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Monitoring of neoadjuvant chemotherapy using multiparametric, ^{23}Na sodium MR, and multimodality (PET/CT/MRI) imaging in locally advanced breast cancer

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Abstract

We prospectively investigated using advanced magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) to identify radiological biomarkers for treatment response in patients receiving preoperative systemic therapy (PST) for locally advanced breast cancer. Patients with a stage II or III breast cancer receiving PST were selected and underwent positron emission tomography (PET), magnetic resonance imaging (MRI), and breast biopsies at baseline and after the first cycle of PST (days 7–8) during the full course of treatment. PET/CT was acquired after injection of 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}FDG , 0.22 mCi/kg) and quantified with standardized uptake value assessment (SUV). Diagnostic breast MRI and sodium (^{23}Na) was acquired at 1.5 T. Total tissue sodium concentration (TSC), response criteria in solid tumors (RECIST), and volumes were quantified. Treatment response was determined by pathological assessment at surgery. Immunohistochemistry values of the proliferative index (Ki-67) were performed on biopsy specimens. Six of nineteen eligible women (43 ± 11 years) who received PST underwent radiological imaging of ^{18}FDG -PET/CT and MRI for at least two cycles of treatment. Five patients had a pathological partial response (pPR) and one had pathological non-response (pNR). TSC decreased 21% in responders with increases in the non-responder ($P = 0.03$). Greater reduction in SUV was observed in responders (38%) compared to the non-responder (22%; $P = 0.03$). MRI volumes decreased after cycle 1 by 42% (responders) and 35% (non-responder; $P = 0.11$). Proliferation index Ki-67 declined in responders in the first cycle (median = 47%, range = 29–20%), but increased (4%) in the non-responder. Significant decreases in TSC, SUV, and Ki-67 were observed in responders with increases in TSC and Ki-67 in non-responders. Our results demonstrate the feasibility of using multi-modality proton, ^{23}Na MRI, and PET/CT metrics as radiological biomarkers for monitoring response to PST in patients with operable breast cancer.

Keywords

Breast; Magnetic resonance imaging; Sodium ^{23}Na MRI; PET; PET/CT; Response; Cancer

Introduction

With early detection and optimal local and adjuvant systemic therapy, most women diagnosed with breast cancer are expected to survive their disease [1]. While several prognostic and predictive factors are currently available to calculate odds of disease free and overall survival, new metrics which could help select women most likely to benefit from specific therapies are needed. Since complete pathologic response following preoperative systemic therapy (PST) correlates with long-term outcome, PST, also referred to as primary or neoadjuvant chemotherapy, is increasingly used as a research platform for new drug investigation. Currently, only 15–30% of patients who receive PST obtain complete clinical or pathological complete response [2]. One potential avenue to increase the likelihood of achieving a complete pathological response in patients is early identification of patients who

will respond to therapy from those who will not. Early recognition of ineffective therapy may allow for administration of different agents, thus enhancing the chance of efficacy while minimizing toxicity. Methods of early response determination are critical for optimal individual “tailoring” of treatments.

Non-invasive imaging tools that could monitor response to PST are particularly attractive. Indeed, magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) are increasingly being used as single modalities to screen and monitor response to PST. Recent studies have demonstrated the benefit of using MRI in patients with known invasive disease with detection of unknown contralateral cancers [3, 4]. In addition, several reports have demonstrated the ability of MRI to assist in monitoring response to treatment using dynamic contrast enhancement (DCE) MRI, volumetrics, and/or spectroscopy [5–9]. PET/CT is not currently used as a breast screening tool, but is utilized for staging and/or detecting metastasis with moderate to high sensitivity and moderate specificity in tumors [10–13]. Through the use of 2-deoxy-2-[18F]-fluoro-D-glucose (^{18}F FDG), quantitative measures of glycolic activity in tumors can be obtained using the standardized uptake values (SUV) from PET/CT data. Growing evidence suggests that PET/CT is a tool that can be used to monitor PST and may provide excellent sensitivity and specificity [14–17]. However, none of the studies reported to date combined proton MRI, multinuclear sodium (^{23}Na), and PET/CT. The combined use of these multimodality-imaging methods (MR/PET/CT) is novel and an active area of research [14, 18]. The use of advanced MRI and PET/CT methods, may allow for non-invasively probing of the physical and metabolic changes in the tumor microenvironment.

In this study, we investigated the relationship between the changes in multiparametric and multinuclear MRI with PET/CT parameters to characterize early evaluation of response to PST within the first cycle of treatment and correlate these radiological parameters with histological parameters.

