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Role of Magnetic Resonance Imaging in the Evaluation of Breast Cancer Response to Neoadjuvant Chemotherapy

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Abstract. *Background/Aim: The aim of the study was to evaluate whether residual tumor assessment by magnetic resonance imaging (MRI) after neoadjuvant chemotherapy (NACT) is fundamental for a successive surgical strategy. Patients and Methods: We collected 55 MRIs performed after NACT. Results: Pathological response rate was 20%. MRI's sensitivity, specificity, PPV and NPV were 50%, 88%, 54% and 86%, respectively. We observed a high variability between the different subgroups, with high number of false positives in luminal A/B tumors. Triple negative and HER2+ tumors had almost the same specificity and sensitivity (81% and 50%). Nevertheless, in the HER2+ group, PPV was greater than that in the triple negative group (71% and 33% respectively) and the NPV of the triple negative group was greater than that of the HER2+ one (90% and 64%, respectively). Statistical analysis showed a weak but significant correlation between MRI and pathological assessment of residual tumor dimension. Conclusion: The present study, confirms literature data about MRI accuracy in diagnosing HER2+ and triple negative tumors, but suggests caution in case of luminal tumors' evaluation.*

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Key Words: Magnetic resonance imaging, breast neoplasms, neoadjuvant chemotherapy, pathological complete response (pCR), imaging complete response (iCR), breast cancer subtypes.

Breast magnetic resonance imaging (MRI) is the most sensitive of the available imaging modalities to characterize breast cancer. The size of the tumor invasive component estimated by MRI closely correlates with that determined with pathological examination. NACT indications are increasing in the last years and the residual tumor assessment is fundamental for the successive surgical strategy (1). MRI can detect small residual cancer nests after neoadjuvant chemotherapy (NACT), but it may overestimate the extent of the residual tumor in some cases (2). However, MRI appears more useful than clinical examination, mammography and ultrasound in determining residual tumor (3-5). Furthermore, its use is recommended by most guidelines because, although it has similar accuracy with breast ultrasound, MRI evaluates better multifocal, multicenter and contralateral tumors (6).

Breast cancers are sub-classified according to immuno-phenotype in luminal A: estrogen receptors and/or progesterone receptors positive (ER/PgR+), Ki67<20, HER2 negative, luminal B HER2 negative (ER+ and/or PgR+, Ki67≥20, HER2 negative), luminal B HER2 positive (ER+ and/or PgR+, any Ki67, HER2 positive), non-luminal HER2+ (ER–, PR–, HER2+), and triple-negative (ER–, PR–, HER2 negative). Luminal, HER2+ and triple negative tumors imaging are different from each other. Luminal A/B subtypes

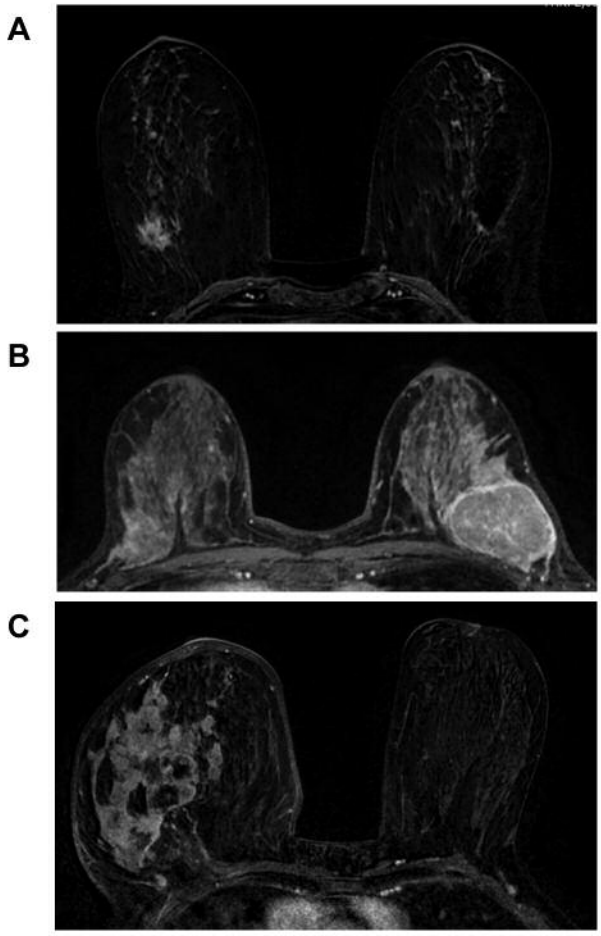

Figure 1. *Breast cancer MRI appearances. A: Luminal A/B tumor: mass with irregular margins. B: HER2+ tumor: mass with regular margins. C: Triple negative tumor: mass with intra-tumoral necrosis.*

