Evaluation of neoadjuvant treatment of breast cancer: MRI or PET?

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Purpose

Breast cancer is increasingly gaining attention of researchers and clinicians for the continuous improvements that have been obtained in recent years in the control of the disease. The introduction of more effective and better tolerated anticancer medical therapies has given a substantial contribution to the improvement of mortality and survival. In terms of survival rate, medical therapy being administered before or post-surgery is equally effective. However, a neoadjuvant approach reduces the tumor mass making it in some cases resectable or in others candidate for conservative surgery. Breast preservation is not the only advantage of neoadjuvant chemotherapy (NAC); as a matter of fact early treatment can be useful to eradicate micro-metastases and to monitor in vivo the effect of the anticancer drugs. The ability to identify non-responders in advance, after the first cycles of NAC, allows to modify and customize therapeutic attitude.

NAC evaluation includes two types of response:

**Reported pathological complete response (pCR):** comparison between the degree of cellularity before treatment (on core biopsy) and after medical and surgical treatment (on surgical specimen).

**Clinical response (cCR):** tumor size modifications evaluated by physical examination (International Union Against Cancer) and imaging exams (ultrasound, mammography).

The morphological changes of the tumor lesion, like size and echo pattern, evaluated with mammography or ultrasound, are not ideal as a response monitor to systemic therapies because both methods do not distinguish between residual disease and fibrosis. Furthermore, chemotherapy causes edema of the mammary gland, making it difficult to evaluate response to treatment and the extent of potential residual disease. Although early stage and tumor size represent two important prognostic features, the primary goal of inductive therapy is the level of pathological response. Many clinical studies have shown that pathological complete response (pCR) plays a major predictive role being associated to an excellent prognosis in terms of long-term survival and relapse-free disease, but to date there are no standard classification systems in grading the pathologic response of the tumor. Our institution adopted the Grade of Tumor Regression (TGR) sec. Miller-Payne which provides a scale of five levels of response. (TGR1# absence of regression; TGR 5 # absence of residual tumor cells).

Therefore new imaging modalities are necessary, which are effective in monitoring tumor response to NAC, and more accurate in estimating the degree of pathological regression.

The purpose of our study was to monitor the response to NAC with MRI and PET, analyzing predictability, in terms of treatment response, and residual disease examined histopathologically.
Starting from January 2005, 48 patients were enrolled (51 ± 11 y) with histological diagnosis of breast cancer (BC), locally advanced (with non-surgical characteristics T3-4, N2-3) or surgically resectable but candidates for radical mastectomy (size> 3 cm, T2) with clinical staging IIA-IV. Our protocol consists of NAC and subsequent surgery with pathological analysis of surgical specimen (TGR sec. Miller and Payne). Only 40 patients completed the study.

An evaluation of the disease with PET and MRI was performed, prior to initiation of therapy (pre-NAC) after 2 cycles, after 4 cycles and the end of therapy. Diameters and T/I curves were analyzed with MRI, SUVmax and #SUV with PET. A double blind evaluation of the results of the two techniques was then compared to the pathologic examinations, which were performed twice: before therapy (core biopsy, Core Needle Biopsy) and on the surgical specimen (degree of tumor regression, TGR, Miller and Payne).

Eligibility criteria:

- Patients older than 18 years with a histological diagnosis of breast carcinoma and eligible for primary chemotherapy with anthracycline-based and taxanes regimens or in clinical trials approved by the ethics committee of our hospital.
- TNM staging: T2-4 N0-3 M0 (patients with oligometastatic disease may be included, if the therapeutic program requires surgery after chemotherapy)
- appropriate clinical conditions for chemotherapy treatment (bone marrow function, renal, liver and heart) and the subsequent surgical treatment.
- Informed Consent.

MRI was performed using a Signa tomographer GE Healthcare 1.5 T with dedicated bilateral phased array coil, with injection of paramagnetic contrast agent (Gd-DTPA). The injected dose was 0.2 mmol/kg with a speed of 2 ml/sec, followed by injection of 15 ml of physiological saline 0.9% NaCl. Our protocol included the acquisition of T2w images (TR 5200.0 sec; TE 40 msec) and 3D fast-spoiled gradient-echo T1W FAT-SAT images (Automatic TR, TE minimum, flip angle 40 ° , BV 65.50 kHz, FOV variable), with 1 pre-contrast acquisition (mask) and 5 post-contrast acquisitions, with a delay of 30 sec.