Methods and materials

Clinical subjects

Women, age 18 or older with stage II or III breast cancer who were candidates for PST were enrolled into two parallel prospective clinical studies. In this report, we include six women who enrolled both in a study correlating PET/CT imaging and response to chemotherapy ($n = 19$), and advanced MRI parameters and response to chemotherapy ($n = 6$). The women included in this report received four cycles of docetaxel 100 mg/m² every 14 days with or without four additional cycles of doxorubicin and cyclophosphamide combination.

The patients underwent MRI and PET/CT evaluation of breast lesions before and after administration of the first cycle of the drug within 7–8 days. In addition, core biopsy samples were taken at baseline and after first cycle for correlation between known histopathological and radiological imaging markers. Our Institutional Review Board approved both protocols, and a written informed consent was obtained from all subjects.

Clinical response and histological tissue classification

Clinical response to treatment was determined by a board certified breast medical oncologist by examination of the breast, and when appropriate, in the axilla, infraclavicular, and supraclavicular regions, and skin at the time of study enrollment, prior to each cycle of PST and prior to surgery.

Pathologic complete response (pCR) was defined as no viable invasive cancer (macro or microscopically) in the pathologic specimen at histological examination. Pathologic partial

response (pPR) is defined as a considerable reduction in tumor cells but presence of $\leq 10\%$ microscopic foci of invasive cancer cells could be detected. Pathologic no response (pNR) was defined in specimens that did not meet the criteria for a pathologic complete or partial response. In addition, hormonal and immunohistochemistry values of the proliferative index (Ki-67) were performed on core biopsy specimens at the each time point.

MRI imaging protocol

Proton MR imaging

The MRI scans were performed on a 1.5 T scanner (General Electric Med. Sys. Waukesha, WI) using a dedicated phased array breast coil (MRI Devices, Milwaukee, WI) with the patient lying prone. Sagittal fat suppressed T₂WI spin echo (TR/TE = 5700/102) and fast spoiled gradient echo images (FSPGR) T₁WI (TR/TE = 200/4.4) with field of view (FOV) = 18 × 18 cm, matrix = 256 × 192, slice thickness, 4 mm, 1 mm gap) were acquired. Dynamic contrast-enhanced FSPGR T₁WI (TR/TE = 20/4, matrix = 512 × 160, slice thickness, 2 mm, 3–4 phases after injection) was obtained after intravenous administration of GdDTPA contrast agent (Omniscan, Amersham Health, 0.2 mL/kg (0.1 mmol/kg)). The contrast agent was injected over 10 s with MR imaging beginning immediately after completion of the injection. The contrast bolus was followed by a 20 cc saline flush. Total scan time was less than 20 min.

²³Na sodium MR and quantification

For quantitative ²³Na sodium MRI, a custom-made ²³Na coil which was inserted into the breast coil. A modified projection imaging sequence was used with a TR of 100 ms (>3 times T_1), an ultrashort TE of 0.2 ms, and 400 μ s adiabatic excitation pulses with six averages from 718 projections were recorded in 12 min [19, 20]. The proton images were co-registered in Matlab (Mathworks, Natick, MA), using Matlab scripts developed in-house. Regions of interest (ROI) were drawn on co-registered proton and ²³Na images to determine the total tissue sodium concentration (TSC) in lesion and normal breast tissue. The TSC in breast tissues was determined as previously described in breast tissue [19]. Total proton and ²³Na MR imaging time was 45 min.

Positron emission tomography and computed tomography (PET/CT)

After the patient fasted for 4 h, an intravenous (IV) access was started and a serum glucose level measured. The patient was injected with the glucose analog ¹⁸FDG. The ¹⁸FDG dose is calculated based on the weight (kg) of the patient as follows: Dose (mCi) = Weight (kg) × 0.22 (mCi/kg). Maximum dose is 25 mCi with weights greater than 114 kg or 250 lbs. Minimum dose is 5 mCi with weights less than 23 kg or 51 lbs. After the uptake phase, which lasts 45–60 min, the patient was positioned and near whole body images are acquired using a PET/CT unit (General Electric Discovery Light Speed).

