Specialty area: Clinical Cancer MRI

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Highlights

Neoadjuvant chemotherapy (NAC) is a systemic treatment of breast cancer prior to surgical therapy. NAC is considered the standard care for patients with locally advanced breast cancers (LABC). These patients are not candidate for breast surgery because of large size tumors (T3-T4) with or without fixed or matted axillary lymph nodes (N2), inflammatory cancers, tumors associated with chest wall or skin infiltration, or cancers with involvement of ipsilateral subclavicular and supraclavicular lymph nodes ([1]).

NAC could also be considered for patients with operable breast cancer to downstage the disease and give option for breast conserving surgery. Metanalysis of randomized trials comparing NAC followed by surgery and surgery followed by adjuvant chemotherapy in patients eligible for surgery, observed in fact a lower mastectomy rate in the NAC group compared to the control one, although the overall survival observed in the two groups was equivalent ([2],[3]).

NAC may:

1) reduce the tumor size allowing a conservative surgery;
2) assess in vivo the response to systemic treatment, allowing to change not effective treatments and so reducing useless toxicity;
3) treat occult systemic disease and increase long term survival.

TALK TITLE – RESPONSE TO NAC: MRI TEST OF CHOICE?

TARGET AUDIENCE - Radiologysts

OUTCOME/OBJECTIVES - To understand the current role of Magnetic Resonance Imaging (MRI) in the evaluation of NAC response (contrast enhanced-MRI, spectroscopy, DWI), advantages compared to conventional imaging and clinical breast examination and limitations of the technique.
To understand when conventional imaging is not necessary to monitor treatment.
To analyze MRI results considering the possible pitfalls of the technique

PURPOSE - Radiologists during and after NAC should assess and quantify tumor response (giving morphological information and evaluation of residual disease for optimal surgical planning), monitor treatment response and try to predict the pathological response early after the beginning of treatment. Practically imaging should answer the following question for oncologists: is a good responder? and for surgeons: is the patient candidate for conservative treatment?
What is the most appropriate tool to assess NAC response?

METHODS - Revision of literature data considering the role of Clinical Breast Examination (CBE), Mammography, Ultrasonography, nuclear medicine and MRI in the evaluation of NAC response

RESULTS - Clinical breast evaluation (CBE), is combined to imaging in the evaluation of systemic therapy response according to World Health Organization. According to RECIST, CBE is considered of limited reproducibility and suggested mainly in superficial lesions ([4]). It is in fact often inadequate to assess the treatment response due to false positives (fibrotic or necrotic tissue following treatment) or on the other hand false negatives due to the resolution of edema or post bioptical hematomas ([5]).
Recently the ACRIN 6657 Trial ([6]) confirmed the inadequacy of CBE in prediction of pathologic complete response (pCR) and residual cancer burden (RCB) compared to the emerging role of MRI.
But why should we consider MRI instead of conventional imaging (mammography and ultrasonography)?
Mammography and ultrasonography are certainly easily accessible and low cost techniques with a widespread diffusion. However many studies have shown a suboptimal evaluation of lesion extent and consequently of treatment response by using only CBE and conventional imaging ([7],[8],[9],[10]).
In particular at mammography an accurate determination of the tumor size depends on the lesion type and the contrast between the lesion and the normal tissue ([5]). Mammographic measurements are usually better evaluated in fatty breasts compared to dense ones. Furthermore the following problems are usually observed:
a)Calcifications may persist or even increase in responders ([11],[12])

b) high fibro-glandular density does not permit the evaluation of the extent of disease and sometimes does not allow to recognize a complete pathologic response ([13])
c) it is difficult to recognize tumoral foci of multifocality or multicentricity
d) it is often not possible to distinguish residual scarring, necrosis and fibrosis from residual malignancy and to predict accurate response after neoadjuvant chemotherapy, especially in responders.
e) architectural distortion may persist also in responders([12]).

