Radiologic Response to Neoadjuvant therapy in luminal Breast Cancers

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Introduction

- locally advanced breast cancer

Advantages:

- Reduce breast tumor size
- Downstage the axilla
- Allowing a more conservative surgery
- Prognosis improvement

Luminal breast cancers

- luminal A, luminal B, her2 positive, triple negative
- Each subtype having a unique biology, prognosis, and response to treatment
- Comprise >70% of all breast cancers ; luminal breast cancers

Cont.

- PCR after NAC in hormone-receptor– positive breast cancer ; 8%
- patients with strongly positive hormone receptor expression neoadjuvant endocrine therapy can be considered
- long duration and limited pCR rates, neoadjuvant therapy for patients with well-differentiated ER-positive disease is not used frequently

Aim of imaging

- Assessment of the response to treatment
  - The main aim of imaging
  - Estimate of residual tumor
  - Both influencing patients' prognosis and surgical strategy

- Early predicting the response to treatment
  - Advanced imaging techniques able to provide functional information and quantitative parameters reflecting tumor biology,

Imaging in Luminal and non Luminal breast cancer

- greatest accuracy of imaging in ERnegative/HER2-positive and triple-negative tumors

- less accuracy in luminal tumors

prior to the start of neoadjuvant therapy

- Diagnostic mammography
  - Digital breast tomosynthesis
- Targeted US
- the optional use of MR imaging before and after neoadjuvant therapy, which may be helpful for occult tumor
- biopsy marker clip placement within the breast tumor and axillary lymph node
- systemic imaging ;clinical stage IIB with advanced axillary disease, stage III, locally advanced, and inflammatory breast cancer

Evaluation of Residual Tumor after NAC

Evaluation of Residual Tumor

- Physical exams
- Digital Mammography and Digital Breast Tomosynthesis
- Ultrasound
- Magnetic Resonance Imaging
- Contrast-Enhanced Spectral Mammography
- Nuclear Medicine Techniques

Size

- tumor size is considered the main parameter to define the tumor responsivity

- All these procedures are basically monitor changes of tumor size

Physical exam

- accuracy of clinical breast examination for pCR in patients ;57%,
  - mammography (74%) and US (79%)

- presence of firm fibroglandular tissue and post therapy fibrosis, can overestimate the amount of residual disease.

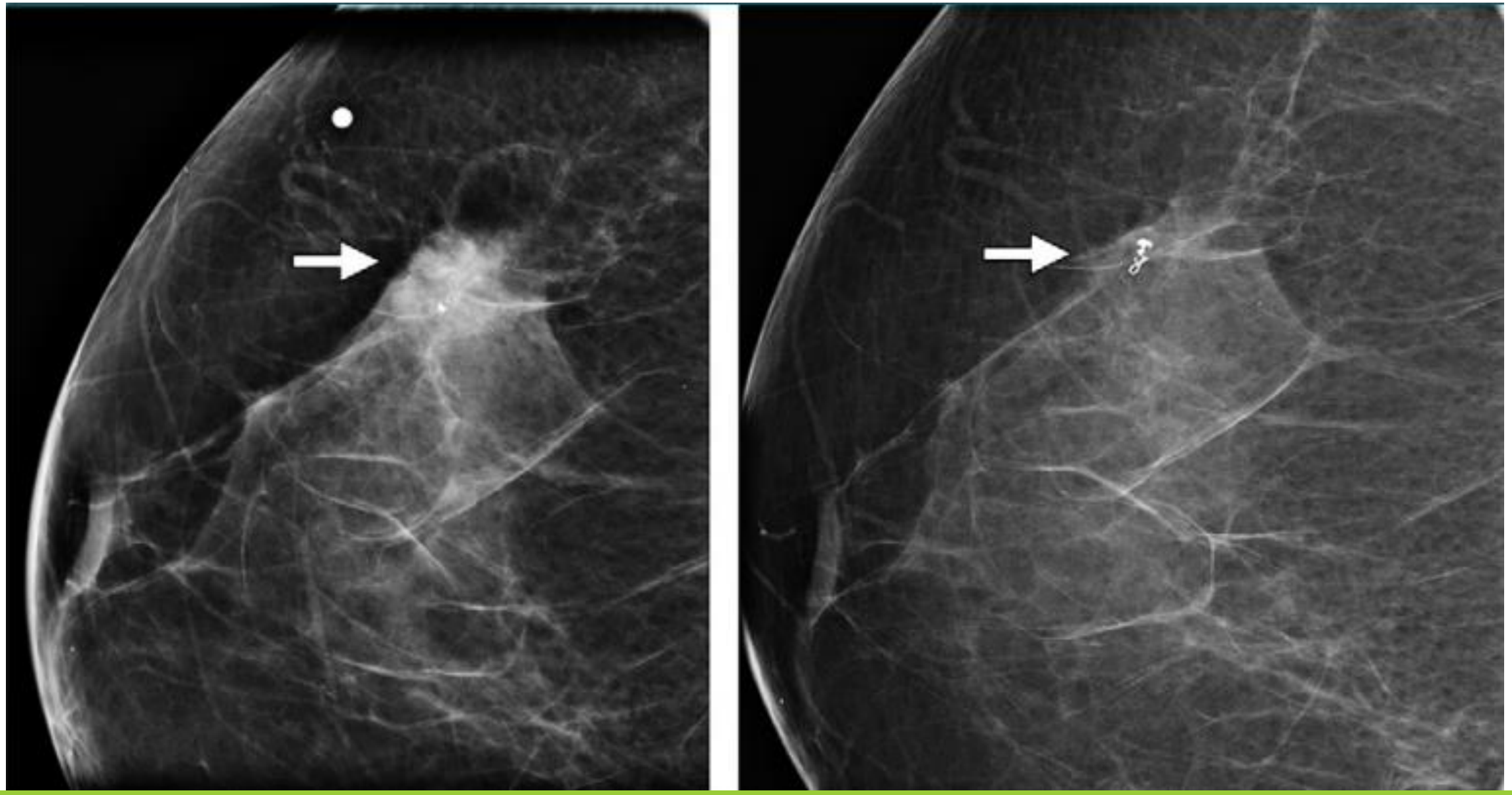
- interval loss of palpability after treatment does not exclude the presence of residual tumor.

