Neoadjuvant Chemotherapy: When and How? Challenges of a Pathologist

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Objectives

- Recognize morphologic features and diagnostic pitfalls associated with response to neoadjuvant chemotherapy/treatment-induced changes
- Identify the predictors of response to neoadjuvant chemotherapy
- Identify reporting guidelines influencing patient selection, management, and outcome

Neoadjuvant Chemotherapy

Definition

- Neoadjuvant chemotherapy is defined as the administration of systemic therapy prior to surgical removal of a tumor
- Neoadjuvant therapy is being used increasingly in the management of breast cancer with similar impact as adjuvant therapy

Neoadjuvant Chemotherapy

Clinical Indications/Patient Selection

- Locally advanced breast cancer
- Inflammatory breast cancer
- Down staging of large tumors to allow breast conservation therapy
- Women under age of 50 and those with ER-negative disease

Neoadjuvant Chemotherapy

The Benefits

- It offers a unique opportunity for the evaluation of treatment response with complete pathologic response acting as a surrogate marker of survival
- It allows more rapid assessment of the efficacy of new therapeutic agents
- It enables early cessation of ineffective treatment

Neoadjuvant Chemotherapy

The Benefits *(continued)*

- It provides an opportunity for individualized therapy
- It allows collection of tumor samples before, during, and after treatment for translational research

Neoadjuvant Chemotherapy

Predictors of Response

- The rate of response varies from 15% to 30% depending on the type of tumor and the type of therapy
- Patients who achieve complete response have improved outcome compared with non-responders

Neoadjuvant Chemotherapy

Predictors of Response *(continued)*

- Small tumor size
- High tumor grade
- High proliferation rate
- Tumor necrosis
- Presence of tumor-associated lymphocytes

Neoadjuvant Chemotherapy

Predictors of Response *(continued)*

- Hormone receptor negative – Her-2/neu oncogene positive tumor
- Triple negative breast cancer

Neoadjuvant Chemotherapy

The Impact of Molecular Subtyping

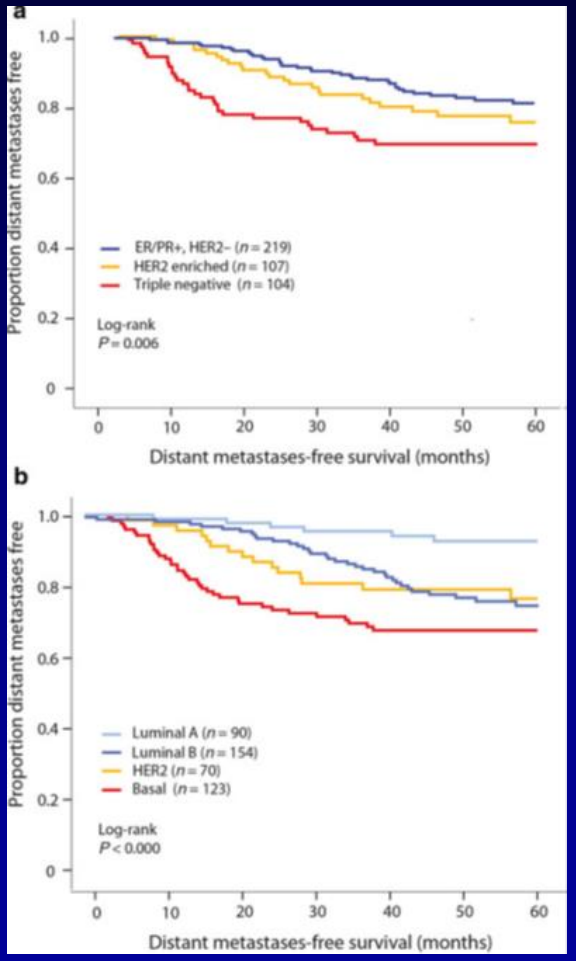
- **BluePrint and MammaPrint**
  - **Better identify patients who my not benefit from neoadjuvant chemotherapy**
  - **This assessment is based on comparison with conventional immunohistochemistry/ fluorescence in situ hybridization**

Gluck S, de Snoo F, Peeters J, Stork-Sloots L, Somlo G. Molecular subtyping of early-stage breast cancer identifies a group of patients who do not benefit from neoadjuvant chemotherapy. Breast Cancer Res Treat. 2013 doi:10.1007/s10549-013-2572-4

Neoadjuvant Chemotherapy

The Impact of Molecular Subtyping

- BluePrint and MammaPrint
  - Enables subdivision of Luminal group into two types, Luminal A and Luminal B, which can not be achieved with standard pathology
  - Luminal A-type have an excellent prognosis and do not benefit from neoadjuvant chemotherapy



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Neoadjuvant Chemotherapy

Procedures Required Prior to Therapy

- Definitive diagnosis of cancer
- Assurance of the availability of sufficient tissue for biomarker studies
- Assessment of the status of hormone receptors and HER-2/neu oncogene

Neoadjuvant Chemotherapy

Procedures Required Prior to Therapy

- Assessment of the status of axillary lymph nodes
  - Clinically positive axillary lymph nodes should be sampled by minimally invasive procedures
  - Clinically negative axillary lymph nodes should be sampled by sentinel node biopsy

Neoadjuvant Chemotherapy

Evaluation of Response

- Clinical examination
- Breast imaging studies
- Pathologic examination of post-treatment specimen

Neoadjuvant Chemotherapy

Clinical Evaluation

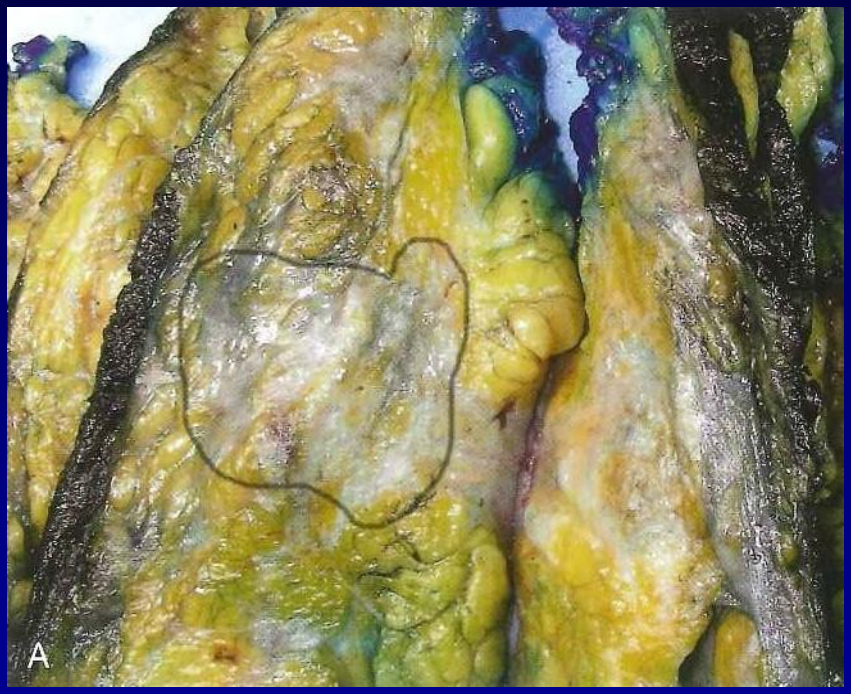
- Assessment of the size of the tumor by palpation
- Breast imaging: MRI, Ultrasound, and Mammography
- The information about neoadjuvant chemotherapy should be communicated to the pathologist

