Role of DWI in defining NCT response and planning breast and axillary surgery in locally advanced breast cancer

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Authors: G. L. Desi, V. M. Doronzio, A. Timpani, G. Giannetto, C. Maglia, V. Vani, F. Cortese, D. Regge, L. Martincich; Turin/IT
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Aims and objectives

Neoadjuvant chemotherapy (NCT) is a management option for locally advanced breast cancer. The aim of NCT is to reduce tumor volume for the purpose of breast conservation and as a prognostic factor. The accurate assessment of residual tumor after neoadjuvant chemotherapy is an important prognostic factor for evaluating outcome and survival of the patient. Inaccuracy in evaluating tumor response will lead to a prolonged chemotherapy course and an unnecessarily wide resection.

Dynamic Contrast-Enhanced MRI (DCE-MRI) represents the most accurate modality in the evaluation of tumor response to NCT. The sensitivity of this modality is higher than that of conventional imaging (mammography and ultrasound), in both the identification of pathological complete response and the assessment of residual disease extent at the end of the treatment. It was recently shown that MRI visualizes tumor response differently depending on the immunohistochemical subtype of the cancer, well correlating with pathology outcome for triple-negative and Her2 type tumors while it results suboptimal in luminal cancers.

Moreover, DCE-MRI contemplating intravenous injection of contrast agent, is not without risks: even though in rare situations, allergies and nephrogenic systemic fibrosis may occur, and recent studies proved gadolinium deposition in basal ganglia; although clinical meaning is not sure, caution is recommended when gadolinium contrast agents are administered, especially in young patients.

Diffusion Weighted Imaging (DWI) has been investigated as a means of overcoming the limitations of DCE-MRI assessment which is reliant on inherent unique tissue contrast mechanism. DW imaging makes use of the variability of brownian motion of water molecules in tissue. It also provides a quantitative imaging biomarker (apparent diffusion coefficient - ADC), which is demonstrated may help to distinguish between benign and malign findings and to implement DCE-MRI specificity. Despite it has been studied for over 10 years, it's not included in clinical practice yet, because ADC value is strictly related to technical protocols and hard to standardize.

For this reason, different authors investigated other potentials of DWI, including the qualitative evaluation of images acquired with large b-values. They concluded that it is not inferior to DCE-MRI for detection of breast carcinoma. Nowadays there is only one study that estimated the role of qualitative evaluation of DWI in the definition of response to neoadjuvant chemotherapy, demonstrating a sensitivity of 97% and a specificity of 89% compared to a sensitivity of 93% and a specificity of 56% of DCE-MRI. However, this study evaluated the assessment of response at breast level.

Then, purpose of this study is to evaluate the role of qualitative DWI in defining breast and axillary NCT response and planning breast surgery.
Methods and materials

Study population

Patients undergoing NCT and MRI at our institution between November 2010 and February 2014 were retrospectively included, with the following inclusion criteria: age between 18 and 65 years, presence of imaging-guided core-biopsy proven Stage II/III operable breast cancer (T > 3 cm) or inoperable locally-advanced breast cancer and unifocal or multiple masses at baseline MRI. Clinical and pathological features are summarized in Table 1.

This study was conducted in compliance with the ethical regulatory issues of our Institution and patients were asked to provide written informed consent before entering the study.

All patients underwent breast MRI (DWI and DCE-MRI) before and after NCT followed by surgery performed between 14 and 35 days after the completion of NCT.

MRI protocol

Examinations were performed with 1.5 Tesla equipment and 8-channels dedicated phased-array coil and patient in prone position.

Morphological (T2 weighted sequences and DWI on axial plan) and dynamic studies were conducted, in particular DWI has been acquired with echo-planar single shot axial sequences (TR/TE 11500/72 ms, matrice 128x 128 pixels, NEX 16, FOV (field of view) 30x30 cm e slice thickness 3 mm) and diffusion coefficient applied on three orthogonal planes at 0 e 1500 s/mm² b-value.