MR image preprocessing and analysis

DCE and volume analysis

MR image analysis was performed using a SUN T2000 server (Sun Microsystems Inc., Mountain View, CA.) using the Eigentool image analysis software (Image Analysis Lab, Henry Ford Hospital, Detroit MI [21]) and DCE-MRI software for visualization of morphology and the uptake curve analysis (DynaCAD, Invivo, Orlando, FL.). Percentage enhancement was calculated as $(SI_{\text{post}} - SI_{\text{pre}})/SI_{\text{pre}} \times 100$, where SI_{pre} is the signal intensity in the pre-contrast image and SI_{post} is the signal intensity in the post-contrast image. DCE kinetic characteristics were assessed, color-coded, and classified by initial

uptake and temporal curve analysis [22]. Response criteria in solid tumors (RECIST) measures were calculated before and after treatment in each patient [23, 24].

PET: standardized uptake values

SUV within the tumor region were obtained from areas of increased signal intensity on the PET scans. The SUV defined as the ratio of tumor ^{18}F FDG concentration (mCi/kg) to whole body concentration (injected dose divided by weight of the patient in kg) were used to assess treatment response and defined as;

$$\text{SUV} = \frac{\text{Activity } (\mu\text{Ci/g})}{[\text{injected dose } (\mu\text{Ci/g})/\text{weight (kg)}]} \quad (3)$$

where activity is obtained from the PET images, the injected dose of ^{18}F FDG, and weight (kg) of the patient is used for normalization [25]. In general, an SUV unit of one is considered normal, whereas, an SUV unit greater than approximately 2.5 is considered suspicious and needs clinical correlation. We have selected 2.5 as our threshold for positive PET/CT. Regions of interest were drawn on the baseline studies and after the first cycle by a board certified nuclear medicine physician.

Statistical analysis

The differences between MRI defined volumes, ^{23}Na concentrations, SUV, and Ki-67 were tested before and after treatment using ANOVA and unpaired *t*-tests. Statistical significance was set at $P < 0.05$.

Results

Pathological results

Six women underwent both PET/CT and MR imaging following one cycle of docetaxel as well as baseline and follow-up core biopsies. Clinical partial response (cPR) was noted in three patients and three had stable disease (cSD). However, at surgery, two patients with clinical stable disease had pathological partial response (pPR) and one of the cPR was classified as a pNR. Thus, five patients had a pathologic partial response (pPR) and one patient had no response (pNR). The histological markers were as follows for this subgroup were as follows: one patient expressed both the estrogen and progesterone receptors (ER+/PR+), two patients had ER+/PR- tumors, one patient was “triple negative” (i.e., ER-/PR-/Her2/neu-), and two were ER-/PR-, but Her2/neu+. Mean baseline Ki-67 was 36% in responders and 70% in the non-responder (Table 1). Following the first cycle of docetaxel, there was a 47% decrease in the Ki-67 (range = 29–20%) in the responders compared to an increase in Ki-67 in the nonresponder (14%; range = 70–80%; $P = 0.06$).

Radiological results

Figures 1 and 2 demonstrate the combination of MRI and PET/CT in a 55 year old woman with an infiltrating ductal carcinoma who responded to the therapy. The baseline scan in Fig. 1a, both proton MRI, ^{23}Na imaging, and PET/CT clearly show primary tumor allowing for metabolic, biochemical, vascular, and morphologic information to be obtained in one setting. After the first cycle of PST, there is evidence of treatment response in both radiological parameters as demonstrated in Fig. 2 with decreases in the Pharmacokinetic PK-DCE, SUV, and sodium images. Conversely, Figs. 3 and 4 demonstrate the power of combining MRI with PET/CT in cases where one or both modalities are equivocal. For

example, in Fig. 3, the patient has invasive lobular breast cancers, which are known for low ^{18}F FDG avidity, but the breast lesion is clearly visualized using proton MRI and ^{23}Na imaging, demonstrating that combining these methods is useful to monitor response to PST and could provide a more complete picture of tumor microenvironment and shown in Fig. 4. Summary statistics of the MRI parameters are shown Table 1.

Sodium concentration

The mean total sodium concentration in breast tumors decreased significantly by 21% (55.2–43 mM; $P = 0.03$) in responders and exhibited no or little change (3%) in nonresponder (56.2–58.1 mM) after the first cycle.

Standard uptake value

Five of the six (5/6) patients had positive (i.e., SUV greater than 2.5) PET/CT findings on the affected breast at baseline screening with no evidence of metastatic disease. One patient with invasive lobular breast cancer exhibited little or no ^{18}F FDG uptake. The mean SUV lean-max significantly decreased after the first cycle of treatment by 38% in responders (SUV: 5.4–3.3; $P = 0.04$) and 22% in the non-responder (SUV: 14–11).

