Breast MRI evaluation of the efficacy of the neoadjuvant radio-chemotherapy protocol (MADD) compared with conventional protocols

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Authors: M. Di Matteo1, E. Bufi1, D. Distefano2, M. Costantini1, P. Rinaldi1, P. Belli1, L. Bonomo1, 1Rome/IT, 2Roma/IT
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Purpose

Neoadjuvant chemotherapy is currently widely employed in patients with locally-advanced breast cancer (LABC) with the purpose to improve the rate of breast-conserving surgery (up to 98% of patients) and the systemic control of the disease. The coupling of preoperative radiotherapy (RT) cycles with neoadjuvant chemotherapy has been proposed for other cancer types. In particular, radiation doses below 0.5 Gy has been demonstrated to enhance the effectiveness of continuous infusion-taxanes; such phenomenon has been termed Low-Dose Hyper-Radio Sensitivity. Nonetheless, no data are currently available over the efficacy of concurrent neoadjuvant radio-chemotherapy in patients with LABC.

Magnetic Resonance Imaging (MRI) is a reliable tool to evaluate the breast cancer response to chemotherapy by measuring tumor diameter changes and by assessing the vitality of residual tumor areas. While, breast MR imaging is not indicated in the early period after radiation therapy. During the first 12-18 months after radiation therapy, contrast enhancement associated with radiation-induced inflammatory changes has been reported to severely impair the interpretation of breast MR images.

The purpose of the present work is to ascertain: 1. Whether the adoption of concurrent neoadjuvant low-dose fractionated RT (LD-FRT) and chemotherapy yields better oncological results in patients with LABC compared with neoadjuvant chemotherapy alone; 2. The diagnostic performance of MRI and DWI-MRI in the context of concurrent LD-FRT and chemotherapy in the prediction of response to neoadjuvant treatment.
Methods and Materials

The MADD protocol has been used in our Institution from August 2008 to February 2011, and is being indicated for patients with histopathologically proven LABC (core-needle biopsy) and scheduled for neoadjuvant.

A total of 18 Patients received the neoadjuvant radio-chemotherapy treatment (NRC), while the control group consisted of 36 Patients who received the same neoadjuvant chemotherapy (NAC) without concurrent LD-FRT.

Figure 1

For all the enrolled patients, study design comprised pre-treatment MRI, intermediate-term MRI, post-treatment MRI, and definitive surgery within 4 weeks after the completion of neoadjuvant therapy.

MRI protocol was the same for all Patients and was performed on a 1.5 T GE scanner.

Table 1

The tumor response to treatment was assessed using RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) classification, based on the longest diameter measure of the target lesion. Under the profile of morphological MRI, we defined the 'Responder' patients those having Complete Response or Partial Response, and the 'Non-responder' patients those having Stable of Progressive Disease. We categorized time-to-intensity curves as either Persisting-type (expressing response to treatment), or Plateau-type and Wash-out type (expressing no response to treatment). According to previous evidence, we adopted a cutoff value of ≤20% increase in ADC (Apparent Diffusion Coefficient obtained from DWI maps) value after the neoadjuvant treatment as indicative of response to treatment itself.

The final diagnosis of tumor response to neoadjuvant treatment was classified according to the histopathological Mandard's TRG (Tumor Regression Grade) criteria after surgical excision. We defined the 'Responder' patients those having TRG class 1, 2 or 3, and the 'Non-responder' patients those having TRG class 4 or 5. The diagnostic performance of either conventional MRI or DWI was weighted against the results of TRG classification.

Figure 2
For each patient belonging to the NRC group, a logistic regression was built by inclusion of all the available baseline variables (Table 2) in order to model the likelihood of each patient to enter the NRC or the NAC group, and the propensity score was calculated for each of them. Subsequently, from the largest pool of patients receiving the NAC treatment we selected patients with a 1:2 ratio having the closest propensity score (maximum allowable difference: 0.1).

Table 2

The statistical analysis was performed using SPSS ver. 11.0 for Windows (Statistical Package for Social Sciences, SPSS, Chicago, IL) and the SAS software for propensity-matching (SAS/STAT ver. 8, SAS Inc.). Continuous data are presented as mean ± standard deviation and categorical variables as percentages. Intergroup comparison was performed using the two-tailed Student's $t$-test or the chi-square test for continuous and categorical variables, respectively. Kendall's rank-correlation coefficient (tau) was used to analyze the correlation between the Mandard's class and the RECIST class, the ADC value and the type of time-to-intensity curves. Diagnostic performance of MRI parameters for the evaluation of the response or non-response status of a tumor lesion was performed by building Receiver Operator Characteristic (ROC) curves. Subsequently, the ROC curves obtained with either method were statistically compared according to the Hanley and McNeil methodology, using the MedCalc software for Windows. The alpha level was 0.05.
**Fig. 1:** Study design and treatment schedule.