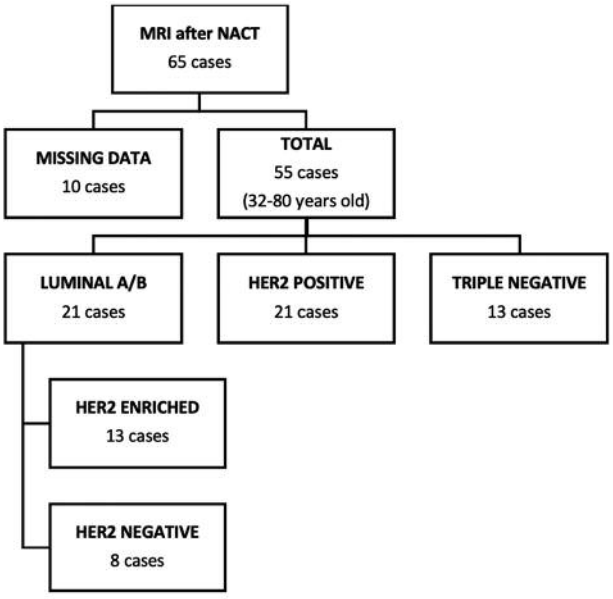

Figure 2. *Sample selection.*

Table I. *Comparison between MRI and histological evaluation of complete or not complete response to NACT. iCR: Imaging complete response; pCR: pathological complete response; TN: true negative; TP: true positive; FN: false negative; FP: false positive.*

	Histological reports		
	pCR	no pCR	Total
MRI			
iCR	6 (TN)	6 (FN)	12
No iCR	5 (FP)	38 (TP)	43
Total	11	44	55

appear more frequently as a mass with irregular margins, while HER2+ tumors often have regular margins and the presence of intra-tumoral necrosis suggests a triple negative immunophenotype (Figure 1) (7). Stratifying the different tumor subtypes (luminal A/B, HER2+, triple negative), MRI's predictive role of pCR is higher for triple negative, HER2+ and "mass forming" morphology tumor (8-11). Association of MRI with diffusion weighted MRI, positron emission tomography - computed tomography (PET-CT) or breast ultrasound can give a more precise indication of pCR, especially for HER2+ subtypes (12-13). Currently, surgical treatment after NACT is based on tumor response, requiring the removal of the residual tumor and not the whole initial tumor bed (14). It is necessary to avoid false negative and false positive imaging complete response (iCR) that could affect the surgical strategy and patient prognosis (15), and identify those cases in which MRI is actually predictive for pCR. The main aim of our study is to estimate MRI accuracy in finding a complete response to NACT. MRI predictive values (positive and negative, PPV and NPV respectively), sensitivity and specificity are calculated comparing MRI reports of iCR/no iCR (radiological images of residual tumor) and post-surgical histological reports of pCR/no pCR (residual tumor on specimen). Besides that, we conducted the same analysis by dividing the whole sample in three subgroups (luminal A/B, HER2+, triple negative tumors). We assessed MRI accuracy in residual tumor dimensions definition.

Patients and Methods

We collected all MRIs performed between 2015 and 2017 in the Breast Unit of Sant' Anna Hospital in Turin, Italy. The inclusion criteria for this study were: female patients with biopsy-proven breast cancer; ≥18 years old; not pregnant & not breastfeeding; treated with NACT at the same hospital with MRI performed after completion of the treatment.

Table II. *Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the whole cohort and of each subgroup.*

	MRI (Triple negative+HER2 + LUMINAL A/B)	Triple Negative	HER2+	Luminal A/B
Sensitivity (%)	50	50	50	100
Specificity (%)	88.4	81	81	0
PPV (%)	54	33	71	0
NPV (%)	86	90	64	95

Table III. *Comparison between MRI and pathological evaluation of complete or not complete response to NACT in luminal A/B tumors group. iCR: Imaging complete response; pCR: pathological complete response.*

	Histological reports (luminal A/B tumors)		
	pCR	No pCR	Total
MRI			
iCR	0	0	0
No iCR	1	20	21
Total	1	20	21

Table IV. *Comparison between MRI and pathological evaluation of complete or not complete response to NACT in triple negative tumors group. iCR: Imaging complete response; pCR: pathological complete response.*

	Histological reports (triple negative tumors)		
	pCR	No pCR	Total
MRI			
iCR	1	1	2
No iCR	2	9	11
Total	3	10	13