Dynamic contrast MRI parameters

There was marked contrast uptake within the lesions on the DCE-MRI with a mean enhancement (curve types 2 and 3) was high at $247 \pm 84\%$ and demonstrated heterogeneously decreased mean enhancement $196 \pm 73\%$ after the first cycle. Mean MRI tumor volume decreased by 42% (responders: 70 ± 79 to $52 \pm 32 \text{ mm}^3$) and 35% (non-responders: 49 to 32 mm^3 cc; $P = 0.11$) after the first cycle. Finally, the RECIST measurements in responders decreased by 18% compared to 14% in the non-responders

Discussion

Significant decreases in TSC and SUV metrics were observed in responders. Moreover, changes in these radiological imaging metrics were consistent with histological changes with decreases in proliferation index Ki-67 in responders, while increases in the Ki-67 were observed in non-responders. These findings are suggestive that radiological imaging biomarkers of sodium and glycolic metabolism could be indicative of tissue response or lack thereof after treatment. We provide compelling evidence that using multimodality proton and ^{23}Na MRI combined with PET/CT imaging is feasible and useful for monitoring PST in patients with operable breast cancer. Indeed, by combining multimodality-imaging methods important functional metrics (TSC and SUV) can be obtained of the tumor microenvironment beyond standard volumetric data and traditional treatment response assessment measurements, such as RECIST [23, 24]. Our data serve as proof of principle that using multi-parametric/modality technology to monitor preoperative therapy could lead to radiological metrics for surrogate biomarkers needed for adaptive therapy in patients [9, 17].

The importance of multimodality imaging is clearly demonstrated in the two cases presented, where, PET/CT showed no uptake of ^{18}F FDG in the breast lesion, but the lesion was clearly visible in the MRI data. This interplay with multimodality imaging could provide two important mechanisms for developing quantitative imaging methods, first, for detection of metastatic disease and second, monitoring of PST efficacy, especially, in cases where there is little ^{18}F FDG uptake or visible changes on the MRI images. This assumes that metastatic disease will be seen with PET/CT, which is a good assumption, since it is currently used for staging of breast cancer patients. Reports have shown that by combining MRI and PET can be used for monitoring and assessing the residual disease for locally

advanced breast cancer during PST [14, 15, 26]. The authors demonstrated that PET could detect pathological no response (pNR) in five of six cases (83%) and MRI defined the extent of macroscopic pathologic residual disease accurately in nine of ten cases (90%), and finally, it was shown that when dynamic contrast MRI (DCE-MRI) metrics were indicative a complete clinical response (cCR) post therapy, the results were confirmed pathologically [14, 15, 26]. PET was found to be more accurate in detecting pNR, while MRI was found to be more accurate assessing cCR and correlated well with pCR. The study suggested that both MRI and PET were complementary in monitoring the response to neoadjuvant chemotherapy. Our data support these findings and extend the use with sodium MRI. Further studies are needed to elucidate at which time point after treatment, if any, radiological biomarkers can be utilized for determining response to treatment. A few reports have demonstrated that after the first cycle of treatment and before the midpoint treatment cycle might be an optimal time point for gauging treatment response [9, 27]. More importantly, the use of volumetrics can be misleading, we noted a significant decrease in tumor volume in both responders and non-responders and it is well known that radiographic morphological or anatomical changes occur later than functional parameters within the tumor [28, 29]. Therefore, it is clear that additional radiological imaging characteristics are needed to obtain functional and metabolic information of the tumor environment such as sodium, SUV, and other quantitative radiological imaging metrics, such as spectroscopy and/or diffusion-weighted imaging with ADC mapping [9, 17, 30–32]. Functional radiological imaging metrics will be able to probe the tumor microenvironment and correlate with histological markers. For example, we noted changes in sodium concentration that were inversely correlated to Ki-67 and the SUV changed in response to the KI-67. These radiological changes are consistent with the cellular responses within the tumor after PST [33, 34]. If the tumor undergoes a response to treatment, then should be a decrease in the proliferation of tumor cells when would lead a decrease in the movement of water in and out of the tumor and the surrounding tissue. These cellular changes would occur within the membrane of the tumor, thus contribute to potentially less sodium concentration and glucose uptake. Whereas, with an increase in proliferating of tumor cells, presumably, more active cells require more nutrients and other tumor microenvironmental factors for growth, so there should be an increase in cellular activity, which is reflected by the changes in sodium concentration, DCE-MRI, and SUV data.

Similar radiological imaging changes have been recently reported using PET using the SUV as a response predictor. Berriolo-Riedinger, et al. [16] demonstrated that a decrease in the SUV of greater than 60% is predictive of a pCR and a change less than 60% was a non-responder in a series of 47 breast cancer patients. However, they did not separate the non-responders into sub groups (partial- vs. no-response) and our preliminary findings in these study supports these results.

