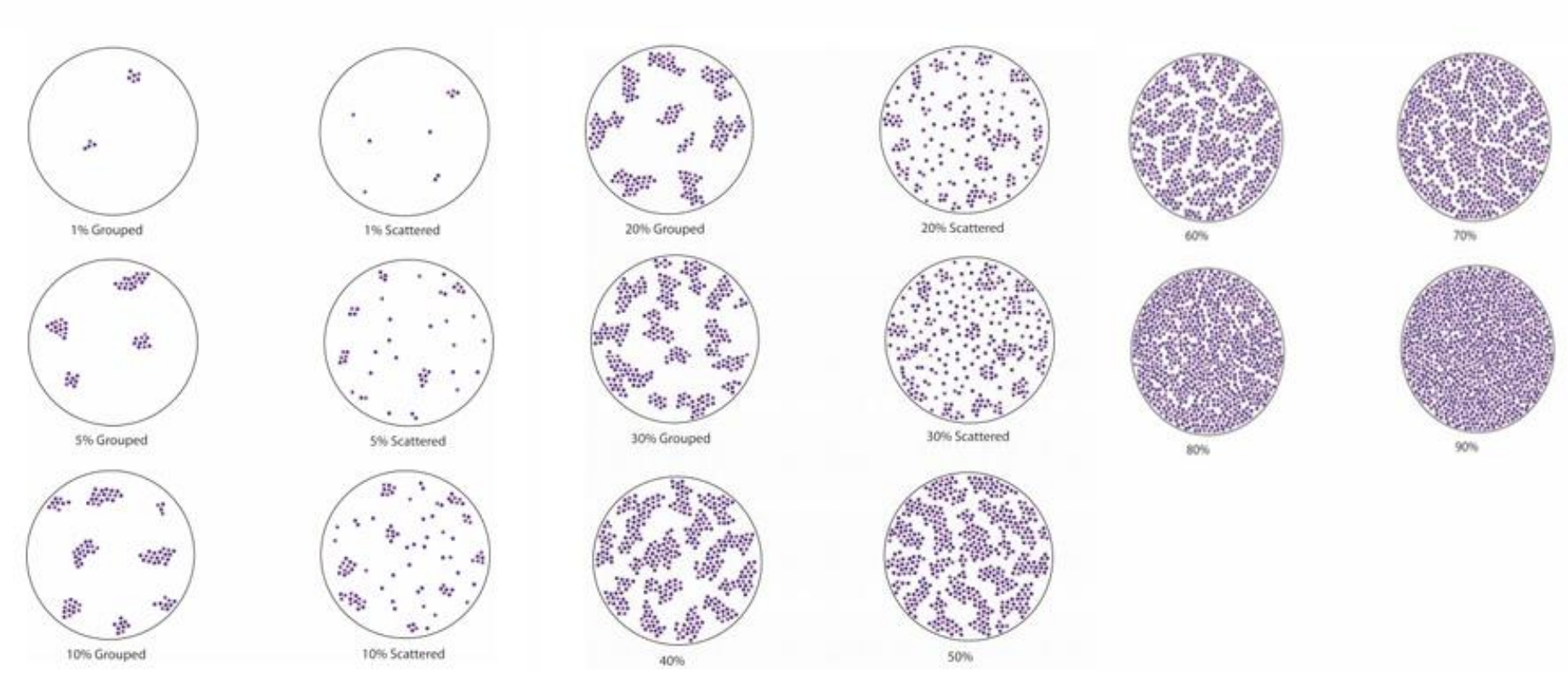


- Two dimensions of largest cross section of entire area involved by tumor

- Sahoo S, Krings G, Chen YY, Carter JM, Chen B, Guo H, et al. Standardizing Pathologic Evaluation of Breast Carcinoma After Neoadjuvant Chemotherapy. Arch Pathol Lab Med. 2023.