According to Croshaw ([14]) ultrasonography could be better than clinical examination and mammography. It is a good technique for evaluating axillary lymph nodes and for the measurement and the follow-up of skin thickening and edema with reported sensitivities of 72–94% and specificity up to 97%([15],[16],[17])
Compared to mammography, US can give not only morphological evaluation but also information on vascularization by using color Doppler and ultrasound contrast media.
However it is an operator dependent technique, with mainly pitfalls in evaluating tumors bigger than the probe or when the tumor is fractioned and multifocal ([18]).
Furthermore according to RECIST ultrasound should not be used as a method of measurement of the lesions because it cannot be reproduced entirely for an independent review.
As regards nuclear medicine, FDG PET and PET/CT can detect early changes of glucose metabolism and have the potentiality to be used in monitoring NAC. According to RECIST their role in response assessment need currently additional studies, however it is reasonable to use these techniques in assessment of progression of disease. PEM (positron emission mammography) has higher resolution of PET in the breast and the potentiality to be used in staging, monitoring treatment as well monitoring for recurrence of breast cancer but it still needs further evaluation.
So how can we answer efficiently to surgeons and oncologists? And why should we consider MRI?
Literature reports for contrast-enhanced breast MR (ce-MR) the highest sensitivity in the detection of invasive cancers (Sensitivity :94-99%), the highest accuracy compared to mammography or sonography in the evaluation of the real extent of the malignant lesion and in the detection of further lesions ([19],[20]), necessary for the decision making between conservative surgery and radical mastectomy ([21], [10]).
So this technique can define the extension of tumor before treatment better than conventional imaging..

DISCUSSION - So why conventional imaging is still required in evaluation of locally advanced breast cancers?

Considering the limits of mammography (calcifications, distortion, high fibroglandular density) and ultrasonography (large or multifocal/multicentric cancers), it is possible to select in which patients MR could be the test of choice in NAC.

But is MR really the optimum in NAC to evaluate the response and to early monitor the treatment effects?
The accuracy of ce-MR is high in predicting disease progression and/ or no-response to treatment ([22],[23],[24]).
As regards the evaluation of treatment response and residual disease, according to literature data there is an excellent correlation between the histological and the MR tumor sizes after neoadjuvant chemotherapy([24],[25],[26]).
Londero et al. ([13]) confirming previous studies ([27],[28]) showed that the correlation between the measurements performed on ce-MR images after NAC and the pathologic specimen were highly statistically significant, higher than mammography and ultrasound.
Even if accuracy of ce-MR is higher compared to clinical breast examination and conventional imaging, underestimation and overestimation of residual disease has been observed.
Underestimation of ce-MR may be influenced by tumor response and chemotherapeutic agent changes within the tumor (especially in patients with residual small invasive carcinoma, DCIS associated, when cancer is multifocal, non-mass or diffuse at initial presentation or with dendritic shrinkage pattern) ([29],[30]). Overestimation has also been observed and it is mainly due to post treatment-induced reactive changes([31]).

So MRI is better than conventional imaging but, is not perfect and we cannot completely trust on it, avoiding surgery, in patients classified as responders.
Recent studies suggest that accuracy of MRI is affected by hormonal receptor status and biologic characteristics of cancer ([32],[33],[34],[35]).
In this regard triple negatives seem to be a particular “kind” of breast cancer. Even if they are more clinically aggressive they usually present with benign imaging features (mass-enhancement, smooth margins at MRI) and respond better to chemotherapy compared to other biological subtypes ([36]). MRI is more accurate in evaluating residual disease in triple negatives compared to other biological subtypes, may be because they usually have mass- enhancement with smooth margins and shrinkage in a focal area, better measurable compared to hormonal-receptor-positive cancers. These types of cancers in fact usually have residual disease detected at Pathology as small foci or scattered cells after treatment causing underestimation of residual disease extent on MRI ([37]).

Similar explanation could be used for the different accuracy of ce-MR in detecting residual disease in patients with HER2 positives and HER2 negatives cancers.

The opportunity of using targeted therapy (Trastuzumab) for HER2 positive cancers gives better response to treatment, while HER2 negative cancers usually reveal at Pathology residual disease (due to the less efficient treatment) with scattered cells/clusters of residual disease confounding the accuracy of MRI([32], [34]).
So when we evaluate the response to treatment by using MRI we should be aware of the histology and biological parameters of the cancers in study.
Furthermore MRI evaluation of NAC should be interpreted always considering hormonal status and biological parameters.
Similar correlation between response to treatment and biological parameters has been observed by using FDG-PET([38],[39]).

And what happens if we consider MRI without contrast medium?
Whoodams showed that by using MR-Diffusion weighted imaging (DWI), is possible to evaluate residual disease with a sensitivity, specificity and accuracy respectively of 97%,89% and 96% compared to ce-MR (93%,56%,89%) and may be advantageous in patients with impaired renal function ([40]).
These preliminary results are very interesting and multicentric trials in a larger group of patients should further investigate a possible role of DWI in the evaluation of residual disease.