Table V. *Comparison between MRI and pathological evaluation of complete or not complete response to NACT in HER2+ tumors group. iCR: Imaging complete response; pCR: pathological complete response.*

	Histological reports (HER2+ tumors)		
	pCR	No pCR	Total
MRI			
iCR	5	5	10
No iCR	2	9	11
Total	7	14	21

Table VI. *Mean, trend, median of tumor dimension evaluated by MRI and post-operative histological report (HR).*

	MRI (mm)	HR (mm)
Mean	29.85	18.33
Trend	15.00	15.00
Median	22.00	15.00

Patients were excluded if they had undergone MRI or any treatment at another hospital and if there were contraindications for MRI or MRI contrast agents. Ten patients were excluded because they underwent surgery or chemotherapy at another hospital. Therefore, a total of 55 patients were included in this study. Patients median age was 56 years old (range=32-80 years). Patients cohort was composed of 21 luminal A/B tumors, 13 triple negative tumors, and 21 HER2 positive tumors. In luminal A/B group, 13 patients out of 21 were HER2 enriched and 8 were HER2 negative (Figure 2). We administered NACT according to this schedule: epirubicin 75-90 mg/mq and cyclophosphamide 600 mg/mq for 4 cycles every 3 weeks followed by paclitaxel 80 mg/mq weekly for 12 weeks, adding trastuzumab in HER2 positive tumors. At the end of the treatment, MRI was performed with an Open MRI Hitachi 0.4 Tesla, MRI Philips Ingenia 1.5 Tesla or MRI Philips Achieva D-Stream 1.5 Tesla. Patients were in a prone position to obtain images before and after administration of Gadobutrole (GadovistTM 1 mmol/ml) 0.1 mmol/kg (0.1 ml/kg) at an injection rate of 2 ml/s. Conservative or radical breast surgery was performed in 33 and 22 patients, respectively. We collected MRI reports of complete response (iCR) or not complete response (no iCR) to NACT and we compared them with post-operative histological analysis of pCR or persistence of residual tumor (no pCR). We conducted a statistical analysis first on the whole sample and then on each subgroup (luminal A/B, triple negative, HER2 tumors). We used a 2×2 contingency table (Table I) and calculated specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV).

Results

We defined sensitivity as the proportion of patients with pCR that were correctly classified by MRI as complete responders (iCR). Specificity was defined as the proportion of patients with residual disease (no pCR) correctly classified by MRI

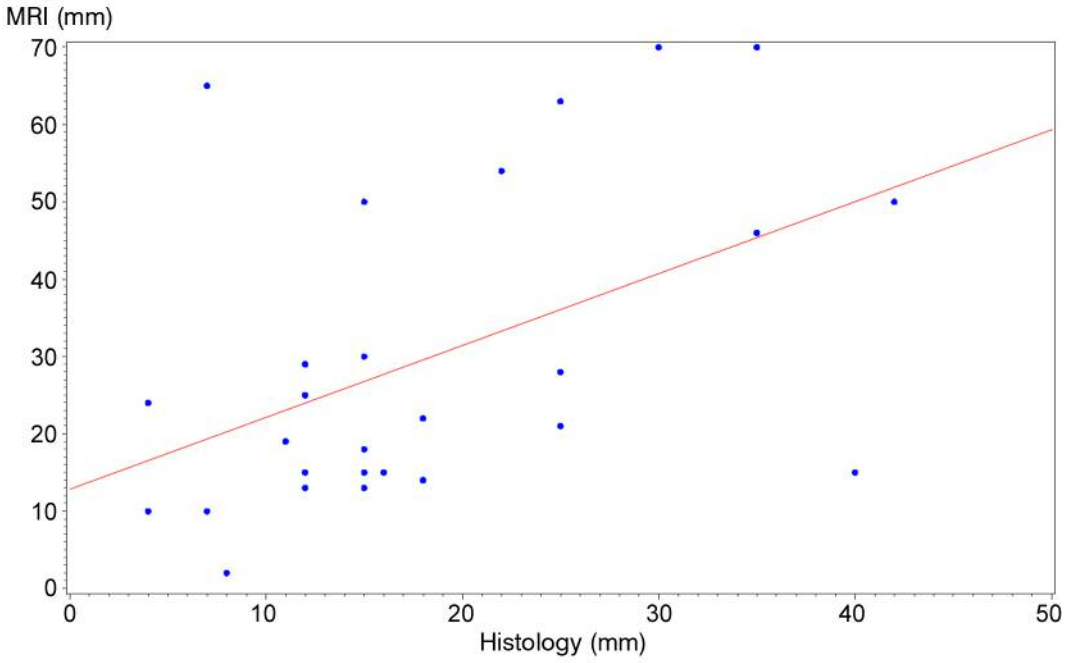

Figure 3. *Correlation between residual tumor dimension assessment (MRI vs. pathology) (Pearson r=0.48, p=0.01).*