Pathologic Evaluation

Graphical Illustration of Residual Tumor Cellularity Percentage



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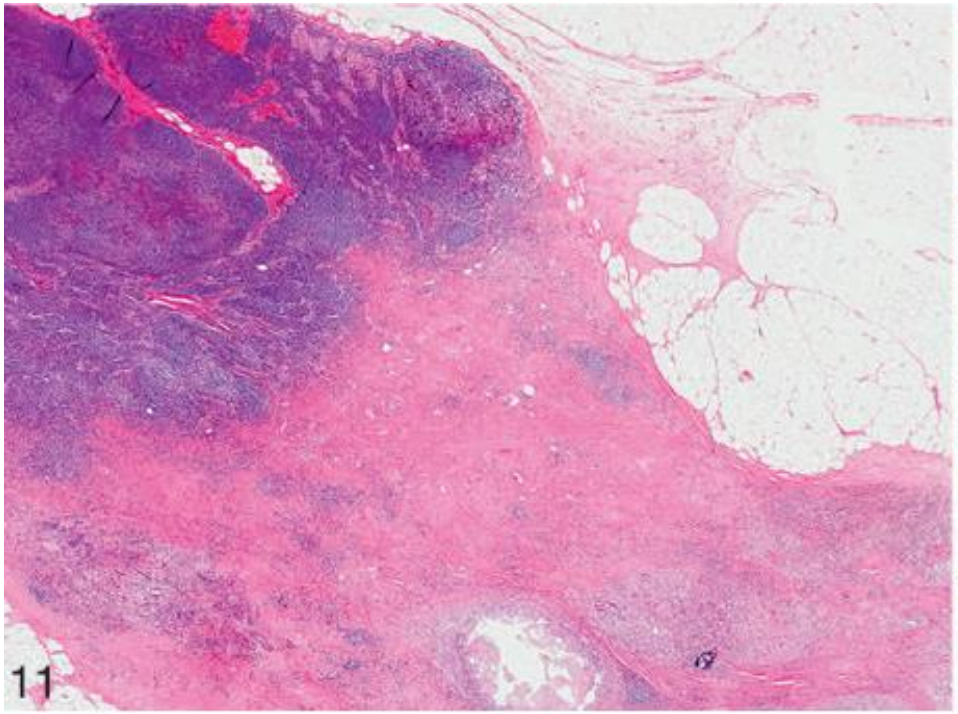
Pathologic Evaluation



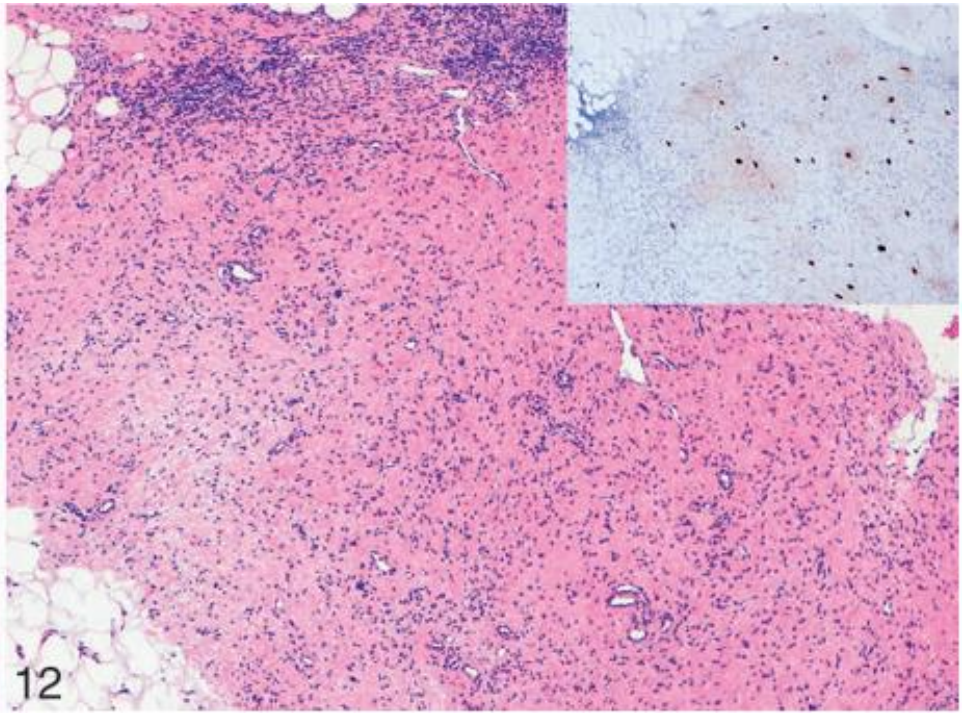


Figure 11. Lymph node with complete response to chemotherapy shows a large area of node replaced by fibrosis and aggregates of macrophages (HE, X20).

Figure 12. A lymph node after neoadjuvant chemotherapy is completely replaced by fibrosis with scattered single tumor cells, better visible on immunostain for cytokeratin AE1/3 (HE, X40; X40 [inset]).

- Sahoo S, Krings G, Chen YY, Carter JM, Chen B, Guo H, et al. Standardizing Pathologic Evaluation of Breast Carcinoma After Neoadjuvant Chemotherapy. Arch Pathol Lab Med. 2023.