In addition MRI is a multiparametric technique that gives information not only on morphology and vascularization but also on metabolites and cellularity of the tumor (differently by conventional imaging).
These features may be used not only to evaluate the response to treatment but also to early monitor treatment effects allowing oncologists to change useless chemotherapy and avoid unnecessary toxicity as well to predict treatment response.

As regards early prediction of response, MR can detect changes in vascularization (dynamic ce-MR), metabolites (Spectroscopy) and cellularity (DWI).

Contrast enhanced- MR is in fact able to evaluate the changes in neoangiogenesis due to chemotherapic agents with a reduction of signal intensity after treatment in Responders([41], [5],[42]).
CE-MR kinetic evaluation has shown different results according to the technique of measurements in use ([43],[44],[45]).
Considering in fact the heterogeneity of these tumors manually and ROI based analysis do not give accurate information about the responses of all the parts of tumor and automated pixel by-pixel analysis of the enhancement kinetics with histograms should be preferred ([2],[46],).
Recent multicenter study of ACRIN trial suggest that MR imaging tumor volume is an automated functional measurement combining both the information of size and of the microvascular properties of tissue, is a more accurate measurement of tumor burden than diameter (only morphological information) and enables earlier detection of treatment response ([6]).
Furthermore which are possible research area of further investigation?
Considering kinetic parameters , Ktrans could be a very interesting parameter to further investigate as a biomarker in the specific response of antiangiogenic or antivascular therapy (Ktrans changes > 40% as a threshold for response) ([47]).
Proton MR spectroscopy (1H-MRS) can detect the high choline metabolites (tCho) associated to increase of cells proliferation and phospholipid metabolism in breast cancer and their possible changes after treatment.
Preliminary studies in small groups of patients by Kvistad and et al. [[48]] and Jagannathan et al([49]) qualitatively demonstrated changes of tCho in responders to NAC. Tozaki et al. ([50],[51]) showed that, soon after the first cycle of NAC, the reduction in the choline signal was more sensitive than Diffusion - weighted imaging in demonstrating pathological response. However conflicting results were observed comparing changes of choline metabolites and volume measurements to predict the pathological response ([52]).
In this regard technical difficulties in quantitative analysis of choline metabolites and problems especially due to the shrinkage of tumors and consequently less tissue available for measurements have limit the widespread diffusion of the technique([41]).
DWI gives information on cellular density and membrane integrity of the lesions.
This information can be used to evaluate residual disease and to early monitor treatment effects.
Diffusion of water molecules is in fact usually restricted in cancers because of high cellularity with low apparent diffusion coefficient values(ADC). After NAC, due to loss of cell membrane integrity in responders, diffusion of water molecules increases, ADC values are consequently higher and may early reveal response to treatment. Pickles et al. ([53]) and Sharma et al. ([54]) showed that the change in ADC after the first cycle of chemotherapy was statistically significant compared with the change in tumor volume and diameter. Nielsen and al. ([55]) and Woodhams et al. ([40]) did not confirm these results possibly due to the lack of standardization in the technique of acquisition and image analysis ([56],[57]). The same reason can explain the contradicting finding of ADC to predict response before treatment with low ADC value observed in responders ([52],[58],[59], [60]), Furthermore the DWI is usually better evaluated in mass and the low resolution limit the use of the technique in small lesions. Non mass enhancement and shrinkage of the tumor could be challenging for ADC measurements after NAC especially in responders.

In the end is there a role for nuclear medicine? Metabolic changes after treatment could be used in monitoring treatment response, but are still under evaluation.

CONCLUSION - So in selected cases breast MRI can be an alternative to conventional imaging to monitor treatment response.
Considered as a multiparametric technique, is a valuable tool to assess the response to NAC. In this regard integration with biological parameters and hormonal status is recommended for decision making.
MRI has also the potentiality to correlate with disease free survival considering kinetics, volumetric evaluation ([61]), DWI, breast stromal enhancement ratio ([62]). However disease free survival correlation require high numbers of patients and long term observation, often difficult to evaluate with the same technical requirements especially considering the continuing technical advances.
For this purpose multicenter trials should be encouraged to evaluate multiparametric MRI in early monitoring of the response to treatment and possibly an integration with nuclear medicine (FDG-PET).

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