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Table 1: MRI protocol. ^ TR: Repetition time. * TE: Echo time. § FOV: Field-of-view. † NEX: Number of Excitation

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Fig. 2: Status of responder or Non Responder to treatment according to the TRG classification, morphological and kinetic MRI changes and ADC variation.

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Table 2: Baseline characteristics of the entire study population. *Includes Invasive and In situ carcinoma. §Triple negative: demonstration at core needle biopsy of Estrogen receptor, Progesterone receptor and HER2 negativity. Luminal: demonstration at core needle biopsy of Estrogen receptor positivity. †Average percentage of cells expressing either the mutated form of p53 or the bcl-2.

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Results

In both groups, we observed reduced tumor dimension after the last cycle vs. baseline (p<0.001), and the RECIST class was directly correlated with the TRG class after the last cycle (p<0.001). Patients in the NRC group displayed a higher frequency of complete/partial response (RECIST class) at the end of treatment compared with NAC patients (p=0.034). Seventeen out of 18 patients in the NRC group could avoid mastectomy.

Table 3

Figure 3

Figure 4

Table 4

The RECIST classification is a reliable tool in predicting the tumor response to neoadjuvant treatment, as supported by the close correlation with the final TRG class (tau=0.77) and by its diagnostic performance for the response to treatment in the overall population (AUC=0.72).

Figure 5

Figure 6

The association of the enhancement kinetics to the RECIST criteria in the evaluation of response to treatment yielded a poorer performance not only in the overall population (AUC=0.65) but particularly in the NRC subgroup (AUC=0.59). If the ADC variation is implemented as a concurrent diagnostic criterion together with the C.E.-MRI parameters, the diagnostic performance is remarkably improved in the general population (AUC=0.79), mainly due to increased specificity.

Figure 7

Figure 8
Table 3: MRI characteristics of the study groups at the time of the last imaging at the end of neoadjuvant treatment, and final histopathological results.

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**Fig. 3:** Pre and post treatment MRI of a Patient enrolled for NRC treatment. According to the RECIST class we had a Partial Response, the time-to-intensity curve became from plateau-type to persisting-type and we also observed an increase in ADC value > 20%.

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Fig. 4: Pre and post treatment MRI of a Patient who received NAC treatment. According to the RECIST class we observed a Stable disease, we didn't notice either an increase in ADC value, or a modification of the time-to-intensity curve.

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### Table 4: Sensitivity, specificity, PPV, NPV and accuracy of either one of the three MRI-derived parameters or their association as predictors of the status of responder to treatment according to the TRG classification.

PPV, NPV: Positive and Negative Predictive Value. Association 2/3 criteria: RECIST class and time-to-intensity curves. Association 3/3 criteria: RECIST class, time-to-intensity curves and ADC value raise.

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Fig. 5: Kendall's rank-coefficient correlation. Correlation between the TRG class and the RECIST class (A), the time-to-intensity curves after contrast agent administration (B) and the ADC variation (C).

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Fig. 6: Entire study population. ROC curves and AUC values for each of the three MRI-derived evaluation parameters.

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**Diagnostic performance: association of 2 or 3 of the MRI derived evaluation parameters**

**Fig. 7:** Study subgroups. ROC curves and AUC values for the association of either of RECIST class and Enhancement Kinetics (upper) or RECIST class, Enhancement Kinetics and ADC (lower). NAC group on the left and NRC group on the right.

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Fig. 8: Entire study population. ROC curves and AUC values for the Association 2/3 criteria: RECIST class and time-to-intensity curves. Association 3/3 criteria: RECIST class, time-to-intensity curves and ADC value raise.

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Conclusion

The NRC may yield superior oncological results in LABC compared with NAC and possibly increase the rate of breast-conserving surgery. The MRI is generally capable of adequate diagnostic performance in the evaluation of response to treatment, despite the use of LD-FRT in association with the established neoadjuvant chemotherapy. Such outcome can only be achieved by the integration of both morphological and diffusion imaging parameters.
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