Radiological assessment of neoadjuvent chemotherapy for breast cancer

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Presurgical neoadjuvant chemotherapy is becoming the standard of care in the treatment of locally advanced breast cancer (BC) and is a treatment option for patients with early stage BC.

The main goal of neoadjuvant chemotherapy is downstaging primary tumors to increase the breast conservation rate.

Clinical trials found that patients who experienced a pathologic complete response after neoadjuvant chemotherapy had significantly higher survival rates than did patients with residual tumor.

Von Minckwitz et. al., Smith IC et al., 2012
• With respect to maximum tumour diameter measurement, the two most commonly used guidelines to assess treatment response are the guidelines of the World Health Organization (WHO) and the Response Evaluation Criteria for Solid Tumours (RECIST).

• In the WHO guidelines, four response categories can be identified:
  1. complete response (CR), in which no more enhancing tumour is visible;
  2. partial response (PR), which is a reduction in diameter of ≥50%,
  3. progressive disease (PD), which is an increase in tumour diameter of ≥25% and which rarely occurs under NAC;
  4. no changes, which is the level between PD and PR
• The RECIST criteria also divide response into four categories:
  1. CR is defined as the absence of enhancing tumour;
  2. PR as a decrease in tumour diameter ≥30%;
  3. PD as an increase in tumour diameter ≥20%;
  4. Stable disease is considered to be the level between PD and PR.

• There is currently no standard approach for the imaging evaluation and follow-up of patients undergoing neoadjuvant chemotherapy (Gaiane et al. 2017)
Clinical Examination

• Historically, patients treated with neoadjuvant chemotherapy have been monitored with regular physical examination (PE) of the breast and axilla for palpable masses and lymphadenopathy.

• However, PE is known to be inaccurate in evaluating the response to neoadjuvant chemotherapy.

• In a data synthesis of six studies, the overall accuracy of PE was 57%, the positive predictive value (PPV) was 91%, and the negative predictive value (NPV) was 31%.

Croshaw et al. 2011
Mammography and breast ultrasound are the most commonly used imaging modalities for tumor diagnosis and neoadjuvant chemotherapy follow-up.

A study by Chagpar et al. evaluated the accuracy of PE, ultrasound, and mammography in predicting the residual size of breast tumors after neoadjuvant chemotherapy and showed that size estimates were only moderately correlated with residual pathologic tumor size, with an accuracy in 66% of patients by PE, 75% by ultrasound, and 70% by mammography.

Decreases in the size and density of the mass on mammography are the most reliable and common indicators of treatment response, whereas changes in calcifications associated with malignancy are often misleading. Microcalcifications can increase, decrease, or remain stable after neoadjuvant chemotherapy.

Adrada et al. 2015
Ultrasound

- Reportedly, ultrasound is more accurate than mammography in estimating residual tumors.

- Keune et al. reported that breast ultrasound was more accurate than mammography in measuring residual disease after neoadjuvant chemotherapy. Ultrasound was able to size the residual disease in 91.3% of cases compared with only 51.9% by mammography ($p < 0.001$).
Ultrasound

• There was no difference in the ability of mammography and ultrasound to predict pathologic complete response.

• When both mammography and ultrasound found no residual disease, the likelihood of pathologic complete response was 80% (Keune et al. 2010)

• The use of both imaging modalities improved the accuracy of predicting a pathologic complete response to neoadjuvant chemotherapy to a greater degree than did the use of either modality alone.
Functional Imaging

- Conventional imaging modalities rely on changes in size or morphologic characteristics to evaluate tumor response. Therefore, they are inherently limited in assessing residual disease and cannot reliably predict pathologic response.

- Functional imaging technologies evaluate vascular, metabolic, biochemical, and molecular changes in cancer cells. These changes occur before morphologic changes, allowing the earlier assessment of response to neoadjuvant chemotherapy.
MRI

• Dynamic contrast-enhanced (DCE) MRI can detect tumor angiogenesis, associated changes in tumor microcirculation, and uptake of contrast material as a result of the increased permeability of the new vessels that form in growing tumors.

• It provides insight into the pathophysiology of tumor response to neoadjuvant chemotherapy and allows an earlier and more accurate assessment of tumor response than does anatomic imaging.
MRI

- The reported sensitivity, specificity, and accuracy of DCE-MRI for residual disease evaluation are 86–92%, 60–89%, and 76–90%, respectively.
  
  Dilani et al, Schultz-Wendtland et al. 2015

- A meta-analysis of 44 studies between 1990 and 2008, including 2050 patients who underwent imaging evaluation of residual disease after neoadjuvant chemotherapy, found that MRI had generally high sensitivity (83–87%) and heterogeneous specificity (54–83%).
  
  Marinovich et al. 2013
MRI

- The reported accuracy of MRI in estimating residual disease after neoadjuvant chemotherapy varies by tumor subtype.