Digital Mammography and Digital Breast Tomosynthesis

- The most reliable indicators ;decrease in size and density
- Higher accuracy of DBT than DM
- More sensitive than physical examination for detecting presence of residual tumor
- Less specific and may underestimate the degree of treatment response

Digital Mammography and Digital Breast Tomosynthesis

- The accuracy depends upon specific tumor morphological characteristics
- Higher for well circumscribed lesions on the pre-treatment examination
- Calcifications and spicules are the biggest challange



Ultrasound

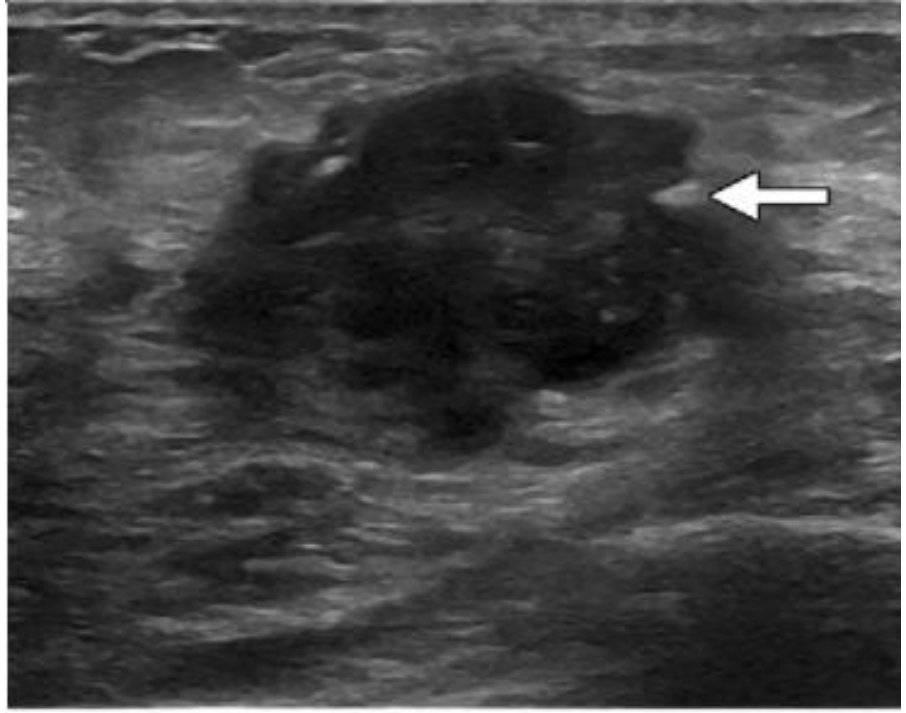
- change in tumor echogenicity and size
- more accurate method than CE or DM in assessing tumor size and residual breast tumors
- most accurate predictor of response in axillary lymph nodes compared with mammography and physical examination

Ultrasound

- Triple negative tumors seem to have the highest NPV and lowest FNR

- Implying that pathologic response to NACT can most reliably be predicted for this subtype

- Operator dependency and shortage of qualified personnel have been an issue in hand-held US



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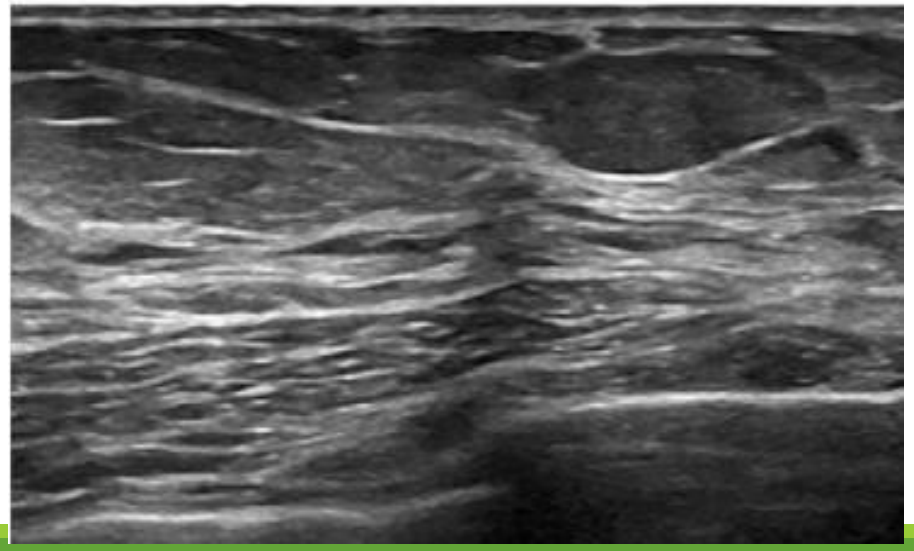