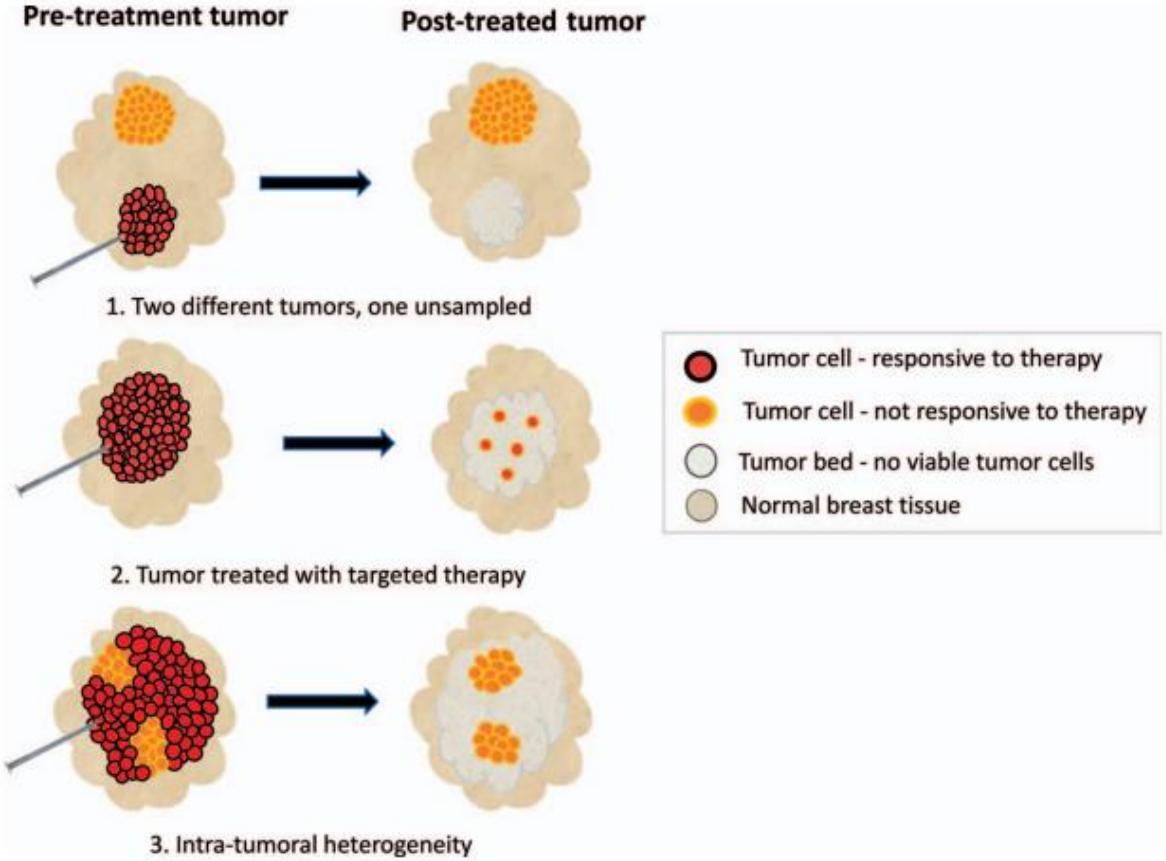
Pathologic Evaluation

Definition of Pathologic complete response (pCR)

- General consensus is that pCR should be defined as no invasive ca in the breast and no metastatic ca in nodes
- DCIS is important for local recurrence but not survival and does not preclude a pCR
- Add prefix “y”

Pathologic Evaluation

Figure 13. *Schematic diagram demonstrates various reasons for discrepant biomarkers between pretreatment and posttreatment tumor specimens.*



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Pathologic Evaluation

- Biomarkers alteration after NAC
- NAC induced change rates were 17.9%, 22.8% and 11.8% for ER, PR and HER2 respectively
  - ER+>- : 8.5%; ER->+: 9.4%
  - PR+>-: 13.5%; PR->+: 9.4%
  - HER2+>-: 10.6%; HER2->+: 1.2%
- Redetection of HR and HER2 status after NAC
- Changes in HR status as prognostic factor

- Li C, Fan H, Xiang Q, Xu L, Zhang Z, Liu Q, et al. Prognostic value of receptor status conversion following neoadjuvant chemotherapy in breast cancer patients: a systematic review and meta-analysis. Breast Cancer Res Treat. 2019.

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Summary

- Neoadjuvant chemotherapt (NAC) increasingly used for early stage operable breast cancer.
- Histopathological changes and biomarker alteration can occur after NAC.
- Pathologic response is an important predictor of survival.
- Evaluation of post NAC specimen requires special attention.
- RCB classification as the preferred method.
- ypTN stage should used by pathologist.

World Cancer Day
4 February

Hari Kanker Sedunia 2024

“Tutup Kesenjangan Perawatan”

Close the care gap

Terima kasih…
Hatur nuhun…
Mauliate…