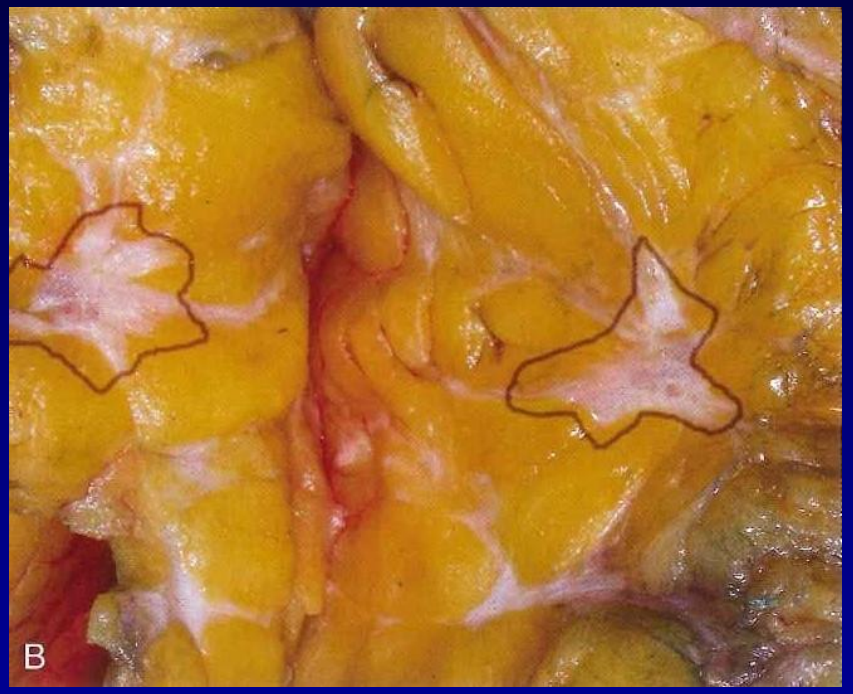
Neoadjuvant Chemotherapy

Gross Examinations

- Access to the information about the size and location of the tumor prior to therapy is critical
- Specimen radiology will assist in identification of clip or microcalcification
- Identification of tumor bed and surrounding tissue are helpful in selecting the right area for tissue sectioning
- Margin assessment is important in case there is evidence of residual tumor is later found by microscopic examination

Neoadjuvant Chemotherapy



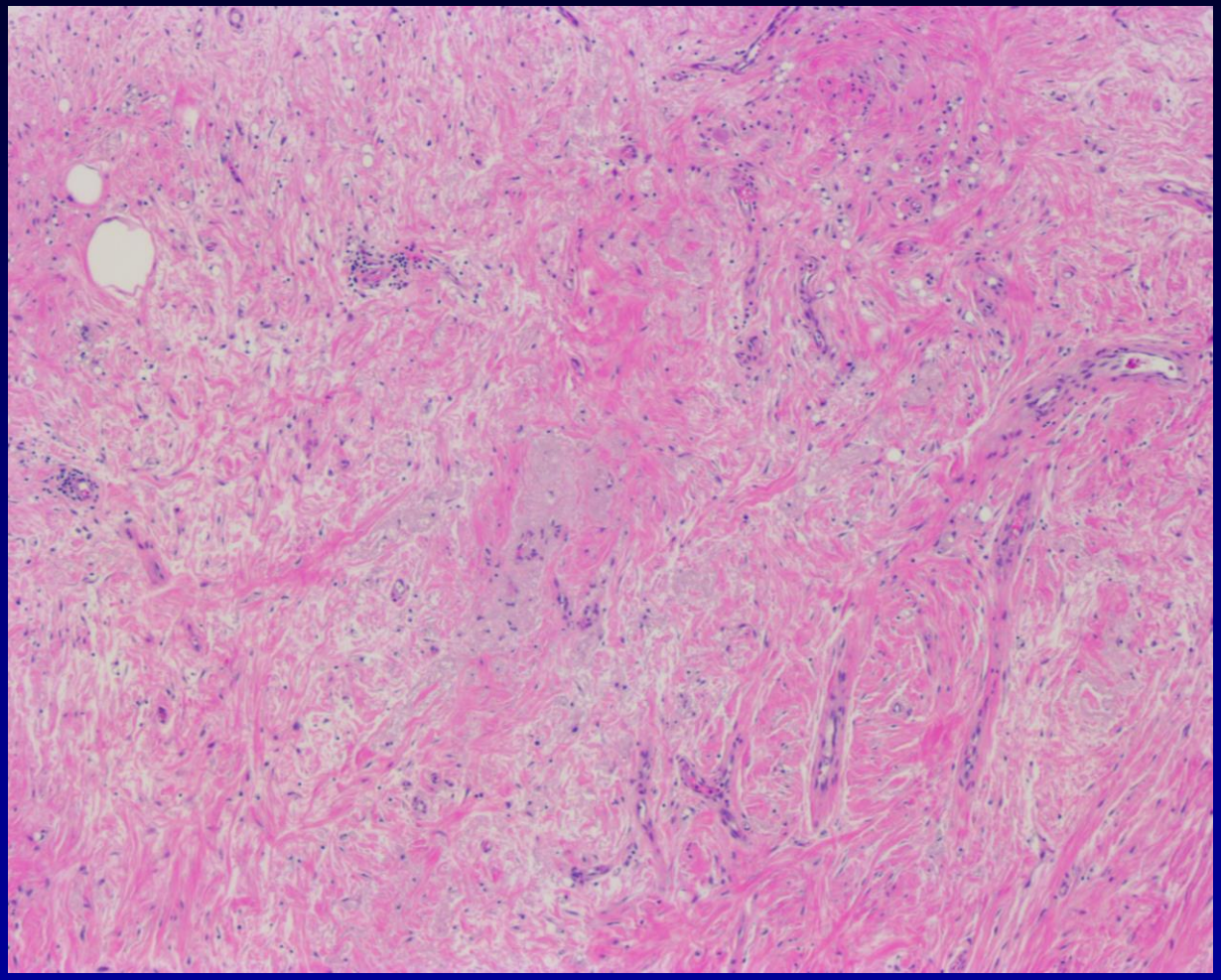


Neoadjuvant Chemotherapy

Microscopic Evaluation

- Recognition of tumor bed characterized by
  - Localized vascular stroma, edema, myxoid changes, lymphocytes, inflammatory cells, and histiocytes
- Treatment Effects
  - Distortion of glandular elements, enlarged cells with bizarre nuclei and cytoplasmic vacuoles