Postprocessing included a reprocessing phase with image subtraction before and after contrast enhancement, calculation of T-SI curves with a Functool dedicated software, and MIP reconstructions.

Two independent radiologists, unaware of anatomic pathology results, performed a multiparameter analysis: dimensional (2 maximum diameters of the lesion, according to WHO criteria), kinetic (peak rate enhancement curves, and T-SI derived curves type
I, II and III, according to Kuhl CK. et al.), morphological (reduction pattern concentric or fragmented) Fig. 1 on page 5 Fig. 2 on page 5. We then monitored the response to therapy by evaluating modifications T-SI curves and the intensity of the peak enhancement in the early phase (120''), the percentage of size reduction and the pattern of reduction (variations of BI-RADS).

PET was performed injecting 370 MBq of 18F-FDG with the patient fasted for at least 6 hours. After 60 minutes, we proceeded to acquisition of PET images for a period of 4-5 minutes per bed position (15 cm), modified with a low intensity CT technique (60 mV, 120 mA). We calculated the value of the maximum SUV (standard uptake value) on the primary lesion, and we evaluated the response to therapy according to EORTC criteria, by calculating the uptake reduction of FDG compared to a baseline value measured before the beginning of treatment.

- **CR:** same metabolic rate as normal tissue
- **PR:**
  - after I cycle 15-25% decrease in SUV
  - after II cycle > 25% decrease in SUV
- **PD:** > 25% increase of SUV or appearance of new lesions
- **SD:** difference of -15% to +25% in SUV; same extension
Fig. 1: Kinetics analysis acquired in a 56-year-old patient with a diagnosis of invasive lobular carcinoma. (A,B) Dynamic contrast-enhanced MR image showed a diffuse and heterogeneous non-masslike enhancement, in the right breast. (C,D) Kinetic analysis was evaluated using manual placement of a region of interest (ROI). (E,F) Kinetic features evaluated included classification of the signal-intensity time curve (washout, plateau or persistent enhancement).

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Fig. 2: Dimensional morphological analysis 61-year-old patient with a diagnosis of invasive ductal carcinoma. According to the WHO criteria, the total tumor size was determined by bidimensional measurements (e.g. the sum of the products of the two longest diameters in the perpendicular dimensions of tumor), before neoadjuvant chemotherapy, NAC (A) and during therapy (B); we also evaluated the pattern of morphological reduction during treatment (fragmented or concentric).

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Results

Pathologic response to NAC (TGR) was good in 28 patients (11 patients TGR-3, 13 patients TGR-4 and 4 patients TGR-5) and poor in 12 patients (4 patients TGR-1, 8 patients TGR-2). Fig. 3 on page 8 Fig. 4 on page 8
At the first examination (pre-NAC) the lesions had a diameter between 3 and 6.6 cm (mean 4 cm). The kinetic analysis of intralesional enhancement showed in all 48 cases, pathological T-SI curves (type II-III), with a percentage of enhancement in the early phase > 110% and PET reported SUV values between 4.5 and 23.

After 2 cycles of NAC in 26/28 patients with TGR 3-5, the PET study showed a reduction of SUV > 25% (responders) while MRI showed a partial response to therapy (reduction of the area of enhancement> 50% and transition from a curve with higher probability of malignancy to one with a lower probability: III#II o II#I) in only 14/28 patients, whilst in the remaining 14 cases MRI showed no response to therapy.

After 4 cycles of NAC, in 27/28 patients PET (SUV disappearance or reduction > 65% of baseline) and in 23/28 MRI (disappearance of enhancement or reduction > 50% with type I curve) have consensually confirmed the histologic exam results (TGR 3-5).