Advanced Imaging Techniques

- NAC monitoring methods such as DM or US or physical examination are not free from limitations

- Functional imaging techniques, such as
  - positron emission tomography (PET)
  - MRI with diffusion weighted imaging
  - diffuse optical spectroscopy

  - changes in the microstructure ,vascularization , and metabolic activity of tumors under the influence of chemotherapy after the first cycle of treatment

MRI

- accurate assessment of primary lesion dimension , loco-regional disease spread, multi focality , multi centricity , and lymph nodes involvement
- more accurate than DM, DBT, and US
- DCE-MRI and diffusion-weighted MR imaging (DWI-MRI) significantly improved the detection, diagnosis, and monitoring of breast tumors

MRI

- Utilization of breast MR imaging for evaluation of response to NAC
  - included as one of the recommended clinical indications by the American College of Radiology and European Society of Breast Imaging
  - included in the NCCN guidelines as an optional tool

- Despite inclusion in several clinical practice guidelines, preoperative breast MR imaging is not universally utilized

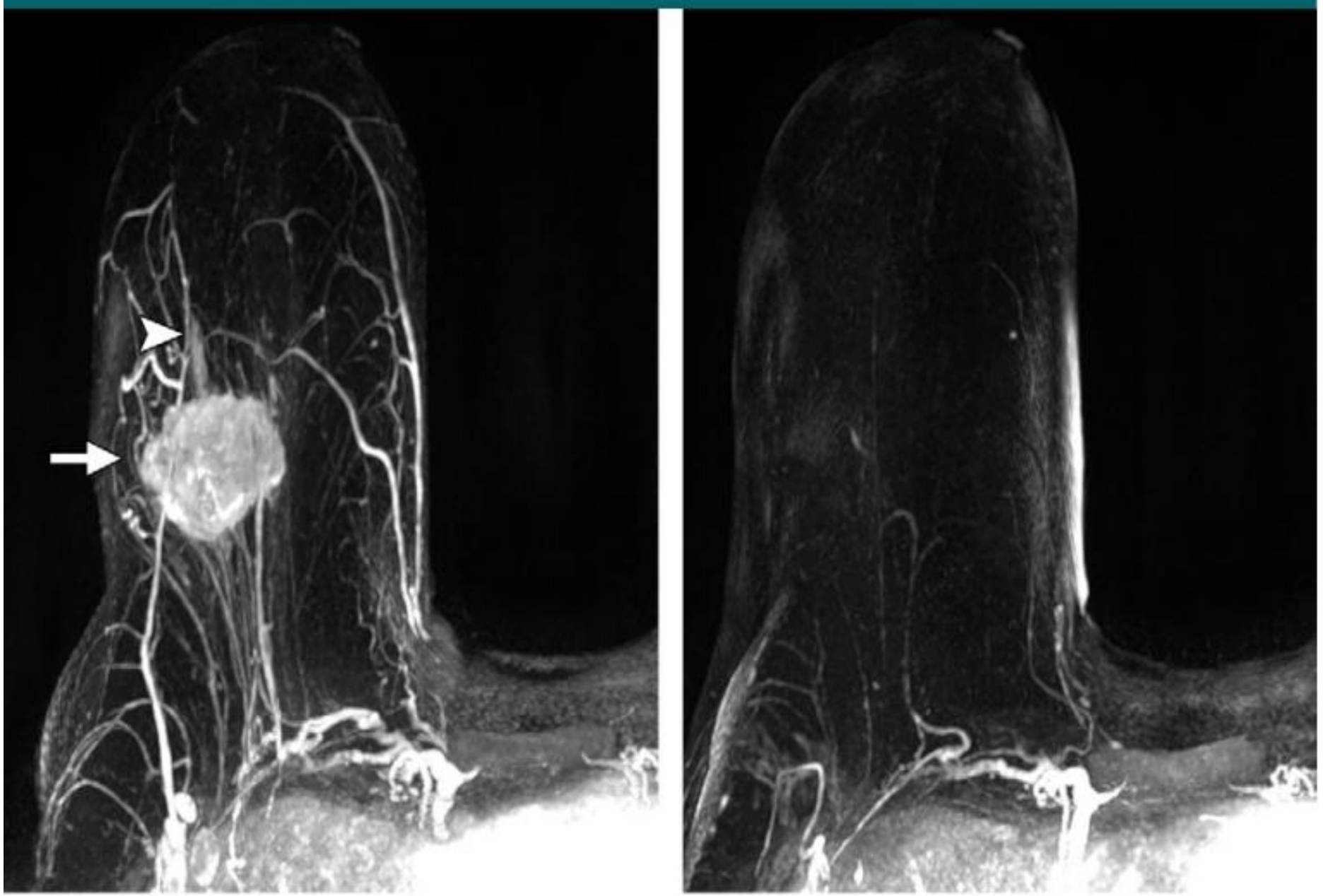
MRI

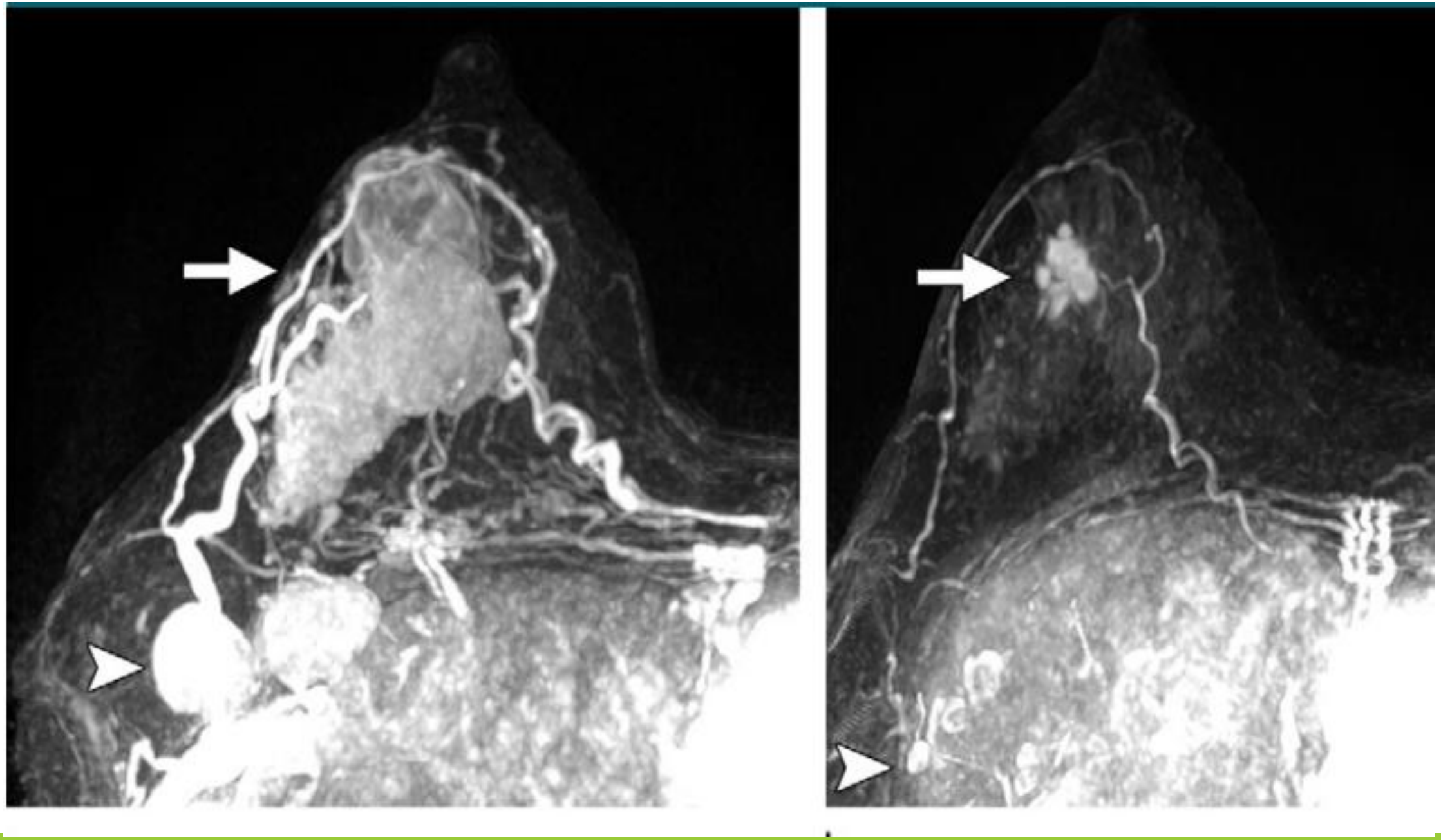
❖diagnostic accuracy

1. greatest in ERnegative/HER2-positive and triple-negative tumors and is less accurate in luminal tumors
2. The type of chemotherapy regimen ;
   - underestimate residual disease in patients treated with taxanes and antiangiogenic drugs, through hypothesized antivascular effects on contrast enhancement
3. The pattern of tumor response ;
   - underestimate ;fragmentation occurs and small foci of residual tumor cells are scattered over a large area
   - overestimate residual disease if there is host response of reactive inflammation and fibrosis