There are, however, some technical limitations to the use of ^{23}Na imaging and PET/CT. First, the ultra-short TE and multinuclear hardware (e.g. coils and transmitters) used here are not widely available. Although the use of ^{23}Na MRI is now finding some applications in the brain, breast, uterus, and heart [19, 35–37], more specific to the present study, any assessment of the clinical value of multiparametric proton, ^{23}Na MRI, and PET/CT in monitoring treatment response of PST will require additional studies in a larger patient population, with subsequent follow-up and histological evaluation to discern the sensitivity and specificity of this approach and exact mechanisms underlying the changes are needed and larger studies are planned.

In conclusion, we have demonstrated that multimodality radiological imaging is feasible for identifying and monitoring PST in stage II and III breast cancer patients and these methods can provide a basis for a comprehensive evaluation of the complex tumor microenvironment

by examining the changes in morphology, sodium concentration, and glucose metabolism in response to therapy.

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Fig. 1. Multimodality PET/CT, dynamic contrast enhanced (DCE), and sodium MR images on a 35 y/o female with stage III breast cancer before preoperative systemic therapy. **a** There is marked uptake of ^{18}F FDG PET within the lesion (SUV = 6.7). **b** Also rapid uptake of contrast agent within the lesion shown on the DCE MR image with a volume (32 mm³). **c** There was high total sodium concentration (42 mM) within the lesion

Fig. 2. Multimodality images on a 35 y/o female with stage III breast cancer at day 7–8 after the first cycle of treatment. **a** There is decreased PET uptake within the lesion (SUV = 3.2). However, there was increased uptake of ^{18}F FDG within the bone marrow due to the administration of pegfilgrastim (Neulasta). **b** Also decreased heterogeneous uptake lesion on DCE-MRI with decreased volume (29 mm³). **c** There was decreased total sodium concentration (41 mM) in the lesion

Fig. 3. Multimodality PET/CT, dynamic contrast enhanced (DCE), and sodium MR images on a 39 y/o female patient with invasive lobular cancer before preoperative systemic therapy. **a** There is little or no uptake of ^{18}F FDG PET within the lesion ($\text{SUV} = 0$). **b** However, there is marked DCE uptake in the lesion with a volume (13 mm^3). **c** There was high total sodium concentration (62 mM) within the lesion. Note, the *curved arrows* point to a cyst within the breast

Fig. 4. Multimodality PET/CT, dynamic contrast enhanced (DCE-MRI), and sodium MR images on a 39 y/o female patient with invasive lobular cancer after the first cycle of preoperative systemic therapy. **a** There is still little or no uptake of ^{18}F FDG PET within the lesion ($\text{SUV} = 0$), but there was increased uptake of ^{18}F FDG within the bone marrow due to the administration of pegfilgrastim (Neulasta). **b** However, there is marked decreased DCE uptake within the lesion and a volume (7.5 mm^3). **c** There was lower total sodium concentration (52 mM) within the lesion. Note, the *curved arrows* point to a cyst within the breast

Table 1

Patient demographics, histopathology, and radiological parameters

Patient	Age	Histological Diagnosis	Phenotype ER/PR/Her2-neu	Pathological Response	Volumes (mm ³)		Sodium (mM)		SUV		Ki-67 (%)	
					Baseline	1st Cycle	Baseline	1st Cycle	Baseline	1st Cycle	Baseline	1st Cycle
1	35	IDC	-/-/+	pPR	46.8	43.4	55.0	39.2	5.6	4.9	60.0	40.0
2	41	ILC	-/-/+	pPR	12.6	7.5	62.2	51.8	0.0	0.0	10.0	2.0
3	35	IDC	+/-/-	pPR	32.4	28.6	42.4	41.1	6.7	3.2	50.0	50.0
4	39	IDC	+/+/-	pPR	208.0	100.0	66.9	41.5	7.4	4.3	12.0	8.0
5	41	ILC	+/-/-	pPR	50.0	30.0	48.5	38.4	2.0	1.2	15.0	2.0
6	68	IDC	-/-/-	pNR	49.2	31.8	56.2	58.1	14.7	11.4	70.0	80.0

IDC Invasive ductal carcinoma, ILC lobular ductal carcinoma, ER estrogen receptor, PR progesterone receptor, pPR pathological partial response, pNR pathological non-response, mM millimolar, SUV standard uptake value