Dynamic study was acquired with a gradient echo 4D fat suppressed sequence on axial plan (TR 8 ms, TE 3.6 ms, flip angle 10°, slice thickness 1 mm, matrix 480x480). Dynamic study contemplates a pre-contrast sequence and five sequences after intravenous injection of paramagnetic contrast medium (gadobutrol 1.0 mmol/ml); this was administered at a dose of 0.1 mmol/kg, 2 ml/s speed, followed by 20 ml of saline solution.

Response to NCT

Response was evaluated measuring by electronic calipers at DWI (b value 1500s/mm²) and DCE-MRI (early phase after iv injection of contrast agent) the diameter of malignant lesions and axillary adenopathies before and after NCT.
Breast level

Concerning breast lesions:

- before NCT, the maximum diameter of each malignant lesion was evaluated. In the case of multiple cancer only the largest was considered as a target lesion;
- after NCT, if the lesion faced concentric shrinkage the maximum diameter was measured; if it underwent fragmentation the extent between more distant foci was considered.

For both DWI and DCE-MRI, Response Evaluation Criteria in Solid Tumors, RECIST 1.1 were applied for the assessment of NCT response, defining as complete response (CR) the disappearance of the target lesion; partial response (PR) the diameter of the target lesion decrease more than 30%; stable disease (SD) as non PR non PD; progressive disease (PD) the target lesion increase more than 20% of its diameter. In addition, it was also reported the extent of residual disease in terms of one versus >1 breast quadrant involved.

Then multidisciplinary team planned the surgical treatment on the basis of DWI and DCE-MRI respectively (when just 1 quadrant was involved breast conservative surgery-BCS was indicated, mastectomy was suggested in all the other conditions) and the results were compared with the surgery actually performed. Figure 1 and 2.

Axillary level

Concerning axillary response, for each patients:

- before NCT, the short axis of the largest lymph node was measured;
- after NCT, the short axis of the same lymph node was considered.

Before and after the treatment, the measured lymph node was considered negative when short axis diameter was <10 mm and positive when it was >10 mm. Figure 3.

Pathological lymph node status was considered as the reference standard (positive versus negative). In particular, pathological negative status was defined as absence of residual invasive tumor in the lymph nodes while positive in the remaining conditions.

Statistics

Those cases in which DWI correctly planned mastectomy or BCS were defined as true positive and true negative respectively; those planned as mastectomy and then...
underwent to BCS as false positive, while those planned as BCS and then underwent to mastectomy as false negative.

Those cases in which DWI correctly or wrongly identified lymph node status were defined as true positive or true negative, respectively; false positive and false negative were defined those cases in which lymph node status was wrongly evaluated as positive or negative, respectively.

Sensibility, specificity and accuracy of DWI in planning breast surgery and in the assessment of axillary NCT response were evaluated.
Table 1: Clinical and pathological features: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PgR, progesterone receptor and HER2, epidermal growth factor receptor 2. Age and tumour size are expressed as median with ranges in parentheses.
Fig. 1: DWI of a 56 y.o. woman. Before NCT (A) in the inferior quadrants of the right breast a mass area of heterogeneous hyperintensity is detectable (major diameter: 60mm). Core-biopsy identified an IDC (ER 99%, PgR 1%, HER2 2+, without gene amplification). After NCT (B), the lesion underwent concentric shrinkage (major diameter: 50mm) and the response was classified as stable disease. The lesion extent at the end of the treatment involved more than one quadrant, so multidisciplinary team correctly planned mastectomy. Pathology confirmed the diagnosis of IDC (ypT2, pN2a).