Neoadjuvant Chemotherapy



Tumor bed with no residual tumor seen

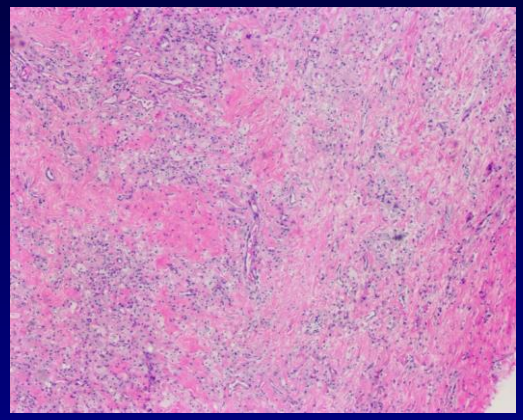
Neoadjuvant Chemotherapy

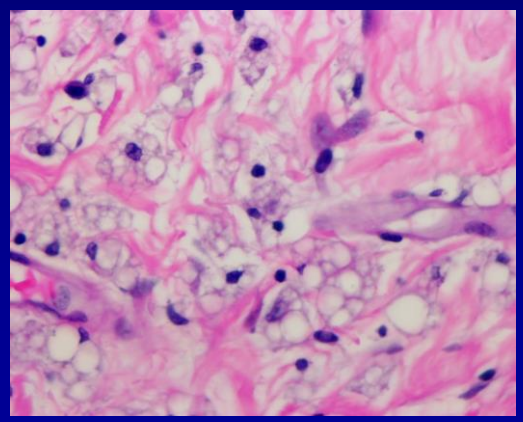
Microscopic Evaluation *(continued)*

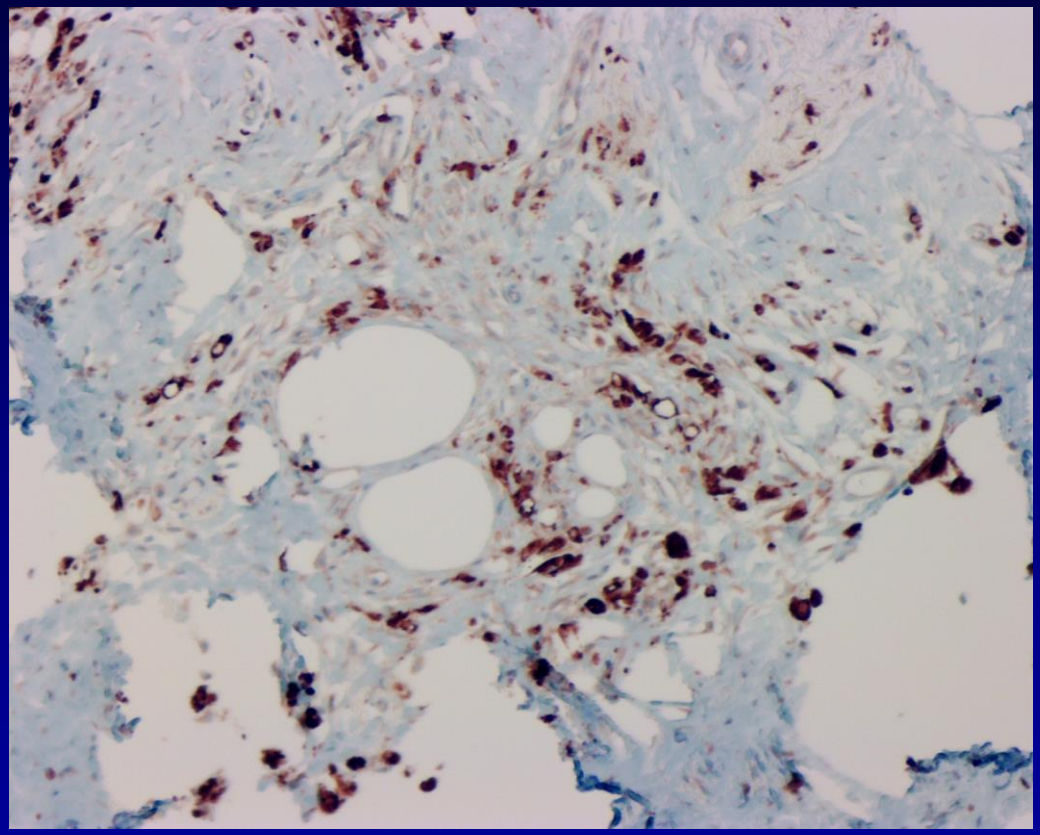
- Identification of residual tumor cells
  - Appear singly or in clusters
  - They present with atypical features
- Immunostains are helpful to distinguish between tumor cells and reactive inflammatory cells
  - Cytokeratin, AE1/AE3 or CK7 as epithelial markers
  - CD68 for histiocytes
  - P63 for myoepithelial cells

Neoadjuvant Chemotherapy

Histiocytic Infiltrate







Confirmation by immunostaining for CD68

Neoadjuvant Chemotherapy

Spectrum of Changes After Therapy

- Complete response
- Partial response
- Minimal or no response
- Progressive disease

Neoadjuvant Chemotherapy

Pathologic Complete Response (pCR)

- Disappearance of all invasive carcinoma in the breast and in the axillary lymph nodes after completion of therapy
  - Residual ductal carcinoma may be present, since this finding does not alter survival

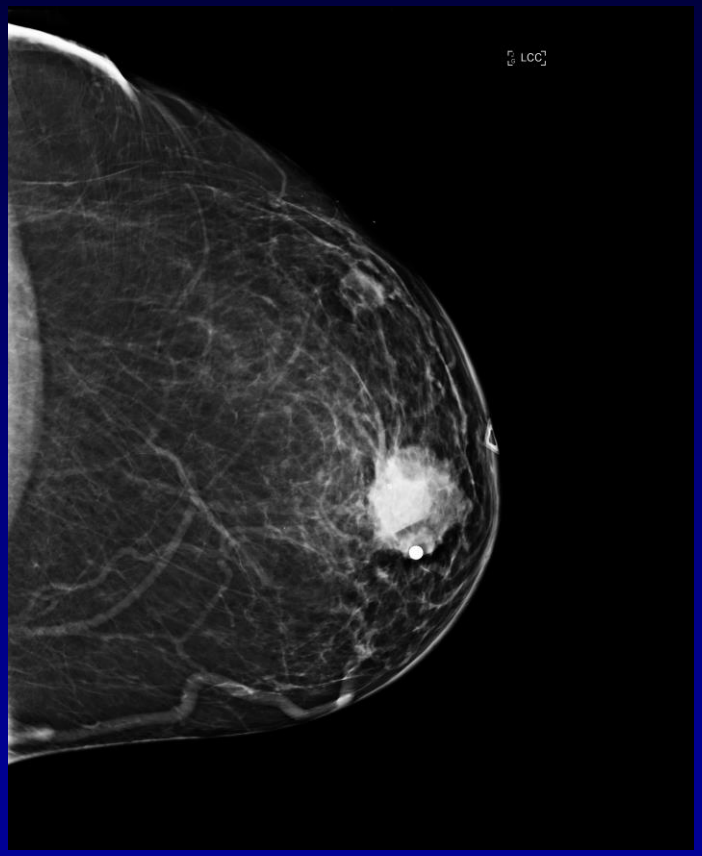
Neoadjuvant Chemotherapy

Clinical Presentation

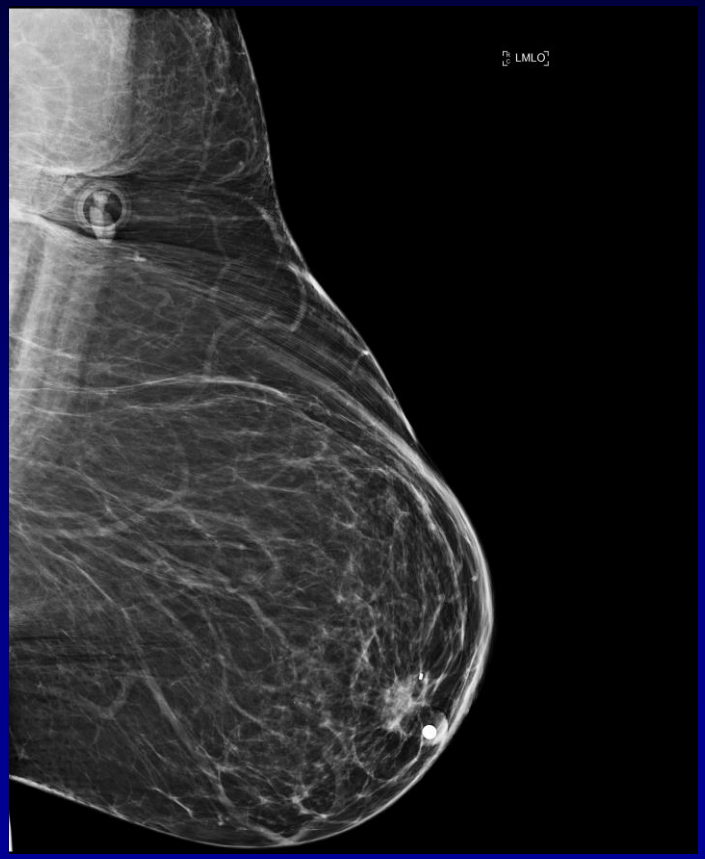
- 52 year old woman with palpable mass measuring 3.6 x 4.1 x 3.2 cm by breast imaging