  Hayashi et al. 2013

- A retrospective analysis of serial DCE-MRI in 166 patients showed that it was the most accurate at predicting tumor response to therapy in triple-negative BC, ErbB-2–positive tumors, and high-grade tumors, with the highest sensitivity for MRI scans performed after two cycles of neoadjuvant chemotherapy.

  Fatayer et al. 2016
MRI

- DCE-MRI neoadjuvant chemotherapy response analysis uses either a semiquantitative analysis, based mainly on tumor size, volume or enhancement, or fully quantitative methods, based on complex pharmacokinetic modeling.

  Woolh DK et al. 2016

- Changes in textural features can be evaluated on contrast enhanced and T2W sequences and have shown promise in predicting response to neoadjuvant chemotherapy.
DWI

- Newer MRI sequence DWI and its quantitative derivative, the apparent diffusion coefficient (ADC), can be used as a surrogate biomarker for the early detection of therapeutic response on the basis of the diffusivity of water, tumor cellularity, and cell membrane integrity.
  
  Wu et al; Bufi et al. 2012

- A retrospective study of DWI in 53 patients undergoing neoadjuvant chemotherapy showed statistically significantly lower ADC values in responders versus nonresponders ($p = 0.004$).
  
  Park et al. 2010

- A meta-analysis of 34 studies showed that the sensitivity and specificity of DWI versus DCE-MRI were 93% and 82% versus 68% and 91%, respectively.
  
  Wu et al. 2012
FDG PET Imaging

- Fluorine-18 FDG PET imaging is a metabolic functional imaging modality that can show changes in tumor metabolism early during neoadjuvant chemotherapy, before morphologic changes are apparent (Groheux et al. Hatt et al. 2013)

- A meta-analysis of 19 studies reported that the pooled sensitivity, specificity, PPV, and NPV of FDG PET in the early detection of response were 84%, 66%, 50%, and 91%, respectively (Wang et al. 2012)

- Dedicated high-resolution positron emission mammography is a novel molecular imaging modality with reportedly high sensitivity (87%) and specificity (85%) for the detection of BC

- PET/MRI is a new hybrid imaging modality that has not yet been well studied in patients with BC.
Molecular breast imaging

• Another functional imaging modality that is used for the diagnostic and neoadjuvant evaluation of BC is 99mTc-sestamibi scanning. It showed a pooled sensitivity of 86% and specificity of 69% (Guo et al. 2016).

• Molecular breast imaging could become a low-cost standard of care for BC patients.
Novel Ultrasound-Based Imaging

- Breast elastography objectively evaluates tumor stiffness, in addition to the tumor’s morphologic characteristics and vascularity evaluated by ultrasound. Research has found that tumor stiffness is associated with tumor progression, including carcinogenesis and stromal factors (Evans et al. 2013).
• Contrast-enhanced ultrasound has shown promise, both qualitatively and quantitatively, in evaluating tumor blood flow changes in the neoadjuvant setting.
• Quantitative ultrasound and diffuse optical spectroscopy application for neoadjuvant chemotherapy prediction and monitoring needs further investigation.
Axillary Nodal Imaging

• An axillary pathologic complete response is seen in 40–75% of patients with biopsy-proven positive nodal disease receiving neoadjuvant chemotherapy Boughey et al. 2015

• Therefore, imaging the axilla before and after neoadjuvant chemotherapy may affect disease management.

• Ultrasound is a fast noninvasive inexpensive modality for axillary nodal imaging.

• A retrospective multimodality analysis of the detection of node-positive disease after neoadjuvant chemotherapy showed that ultrasound had the highest sensitivity (70%), followed by FDG PET/CT (63%) and MRI (61%) Hieken et al. 2013
Conclusion

- Neoadjuvant chemotherapy is becoming the standard of care for patients with locally advanced breast cancer.
- Conventional imaging modalities used for the assessment of tumor response to neoadjuvant chemotherapy rely on changes in size or morphologic characteristics and, therefore, are inherently limited.
- Functional imaging technologies evaluate vascular, metabolic, biochemical, and molecular changes in cancer cells and have a unique ability to detect specific biologic tumor markers, assess therapeutic targets, predict early response to neoadjuvant chemotherapy, and guide individualized cancer therapy.
- Clinical breast examination and routine breast imaging with mammography and ultrasound remain the standards of care for the follow-up of patients undergoing neoadjuvant chemotherapy.
Conclusion

• DCE-MRI is superior for predicting treatment response and evaluating residual disease. Newer MRI sequences, such as DWI with ADC analysis, as well as advanced imaging software using texture analysis and quantitative dynamic contrast measurements, are promising tools for predicting response, leading to the early modification and tailoring of neoadjuvant chemotherapy regimens.

• There is ongoing research into the use of FDG PET/CT, hybrid PET/MRI modality novel ultrasound-based and optical imaging in the neoadjuvant setting.

• In this era of personalized medicine, tailoring imaging modalities to biologic and molecular features seems to be a feasible future imaging goal.
Thank you for your attention!