MRI

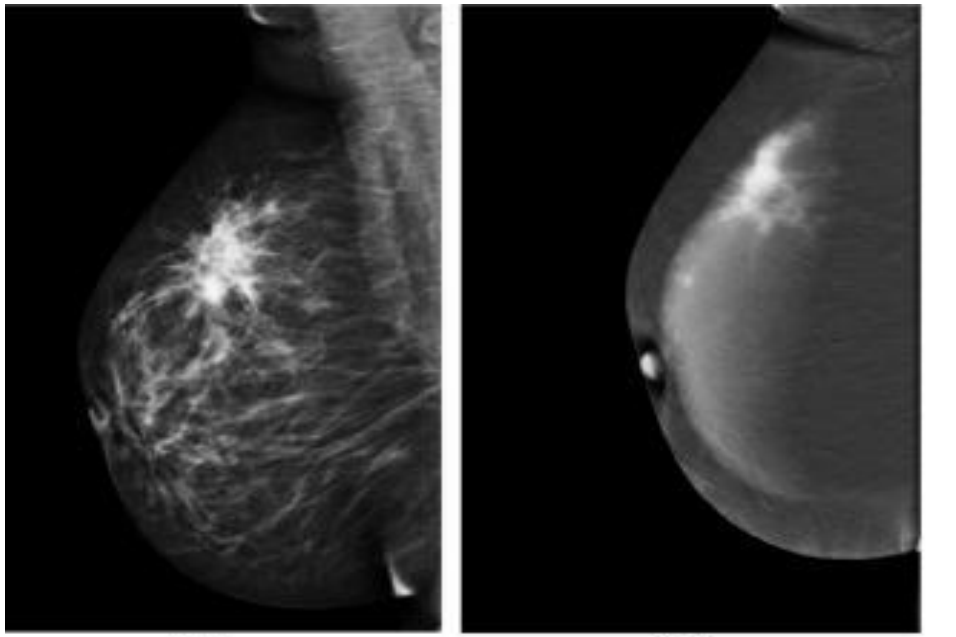
- Tumor molecular subtype is one key factor
- the ER-negative tumors have higher contrast uptake on MRI after NAC than the ER-positive ones
- Accuracy of MR imaging is greatest in ER-negative/HER2-positive and triple-negative tumors and is less accurate in luminal tumors
- MRI for predicting pCR is generally more accurate in tumors that have a better response





Contrast-Enhanced Spectral Mammography

- Combines DM to intravenous administration of a contrast agent
- Allowing the assessment of neo-angiogenesis in patients who cannot undergo MRI
- CEM was comparable to MRI



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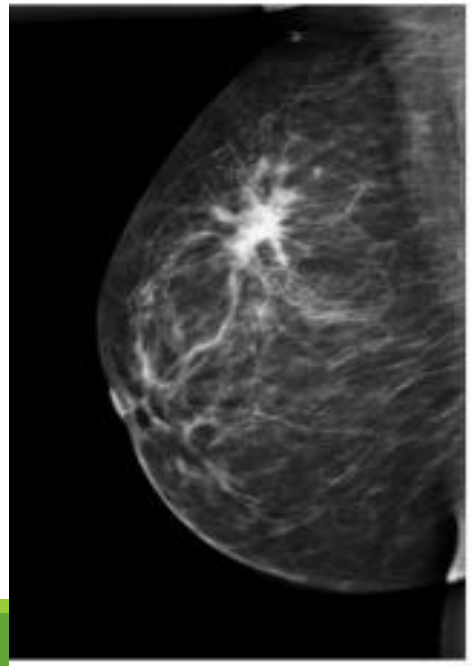

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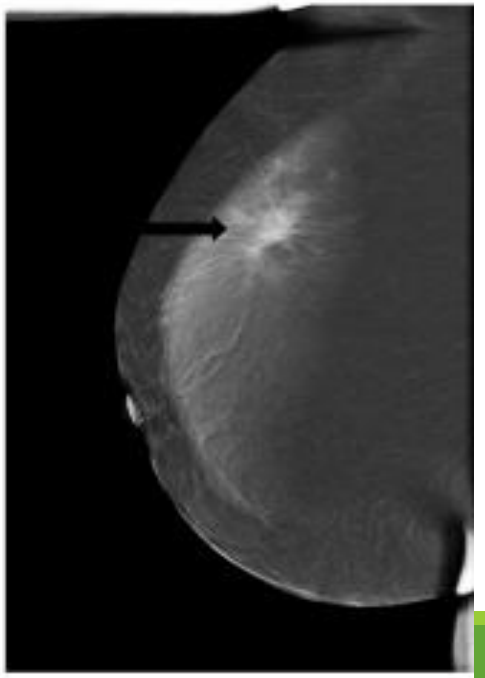
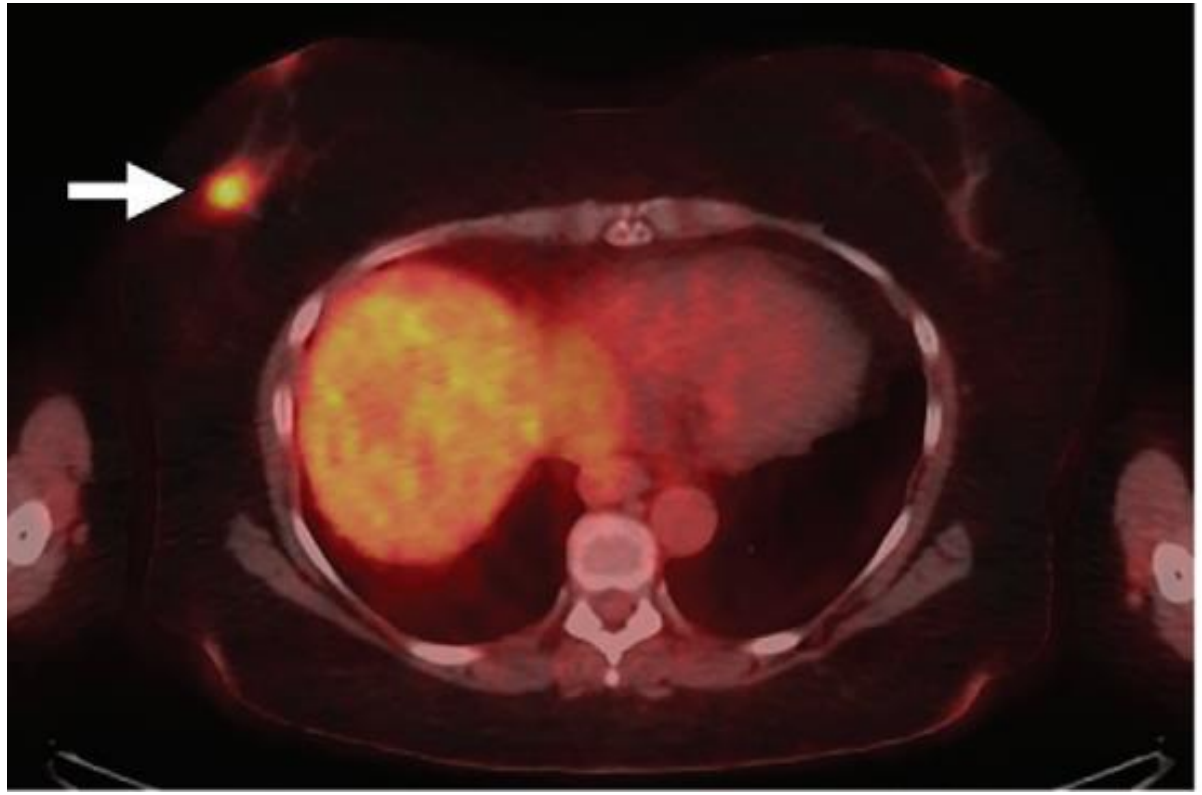