Neoadjuvant Chemotherapy

Breast Imaging



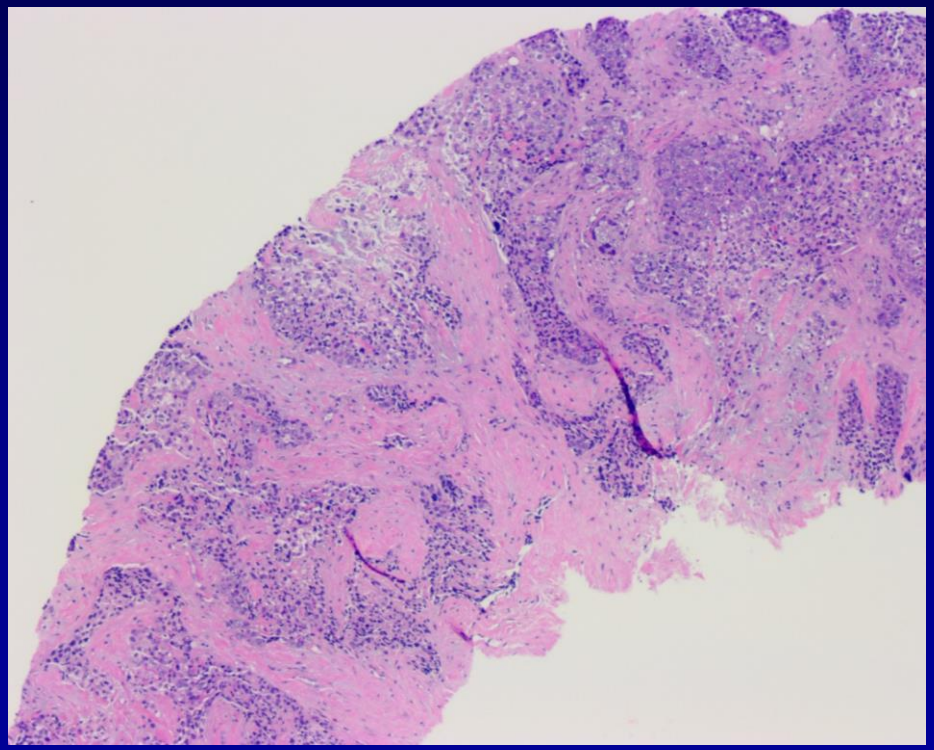
Pre-treatment



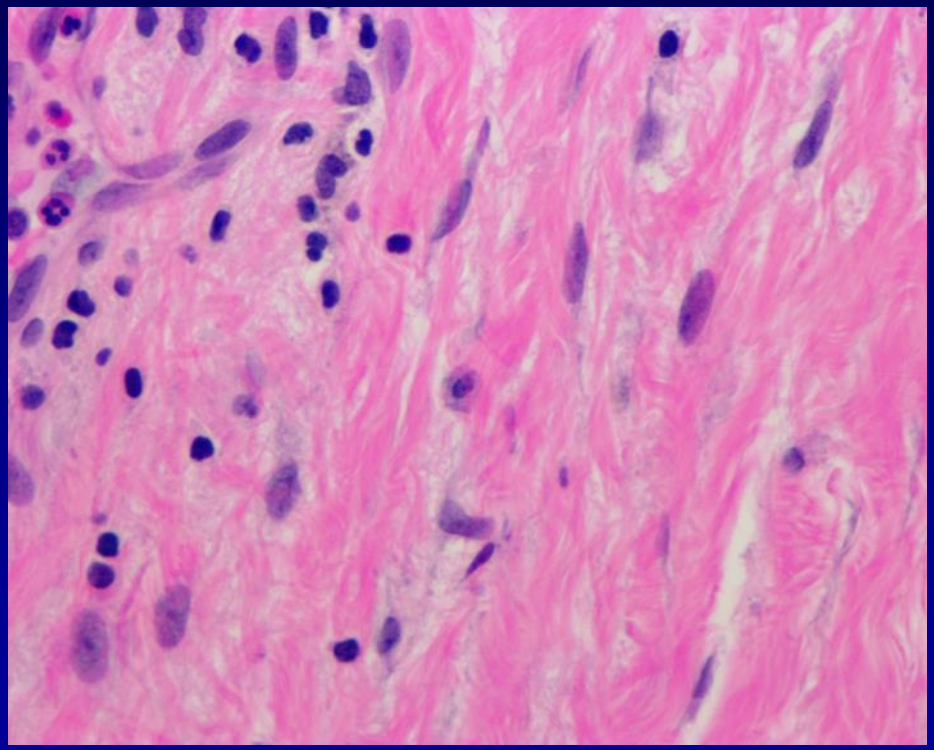
Post-treatment

Neoadjuvant Chemotherapy

Diagnostic Core Biopsy
Poorly Differentiated Ductal Carcinoma



Pre-treatment



Post-treatment

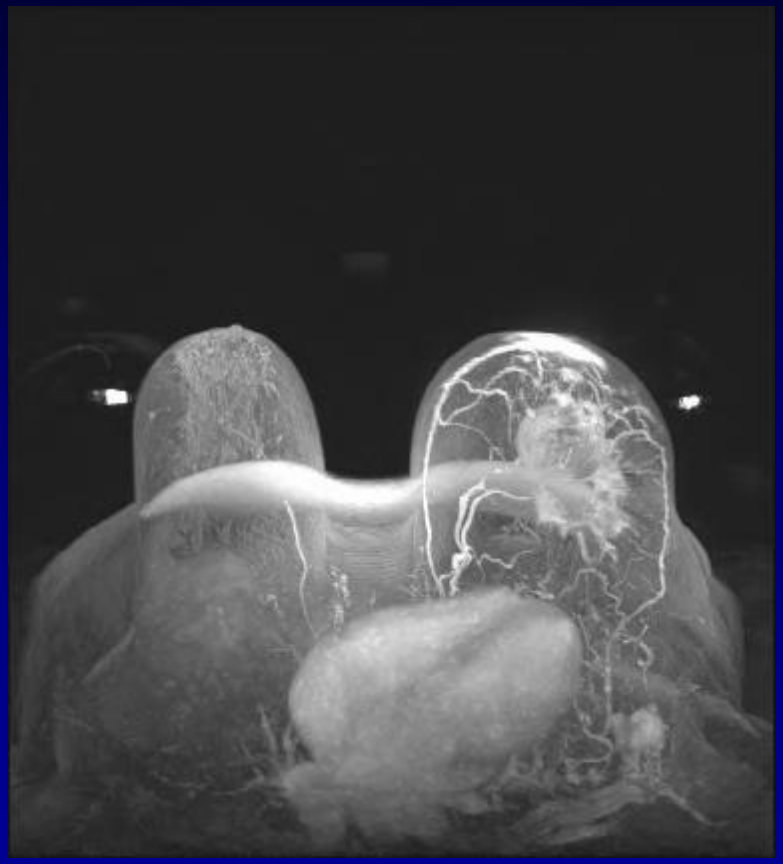
Neoadjuvant Chemotherapy

Clinical Presentation

- 58 year old woman with a large enhancing mass in the left breast, measuring at least 4.7 x 5.6 x 7.9 cm