as such (no iCR). We tested the association between iCR and pCR (χ-square=8.63, p=0.0003). The pathological response rate to NACT was 20% (11 out of 55 cases). Among cases that responded completely (pCR), 6 out of 11 were correctly identified as iCR by MRI (TN), but 5 out of 11 were wrongly identified as not iCR by MRI (FP; 45%). Among cases that responded partially to NACT (not pCR), 6 out of 44 were wrongly identified as iCR by MRI (FN; 13%), but 38 out of 44 were correctly identified as not iCR by MRI (TP). MRI's sensitivity, specificity PPV and NPV, were 50%, 88%, 54% and 86%, respectively. After subtype stratification, we observed a high variability in sensibility, specificity, PPV and NPV values between the different subgroups (Table II). MRI leads to non-specific and heterogeneous responses with a high number of false positives in luminal A/B tumors (Table III). Triple negative and HER2+ tumors (Tables IV and V) had almost the same specificity and sensitivity (81% and 50%). Nevertheless, PPV was greater in the HER2+ group compared to the triple negative group (71% and 33%, respectively) and the triple negatives' group NPV was greater than that of the HER2+ one (90% and 64%, respectively). Finally, in the subgroup of no pCR patients, we analyzed the correlation between MRI and pathologic assessment of residual tumor dimension, calculating the Pearson's r, p, mean, trend and median for both the complete patient series (Table VI) and the three different subgroups. Statistical analysis of the whole cohort showed a weak but significant correlation between MRI and pathological assessment of residual tumor dimension (Figure 3). Stratification in the three subgroups did not result in statistically significant differences (Figure 4), however, the correlation was very low (0.23) in the group of luminal tumors (the largest group of our series).

Discussion

In our study, MRI after NACT had a sensitivity, specificity, PPV and NPV of 50%, 88.4%, 54% and 86%, respectively. These data agree with the current literature, in particular with a systematic review published in 2013 (3). Our analysis revealed that MRI sensitivity and specificity values are very variable between the three histotypes. MRI has a very low specificity in predicting pCR in luminal A/B tumors, so, in this subgroup, surgery strategy cannot rely only on MRI data. Nevertheless, MRI specificity was higher (81%) in HER2+ subgroup than in luminal A/B one. MRI sensitivity and specificity were 50% and 81%, respectively, in triple negative group analysis. Our data agrees with literature: MRI predicts better pCR in triple negative and HER2+ tumors. However, our study deviates slightly from the other studies that have reported higher levels of sensitivity, specificity and PPV (88.9%, 91.4% and 72.7% respectively) in triple negative analysis (8). Evaluating this data, subgroups dimension discrepancy (with lower percentage of triple negatives compared to the others subgroups) and the different numbers of pCR in luminal A/B, triple negative and HER2+ tumors (5%, 23% and 33%, respectively) must be considered.