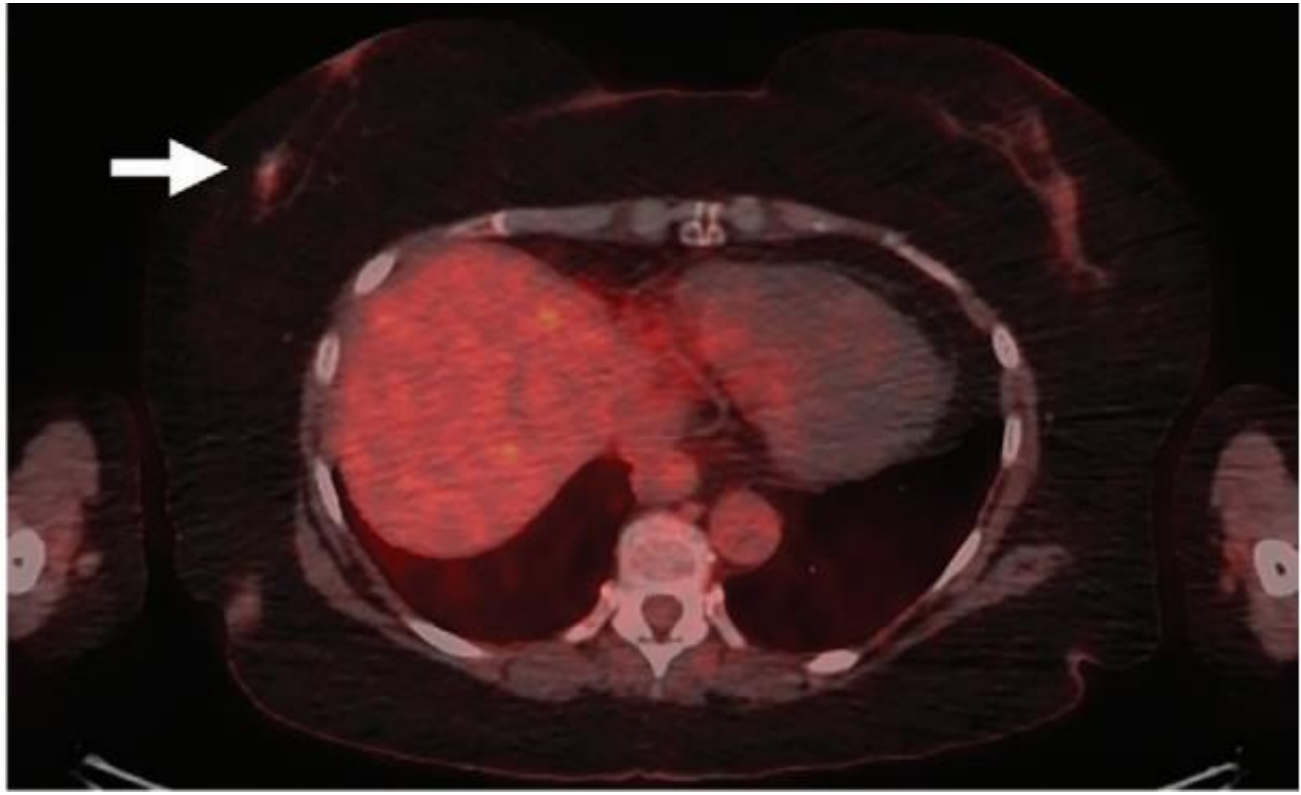
(D)