Neoadjuvant Chemotherapy

Breast Imaging



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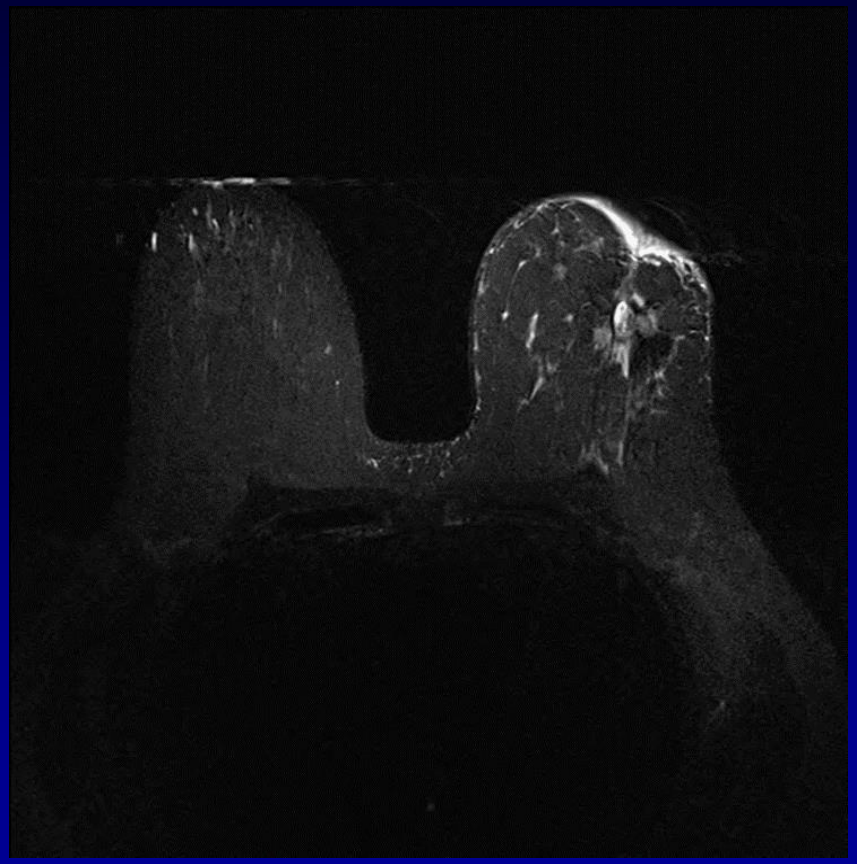
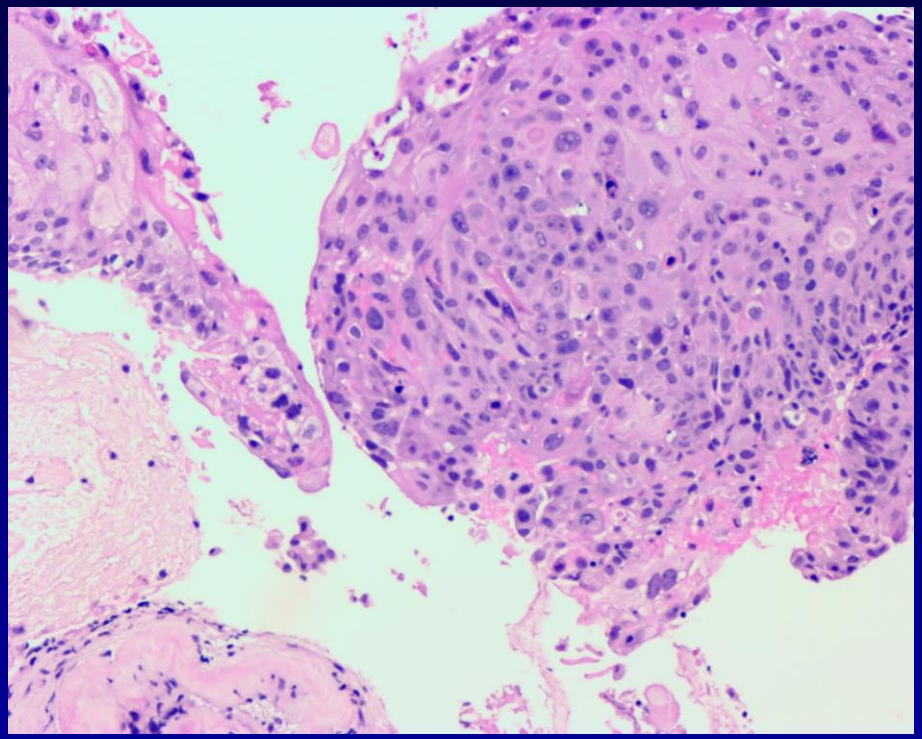


Post-treatment

Neoadjuvant Chemotherapy

Diagnostic Core Biopsy
Poorly Differentiated Ductal Carcinoma



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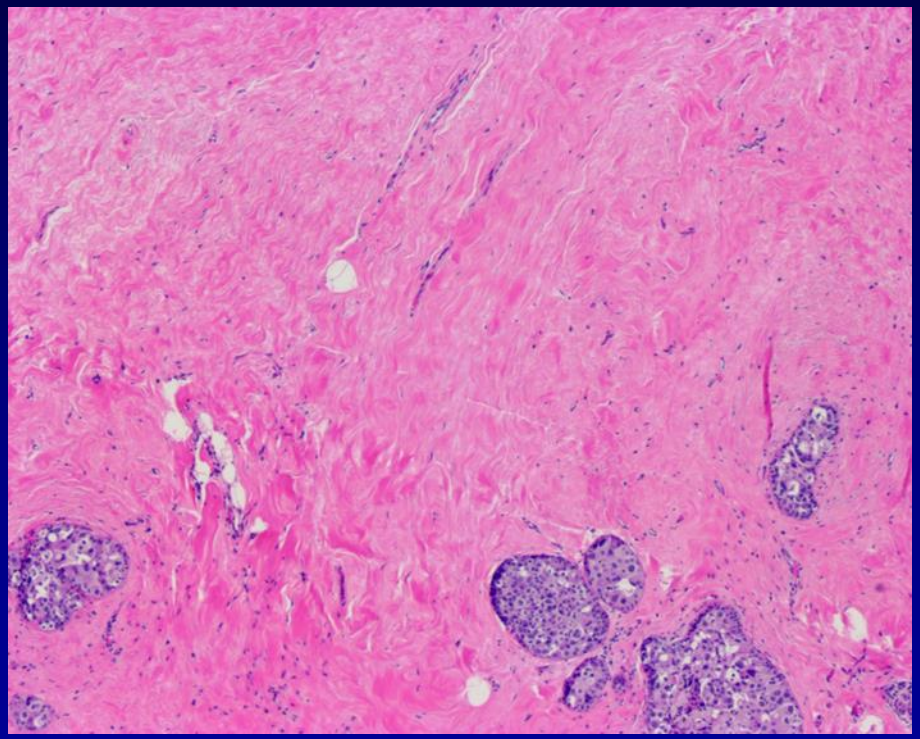