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**Fig. 2:** DWI of a 56 y.o. patient. Before NCT (A) between the upper quadrants of the right breast a mass area heterogeneous hyperintensity is detectable (major diameter: 35mm). Core-biopsy identified an IDC (ER 80%, PgR neg, HER2 score 3+). The lesion showed long spicula indicative of intraductal disease, which was confirmed as DCIS at a core-biopsy. After NCT (B) the lesion underwent fragmentation but its extent was substantially unchanged (major diameter: 25mm) and the response was classified as stable disease. The lesion extent at the end of the treatment involved one quadrant, so multidisciplinary team correctly planned BCS. Pathology confirmed the diagnosis of IDC (ypT2, ypN0.)

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Fig. 3: DWI of a 64 y.o. woman. Before NCT (A) a round heterogeneous area of hyperintensity referring to an lymph node can be observed in the left axilla. Its short axis was 25mm and was classified as positive adenopathy. After NCT (B) the short axis of the node is 4mm and it was considered negative. The pathologic axillary status was positive. In fact, in 2/14 excised nodes, residual tumor cells were identified.

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Results

5/44 patients were excluded (2 due to technical problems and 3 for lack of surgical information).

Breast level

Before NCT, both DWI and DCE-MRI identified 24 unifocal tumors and 15 multiple disease. The mean size was 49 mm (range 14-87mm) at DWI and 37.5 (range 30-50mm) at DCE-MRI.

After the treatment, at both DWI and DCE-MRI concentric shrinkage was observed in 21 cases while fragmentation occurred in the remaining 18. At DWI the mean size was 34 mm (range 0-82 mm) while at DCE-MRI it was 34 (range 0-58mm).

The assessment of response for DWI and DCE-MRI is summarized in Table 2.

18 patients underwent to conservative surgery and 21 patients to mastectomy.

DWI correctly suggested surgical treatment in 33/39 cases, planning BCS in 16/18 cases: 13 mass lesions with concentric shrinkage and 3 non-mass lesions. Mastectomy was correctly planned by DWI in 17/21 patients: 4 mass lesions with concentric shrinkage and 13 non-mass lesions. Figure 1 and 2.

False positive cases were 2 when DWI overrated the lesion extent due to fragmentation after NCT; false negative cases were 4 when DWI underrated the lesion extension after fragmentation. All the discordances were observed in non mass lesions.

Sensitivity, specificity and accuracy of DWI in planning breast surgery were 81% (17/21), 89% (16/18) and 85% (33/39), respectively. Table 3.

Axillary level

Concerning lymph node, before NCT DWI identified 14 patients as negative (short axis <10mm) and 25 patients as positive (mean short axis 16mm; range 10-30); after the treatment 15/25 patients resulted as negative (mean short axis 5mm; range 0-9) and 10/25 as positive (mean short axis 11mm; range 11-20).

Pathological nodal status was classified as positive in 21 patients and negative in 18 patients. Concordance between DWI data and the reference standard was observed in 20/39. False positive cases were 4, while false negative cases were 15. Figure 3.

Sensibility, specificity and accuracy of DWI in the evaluation of axillary response to NCT were 30% (6/21), 78% (14/18) and 51% (20/39), respectively. Table 4.
Table 2: Classification of Imaging tumor response at breast level following RECIST (Response Evaluation Criteria in Solid Tumors) criteria. DWI Diffusion Weighted Imaging; DCE-MRI Dynamic Contrast-Enhanced MRI; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3: Performance of DWI in planning breast surgery.
Table 4: Diagnostic performance of DWI at axillary level.

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<th>DWI</th>
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<td>Positive</td>
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<td>Negative</td>
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<td>Accuracy</td>
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Conclusion

This study demonstrates that the role of DWI in defining tumor response and planning breast surgery after NCT is more than promising.

DWI resulted comparable to contrast enhanced MRI in the assessment of NCT response, showing similar results in defining PR, SD, and PD. DWI resulted inferior to DCE-MRI in defining CR (4 cases vs 10 cases) and this can be due to either different spatial resolution or presence of residual DCIS in the tumoral bed. Our study demonstrates that, despite this difference in the assessment of CR, this fact had no impact on planning the surgical treatment which was correctly defined in 85% of cases. Figure 1 and 2.