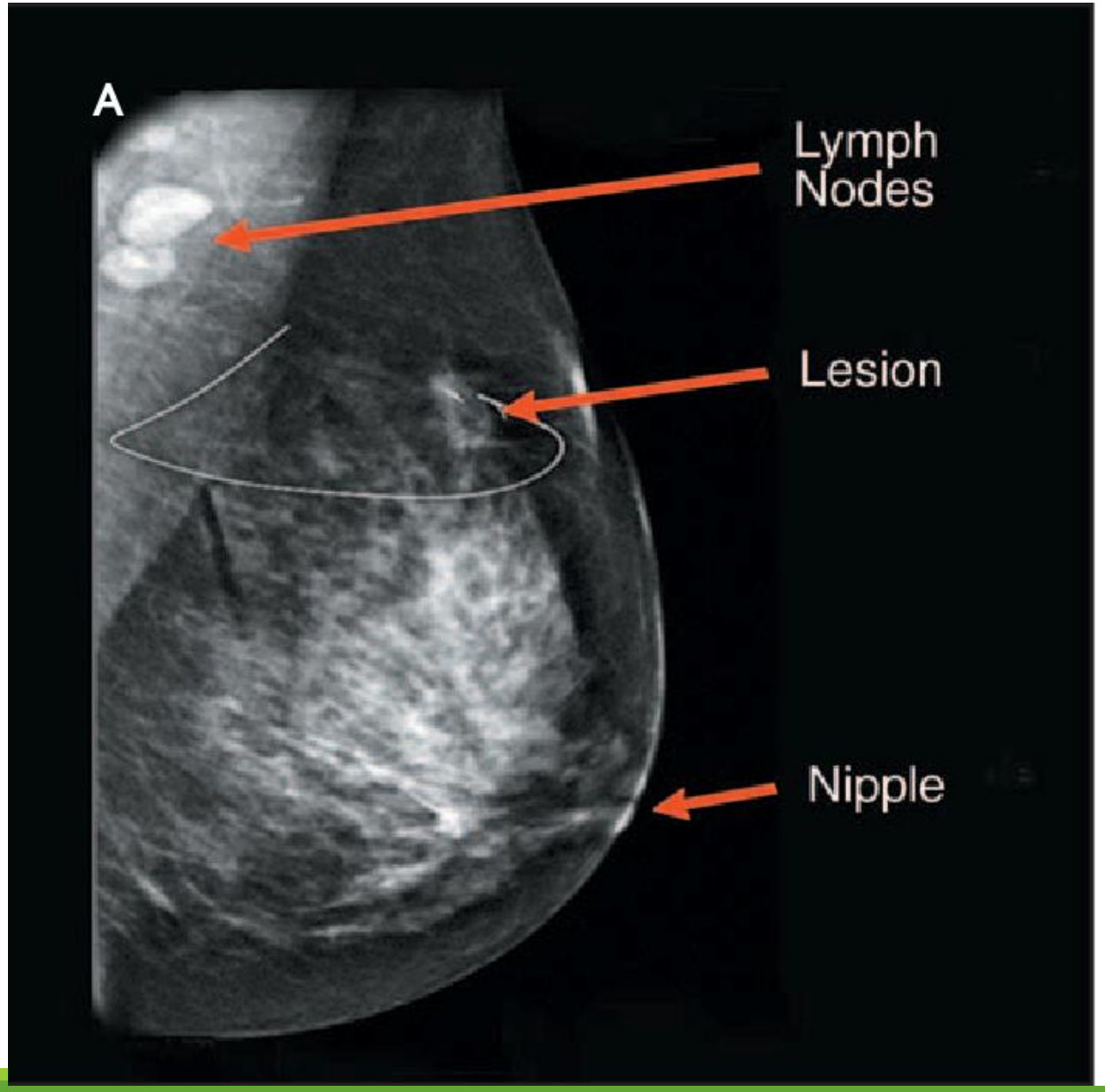
Nuclear Medicine Techniques

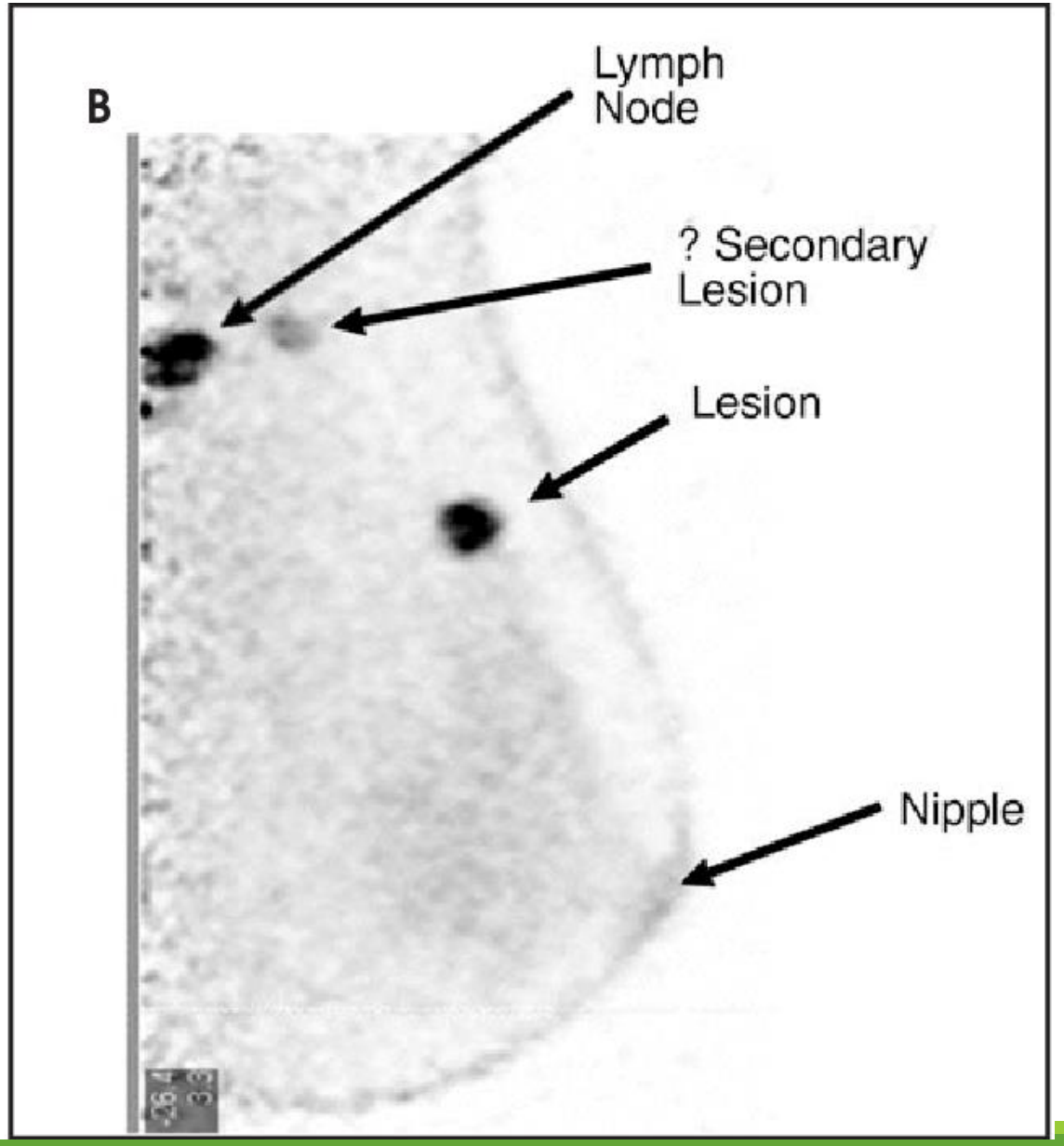
- (PET/CT) showed a tendency toward underestimation of the residual tumor with relatively low specificity and PPV

- positron emission mammography (PEM) has shown higher sensitivity and specificity than PET/CT in particular for lesions smaller than 2.5 cm






A
Lymph Nodes
Lesion
Nipple


B
Lymph Node
? Secondary Lesion
Lesion
Nipple

Limitation in hormone receptor positive tumor

The use of [18F]FDG PET SUVmax or SULpeak to stratify response in ER+/HER2− breast cancer is met with challenges.

1. pre-treatment [18F]FDG uptake for this group is low making quantification of post-treatment change difficult

2. ER+/HER2− tumors have variable chemosensitivity and rarely achieve pCR in the NAC setting

3. SUV prediction of response is more accurate at early time points during NAC, but ER+/HER2− tumors are slow to respond

Molecular breast imaging (MBI)

- dedicated gamma cameras and an injected radiopharmaceutical such as technetium-99m Sestamibi

- MBI can be performed as an alternative in patients with contraindications for performing MRI

- in breast cancer patients to assess disease extension, and response

overestimation of residual disease

- Fibrosis
- necrotic tumors
- residual benign masses

underestimation Residual tumor

- Non mass lesions
- invasive lobular carcinoma
- hormone receptor–positive tumors
- nonconcentric shrinkage patterns
- the use of antiangiogenic therapy
- late-enhancing foci

Prediction of Response to NAC

Prediction of Response to NAC

- Early prediction of response is crucial