Post-treatment

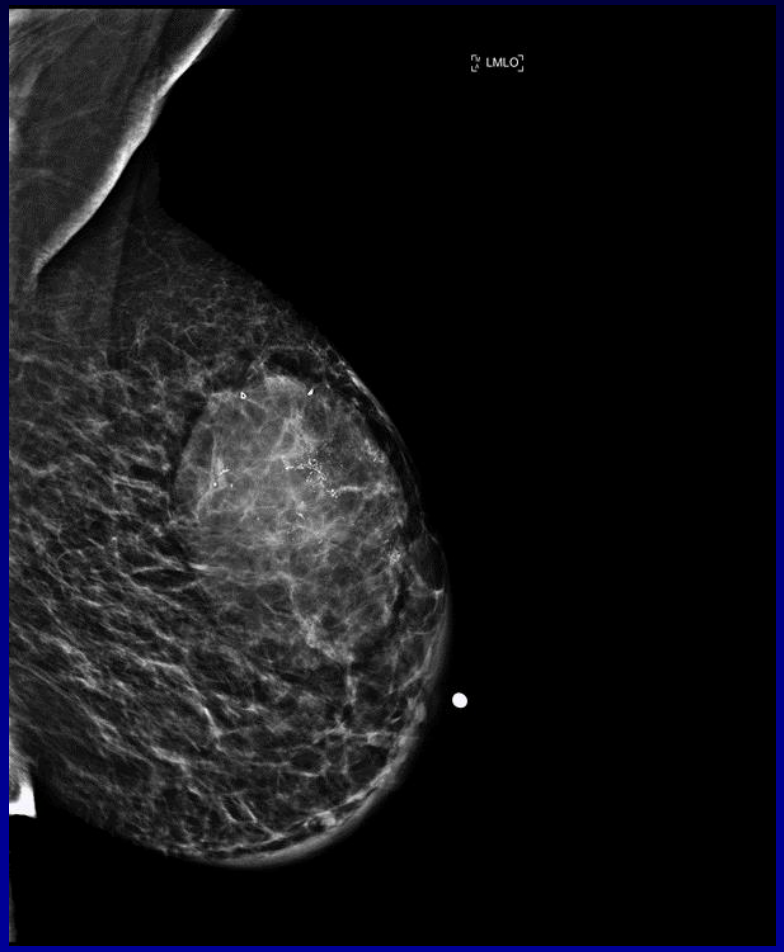
Neoadjuvant Chemotherapy

Clinical Presentation

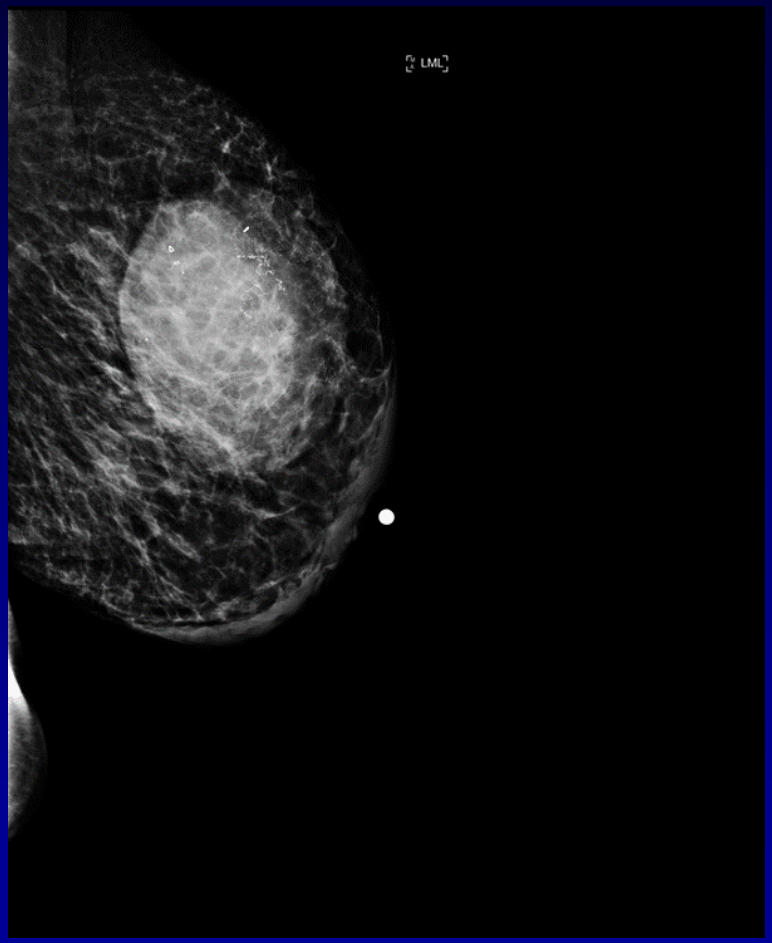
- 59 year old woman with 5cm palpable mass in the left breast on diagnostic mammogram

Neoadjuvant Chemotherapy

Pathologic Findings



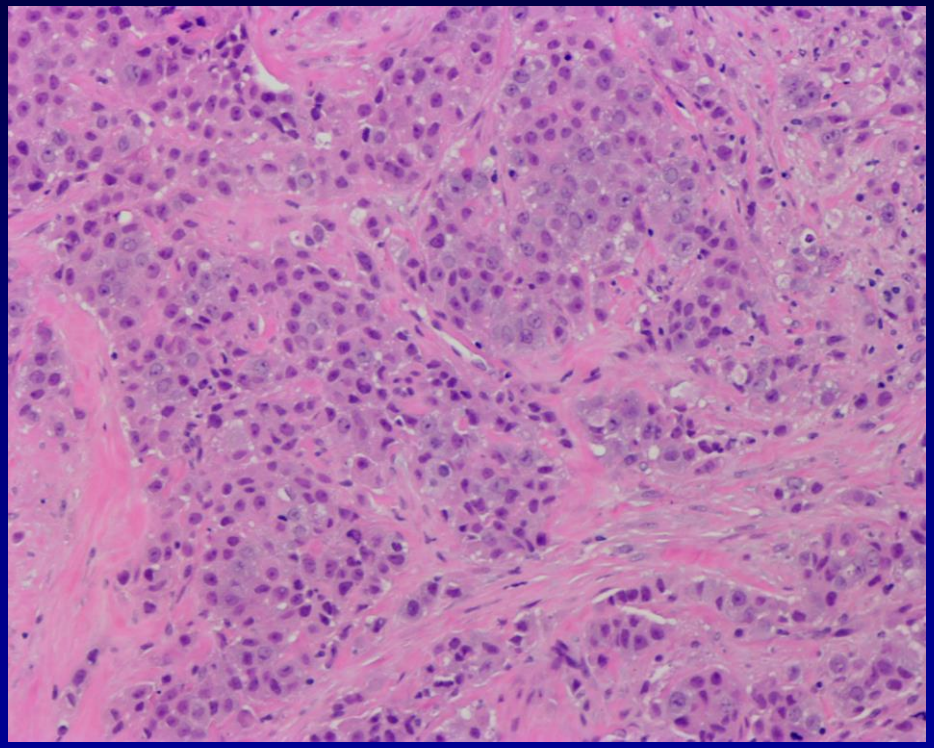
Pre treatment



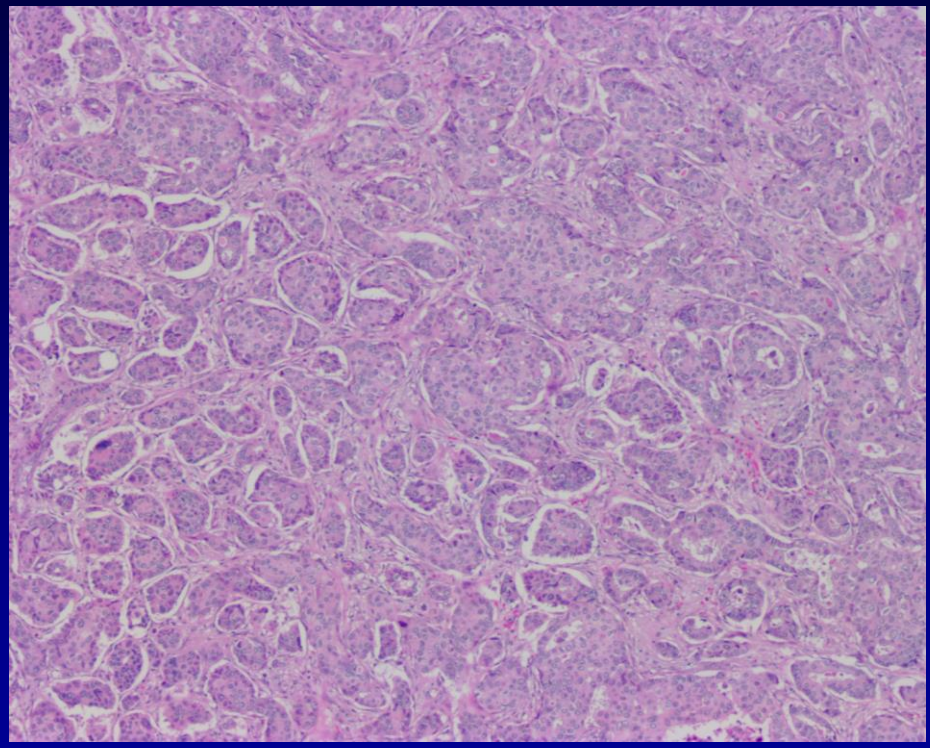
Post treatment

Neoadjuvant Chemotherapy

Pathologic Findings



Ultrasound Guided
Core Biopsy



Lumpectomy

Neoadjuvant Chemotherapy

Evaluation of Response

- Clinical examination
- Breast imaging studies
- Pathologic examination of post-treatment specimen

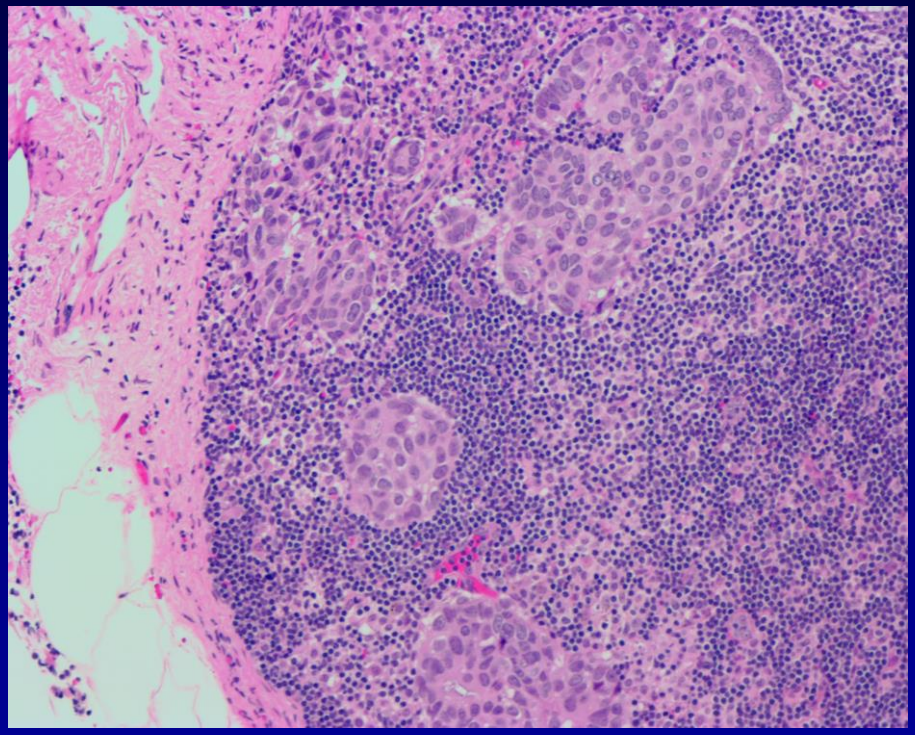
Neoadjuvant Chemotherapy

Assessment of post-treatment lymph nodes

- Pronounced lymphoid depletion, atrophy and fibrosis may represent complete response to therapy
- Residual tumors may be better identified by immunostaining for cytokeratin