Of the 24/28 patients with residual disease (TGR 3-4), PET showed complete response (SUV=0) in 9 patients after the 2nd cycle of NAC, that reached the number of 15 after the 4th cycle and 22 at the end of therapy.
In contrast, after 2 cycles of NAC, MRI showed complete response in none of the 24 patients, whereas a complete disappearance of enhancement was reported in only 2 cases after the 4th cycle, and in 9 cases at the end of therapy. Fig. 5 on page 9 Fig. 6 on page 10 Fig. 7 on page 11
Of the 12 patients with poor pathological response (TGR 1-2) in 10 cases, MRI confirmed a modest reduction of the lesion at the end of therapy (reduction of the enhancement area <50% and T-SI curves type II or III), while PET in 6/12 patients showed a good regression of the underlying disease with a SUV percentage reduction > 65%.
Fig. 3: Example of favorable response predicted by MRI in 36-year-old woman with a diagnosis of invasive lobular carcinoma. Note segmental, non mass like confluent enhancement on maximum-intensity-projection MR image, in right breast, obtained before neoadjuvant chemotherapy (A), after four courses (B) and at the end of NAC (C). T-SI curves taken before the first cycle chemotherapy, type 3(D), after the 4th cycle of chemotherapy, type 1 (E) and at the end of therapy, type 1 (F).

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Fig. 4: Example of poor response predicted by MRI in a 42-year-old woman with a diagnosis of invasive ductal carcinoma (non-responder). Dynamic Contrast-enhanced MRI, obtained before NAC (A), after 4th cycle (B) and at the end of therapy (C), demonstrates in the right breast, a mass with irregular margins, that does not show change in size and in signal enhancement during therapy. The T-SI curve of the lesion, prior to NAC (D), shows a rapid homogeneous enhancement in the early dynamic phase with washout, type 3. After 4th cycle (E) and at the end of therapy (F) there are no changes.

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Fig. 5: 52-year-old woman with favorable response to NAC (TGR 3). PET showed a complete response to therapy after only two cycles of NAC (disappearance of uptake). Maximum-intensity-projection MR image obtained before neoadjuvant chemotherapy (A), after two courses (B) and at the end of therapy (C). MRI, at the end of NAC, revealed residual foci of enhancement with type 2 curve (D), according to definitive histological.

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Fig. 6: 56-year-old woman with favorable response to NAC (TGR 4). PET showed a complete response to therapy after only two cycles of NAC (disappearance of uptake). Maximum-intensity-projection MR image obtained before neoadjuvant chemotherapy (A), after two cycles (B) and at the end of therapy (C). After two cycles MRI shows only a partial response, with reduction of the area of enhancement > 50% (D, before NAC and E, after 2nd cycle) and transition from a curve type 3 to type 2 (F, before NAC and G, after 2nd cycle). At the end of therapy MRI demonstrated a complete disappearance of enhancement (C).

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**Fig. 7:** 46-year-old woman with favorable response to NAC (TGR 4). PET showed a complete response (SUV=0). Note non-mass like confluent enhancement, in the left breast, on maximum-intensity-projection MR image, obtained before NAC (A). MRI showed, after 4th cycle (B), a partial response to therapy and at the end of therapy residual foci of enhancement (C). The T-SI curve of the lesion, prior to NAC, showed a type III (D), after 4th cycle (E) and at the end of therapy (F) a type II-I.
Conclusion

MRI has shown to be a valid technique in the evaluation of the response to therapy due to its correlation with the anatomopathological data.

In the early stages (first 2-3 cycles) PET remains the method of choice for high sensitivity, capacity of early recognition of patients responsive to therapy. On the contrary MRI responsivity to chemotherapy is expressed mainly after the IV-VI cycle of NAC, as in early stages there are changes related to the vascularity of the gland that may be difficult to read. Nonetheless the dimensional and kinetic analysis on MRI appears to be a reliable indicator for follow-up, because of its correlation with SUVmax.

After the fourth cycle and at the end of therapy, PET may in most cases overestimate response to treatment showing zeroing of the SUV values, while MRI can still give useful data from the lesion (size reduction by fragmentation). In particular, the MRI shows a high sensitivity in the preoperative phase, providing an accurate estimation of the presurgical regression degree, especially in patients with a non-complete response, which may benefit from a different or prolonged treatment regimen.
References


Personal Information

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