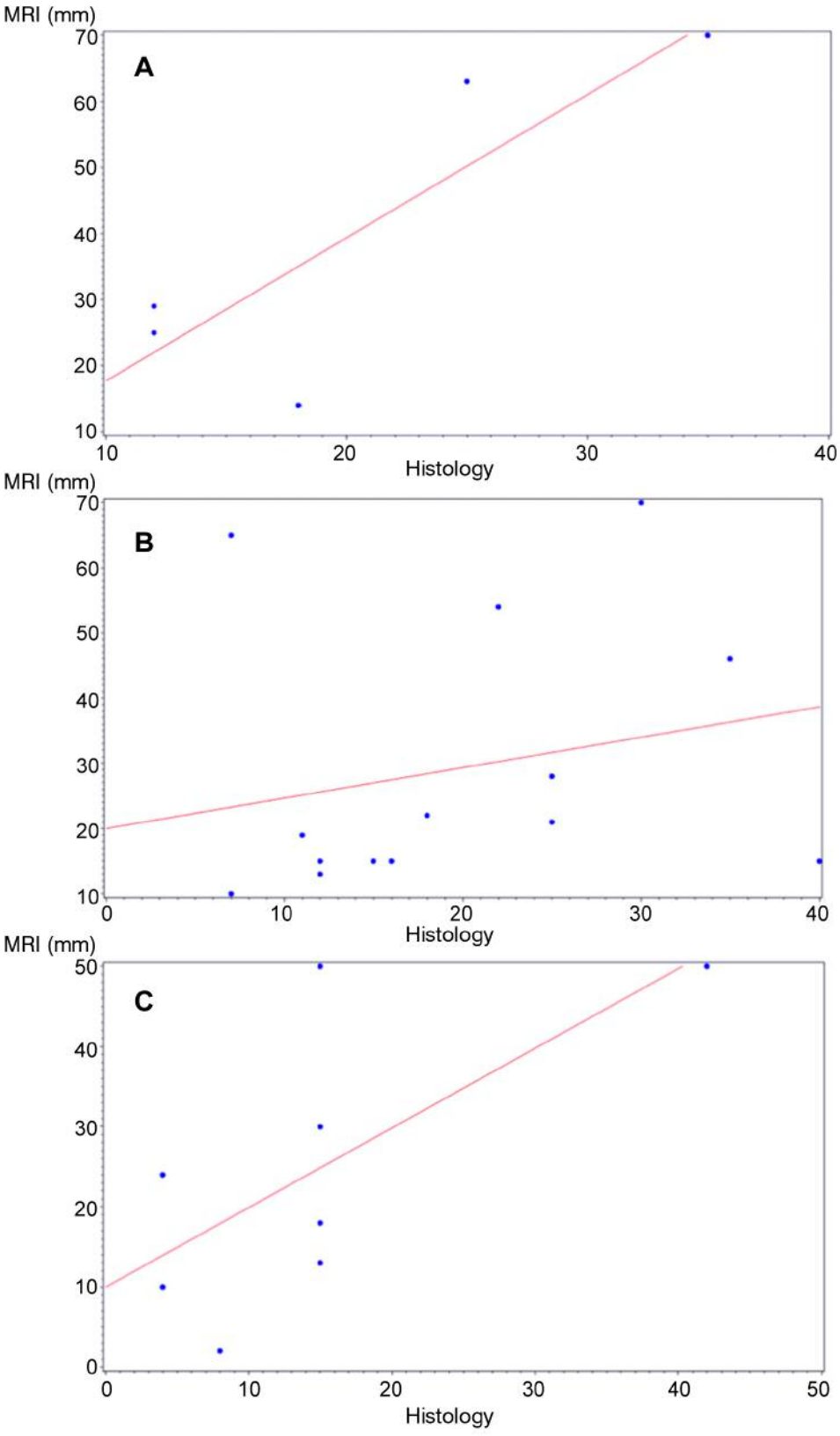

Figure 4. *Correlation between residual tumor dimension assessment (MRI vs. pathology) in each tumor subgroup. A: Luminal A/B tumors (Pearson r=0.23, p=0.42). B: Triple negative tumors (Pearson r=0.85, p=0.06). C: HER2+ tumors (Pearson r=0.67, p=0.07).*

Considering only patients who do not reach pCR after NACT and comparing MRI and pathologic assessment of residual tumor dimension, Pearson's r was 0.48 (p=0.01) which, although weakly, is statistically significant. Stratifying tumor subtypes, MRI accuracy did not seem reliable in luminal tumors response evaluation. Although this group is the largest one, the correlation was very low and not statistically significant. The correlation was higher and significant in triple negative and HER2+ tumor assessment (0.85 and 0.67, respectively). NACT indications were increasing and the successive surgical approach depended on residual tumor and not on initial tumor bed, so a reliable predictive method of pCR is strongly advisable. Our study, confirms literature data about MRI accuracy in HER2+ and triple negative tumors, but suggests caution in the case of luminal tumors' evaluation. Therefore, looking at the results obtained, MRI has an FP rate of 45% and an FN rate of 13%, thus leading to over-treatment in 45% and under-treatment in 13% patients. However, since recent literature indications for surgery approach after NACT might range from surgery abstention in iCR patients (16) to the asportation of the entire area involved at the beginning of medical treatment in not iCR patients, further histological examination could be suggested in association with MRI, especially in luminal subtypes.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Pasquero Giorgia: Substantial contributions to acquisition of data; Surace Alessandra: Substantial contributions to acquisition of data; Ponti Antonio: Substantial contributions to analysis of data; Bortolini Massimiliano: Revising the article critically for important intellectual content. Tota Donatella: Substantial contributions to acquisition of data. Mano Maria Piera: Substantial contributions to conception and design of the study. Arisio Riccardo: Substantial contributions to analysis of data. Benedetto Chiara: Substantial contributions to organization of the conduct of the study; Baù Maria Grazia: Substantial contributions to conception and design of the study.

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