Neoadjuvant Chemotherapy

Sentinel Lymph Node Biopsy



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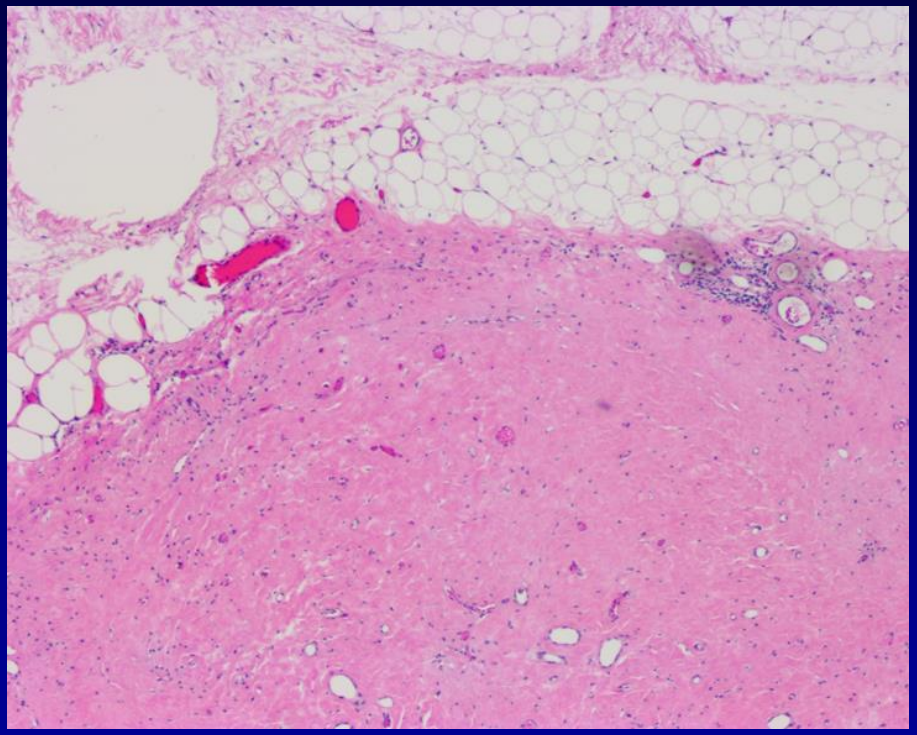


Post-treatment

Neoadjuvant Chemotherapy

Treatment Effects

- Tumor Size
  - Easy to measure if there is no or minimal response to therapy
  - Challenging if the tissue response to therapy makes the measurement of the actual isolated and clusters of residual tumor difficult

Neoadjuvant Chemotherapy

Treatment Effects

- Tumor cellularity
  - Can be used as a measure of response to therapy
  - This assessment may be complicated by the presence of associated chemotherapy induced tissue reaction resulting in overestimation of cellularity
  - Change in tumor cellularity requires access to tumor tissue prior to chemotherapy
  - Loss of tumor cellularity correlates with better clinical outcome

Neoadjuvant Chemotherapy

Impact on Prognostic Factors

- **Tumor Grade**
  - **Residual tumors may appear to be higher or lower grade**
  - **Ultimately the pre-treatment of tumor remains to be an independent prognostic factor**

Neoadjuvant Chemotherapy

Impact on Prognostic Factors

- Lymph Nodes
  - The status of lymph nodes after therapy is the most important prognostic factor
    - Patients with no residual tumor in breast who have residual tumor in lymph nodes have worse prognosis compared to patients who have residual tumor in breast and no residual tumor in lymph nodes
    - The evidence of treatment effect in lymph nodes with residual metastasis is associated with a better prognosis

Neoadjuvant Chemotherapy

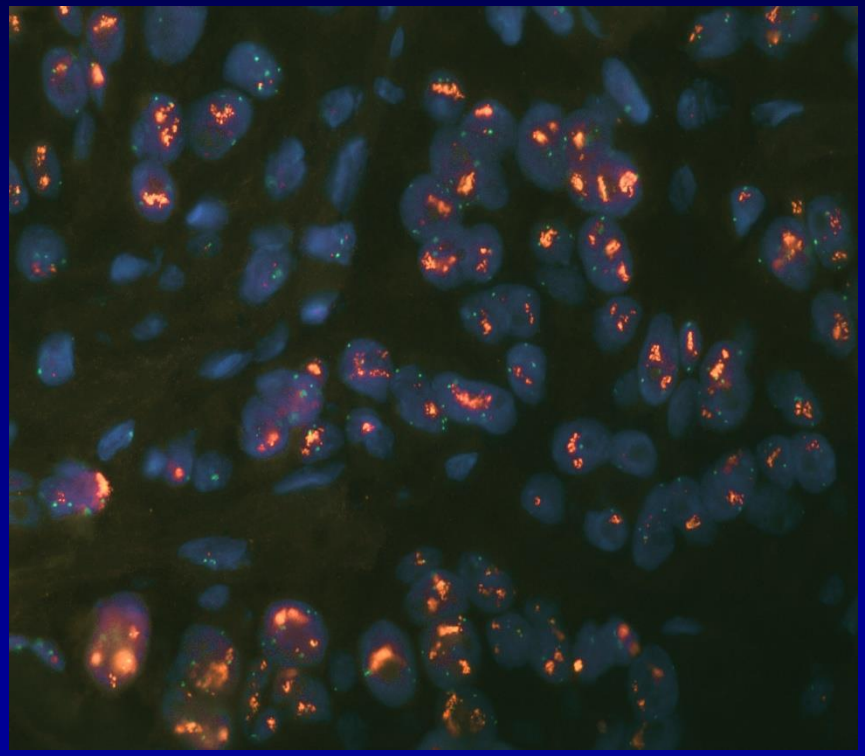
Impact on Prognostic Factors

- Patients who achieve pCR experience better outcomes regardless of tumor subtypes
  - Patients with HER-2/neu oncogene positive and triple-negative breast cancer who fail to respond to therapy have a worse outcome compared to patients with hormone receptor positive tumors (triple-negative paradox)

Neoadjuvant Chemotherapy

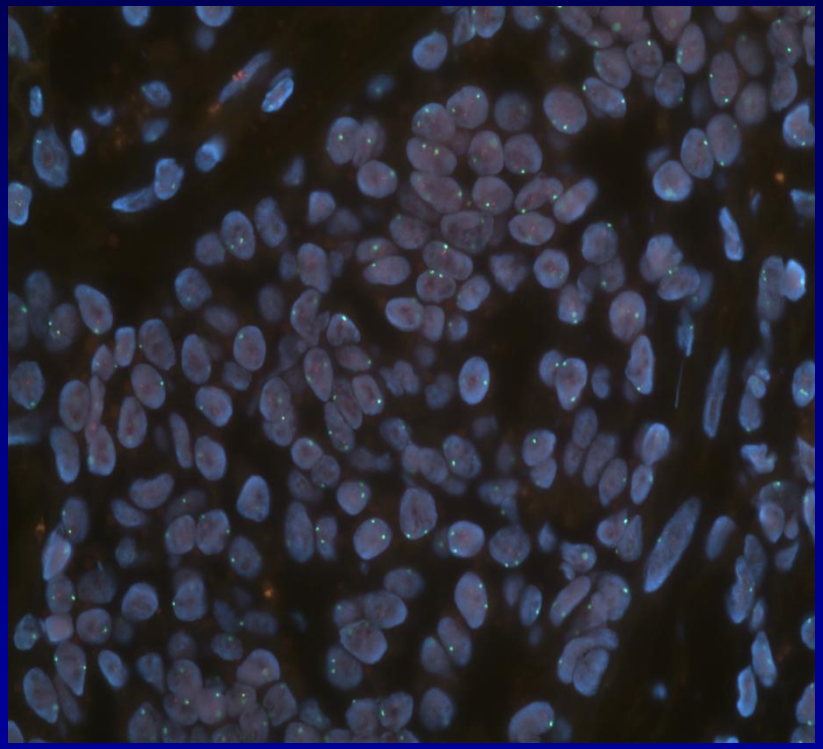
HER 2/neu Amplifications

Amplified



Pre-treatment

Non-Amplified



Post-treatment

Neoadjuvant Chemotherapy

Impact on Prognostic Factors

- Discrepancy between pre- and post-treatment
  - Hormone Receptor: 8-33%
  - HER-2/neu oncogene: up to 32%
- Compounding factors for discrepancies
  - Variability in tissue processing and fixation, lab errors, tumor heterogeneity
  - Change in tumor biology