Otherwise, DWI is not good performing in axillary lymph node status evaluation after NCT (accuracy value 51%). This result was expected considering that similar findings have already been reported in the literature. Figure 3.

This study confirm the emerging thesis that non-contrast MRI is suitable in clinical practice, moreover these results were obtained in a real daily clinical practice situation.

Omitting the use of contrast agents could lead to a less invasive and less long exam for patients as an immediate consequence, making MRI more easily tolerable.

Instead, indirect consequences could affect the nullification of potential risks deriving from gadolinium administration. First of all allergic reactions, even though they are rare (0.03% of severe reaction in literature), represent a concrete risk and a contraindication of further administration of intravenous paramagnetic contrast agent. Secondly, the risk of nephrogenic systemic fibrosis could be avoided, which represents a contraindication to contrast agent administration, even though it's rare. Moreover, as recently demonstrated by many Authors, after repeated administrations, gadolinium deposits in basal ganglia; even though by now it is without clinical meaning, it is still object of study, but it is universally accepted the recommendation of selecting Patients to administrate with contrast agents.

Considering these advantages, non-contrast MRI in selected Patients could bring a patient care targeted to not expose women to avoidable risks.

Considering our study, contrast agents could be used in those patients who have a non-mass lesion pre-NCT: in fact our results shows that DWI is more performing in the assessment of the response of mass lesions.

Last but not least we have to consider the potential costs reduction. The avoidance of contrast agent, in the face of a comparable diagnostic accuracy to contrast enhanced MRI, could reduce the total cost of the exam.
It has to be underlined, that, to use DWI in clinical practice, the exams have to be performed with an equipment at the state of the art and by a highly qualified staff: this combination makes possible to obtain high quality images.

In conclusion, taking into account the limitation of the study, as the small series and the necessity of further investigations on this scenario, our study demonstrates that DWI is suitable for clinical practice in defining NCT response and planning the surgical treatment at breast level but it does not demonstrate satisfactory diagnostic performance in the assessment of axillary nodal status after NCT.
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Personal information

DESI GIAN LUCA, University of Turin, IRCCS-FPO Candiolo, Strada Provinciale, 142 - KM 3.95, 10060 Candiolo (TO), Italy; gianlucadesi.md@gmail.com;

DORONZIO VALERIA, University of Turin, IRCCS-FPO Candiolo, Strada Provinciale, 142 - KM 3.95, 10060 Candiolo (TO), Italy; valeriamaria.doronzio@ircc.it;

TIMPANI ALESSANDRA, University of Turin, IRCCS-FPO Candiolo, Strada Provinciale, 142 - KM 3.95, 10060 Candiolo (TO), Italy; alessandra.timpani@ircc.it;

GIANNETTO GIULIANA, University of Turin, IRCCS-FPO Candiolo, Strada Provinciale, 142 - KM 3.95, 10060 Candiolo (TO), Italy; ggiannetto27@gmail.com;

MAGLIA CLAUDIO, University of Turin, IRCCS-FPO Candiolo, Strada Provinciale, 142 - KM 3.95, 10060 Candiolo (TO), Italy; claudio.magli@ircc.it;

VANI VANINA, University of Pisa, AOUP - Azienda Ospedaliera Universitaria Pisana, Via Paradisa, 2, 56124 Pisa (PI), Italy; vanina.vani@gmail.com;

CORTESE FRANCESCO, University of Turin, IRCCS-FPO Candiolo, Strada Provinciale, 142 - KM 3.95, 10060 Candiolo (TO), Italy;

REGGE DANIELE, University of Turin, IRCCS-FPO Candiolo, Strada Provinciale, 142 - KM 3.95, 10060 Candiolo (TO), Italy; daniele.regge@ircc.it;

MARTINCICH LAURA, IRCCS-FPO Candiolo, Strada Provinciale, 142 - KM 3.95, 10060 Candiolo (TO), Italy; laura.martincich@ircc.it
References