  - increasing survival
  - lowering toxicity
  - Costs

- It could avoid unnecessary further drug administration in patients who do not respond

- MRI, hybrid-imaging and AI modalities have been proposed for this purpose

Magnetic Resonance Imaging

- Functional imaging techniques, such as DWI-MRI and DCE-MRI,MR spectroscopy
- depicting biological properties of tumors, such as cellularity and neo-angiogenesis
- trough the extraction of quantitative DWI-MRI (apparent diffusion coefficient, ADC) and DCE-MRI (Ktrans, Ve, Kep, iAUC) parameters that may change earlier during the course on NAC, before any morphological changes are detectable
- changes in kinetic MR imaging and ADC value after one to two cycles of neoadjuvant chemotherapy ;predict pathologic response

Hybrid Imaging Techniques

- Hybrid-Imaging using PET/CT could be extremely useful in early response prediction as it assesses both morphological and functional cancer features

- PET/MRI is the hybrid newest imaging technique which allows the simultaneous collection of morphologic, metabolic, and functional parameters with higher contrast resolution compared to PET/CT

- The main limitation of PET is the assessment of small tumors as it has low spatial lresolution. PEM could overcome such limit as it is accurate for the evaluation of small lesions

- 18F-FDG PET/MRI could be used to predict non-pCR after the first cycle of NAC.

Take home message

- Imaging is less accuracy in luminal tumors
- tumor size is considered the main parameter to define the tumor responsivity
- MRI is most accurate assessment of primary lesion dimension