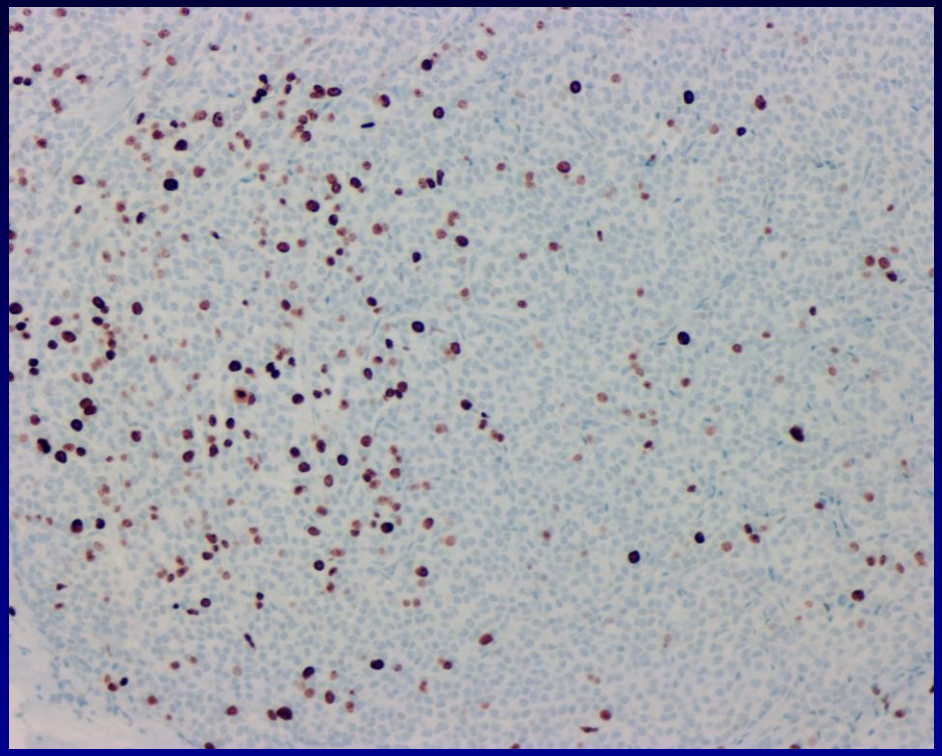
Neoadjuvant Chemotherapy

Impact on Predictive Factors

- Change in the proliferation index as determined by Ki-67 is the reflection of survival benefit
- Ki-67 can be considered as a surrogate biomarker in residual tumors to personalize additional therapy

Neoadjuvant Chemotherapy

Ki-67



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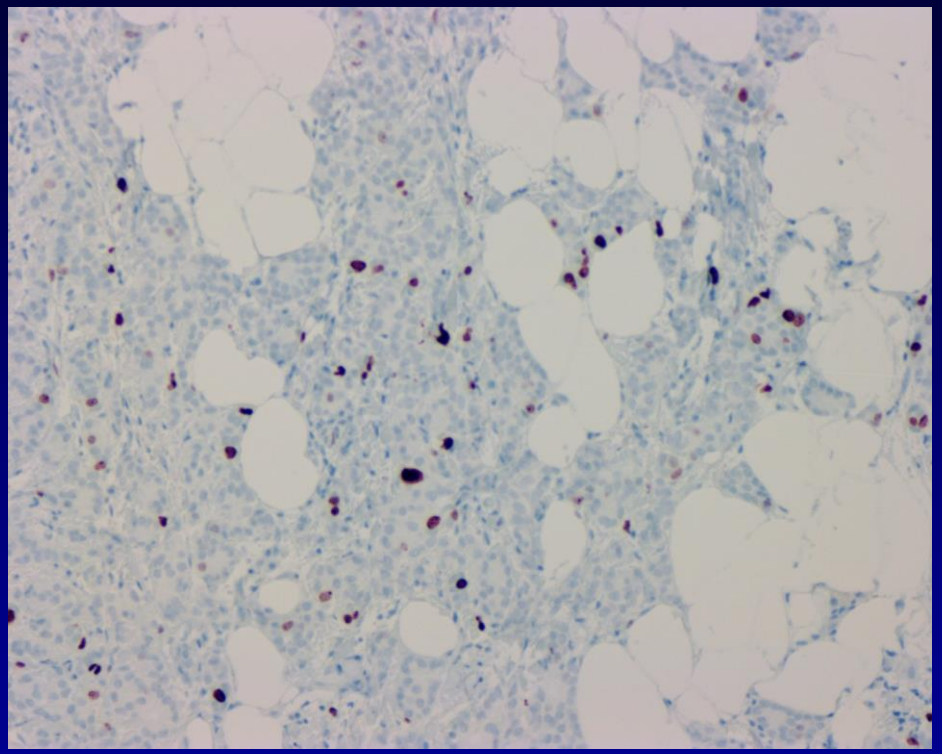

Post-treatment

Neoadjuvant Chemotherapy

Different Systems of Characterization of Response to Therapy

- NSABP-18
- Miller-Payne Grading System
- Residual Cancer Burden System
- Magee Method

Neoadjuvant Chemotherapy

Pathology Reporting

- Assessment of response to the tumor
- Size of the tumor bed
- Size and extent of residual tumor
- Tumor cellularity compared to primary tumor
- Tumor grading

Neoadjuvant Chemotherapy

Pathology Reporting

- Viability as assessed by Ki-67 immunostaining, presence of mitosis and necrosis
- Lymphovascular invasion
- Presence of ductal carcinoma in situ
- The status of margin with respect to tumor bed
- Inclusion of prefix pT for pathologic staging

Neoadjuvant Chemotherapy

Pathology Reporting – Lymph Node Status

- Number of lymph nodes
- Number of lymph nodes with metastasis and the size of the largest deposit
- The status of treatment response
- Presence or absence of extranodal involvement

Neoadjuvant Chemotherapy

The Status of Variability of Pathology Reporting

- Report of a central review of histopathology reports within a multicenter neoadjuvant clinical trial in United Kingdom
- Out of 825 surgical reports, there was 347 discrepancies
  - Laterality
  - The status of lymph node metastasis
  - Response to therapy

Neoadjuvant Chemotherapy

What a Pathologist Should Know

- Immunostains for epithelial and myoepithelial markers and markers for macrophages may be used for assessment of presence or absence of residual tumor cells
- Ki67 may be used to grade the degree of response to neoadjuvant chemotherapy
- The status of ER PR and HER-2/neu oncogene may change as the result of neoadjuvant chemotherapy
- Adherence to the established guidelines for reporting of neoadjuvant chemotherapy is important for accurate reporting of pathologic response and patients following management

Summary

Guidelines in Breast Pathology Reporting of Neoadjuvant Chemotherapy

- Neoadjuvant chemotherapy has become a major trend in breast cancer care
- Establishment of an integrated multidisciplinary care among pathologists, radiologists, surgical and oncologists are essential for accurate assessment of response to neoadjuvant chemotherapy
- Access to the information about diagnostic, and prognostic/predictive information of breast tumor and sentinel lymph node prior to neoadjuvant chemotherapy are essential for appropriate reporting of pathologic response to therapy


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