Published in final edited form as:

Magn Reson Med. 2017 September ; 78(3): 1147–1156. doi:10.1002/mrm.26505.

Voxelwise Analysis of Simultaneously Acquired and Spatially Correlated ^{18}F -Fluorodeoxyglucose (FDG)-PET and Intravoxel Incoherent Motion Metrics in Breast Cancer

Jason Ostenson, MS^{1,2,7}, Akshat C. Pujara, MD^{1,2}, Artem Mikheev, PhD^{1,2}, Linda Moy, MD^{1,2}, Sungheon G. Kim, PhD^{1,2}, Amy Melsaether, MD^{1,2}, Komal Jhaveri, MD^{3,6}, Sylvia Adams, MD³, David Faul, PhD⁴, Christopher Glielmi, PhD⁴, Christian Geppert, PhD^{4,5}, Thorsten Feiweier, PhD⁵, Kimberly Jackson, BS^{1,2}, Gene Y. Cho, MS^{1,2}, Fernando E. Boada, PhD^{1,2}, and Eric E. Sigmund, PhD^{1,2}

¹Department of Radiology, New York University School of Medicine

²Center for Advanced Imaging Innovation and Research (CAI²R), NYU Langone Medical Center, New York, NY USA

³Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY USA

⁴Siemens Healthcare, New York, NY USA

⁵Siemens Healthcare, Erlangen, Germany

⁶Memorial Sloan-Kettering Cancer Center, New York, NY USA

⁷Vanderbilt University Institute of Imaging Science, Nashville, TN USA

Abstract

Purpose—Diffusion weighted imaging (DWI) and ^{18}F -FDG-PET independently correlate with malignancy in breast cancer, but the relationship between their structural and metabolic metrics are not completely understood. This study spatially correlates diffusion, perfusion, and glucose avidity in breast cancer with simultaneous positron emission tomography/magnetic resonance (PET/MR) imaging and compares correlations with clinical prognostics.

Methods—In this HIPAA-compliant prospective study with written informed consent and approval of the institutional review board, using simultaneously acquired FDG-PET and DWI, tissue diffusion (D_t) and perfusion fraction (f_p) from intravoxel incoherent motion (IVIM) analysis were registered to FDG-PET within 14 locally advanced breast cancers. Lesions were analyzed using two-dimensional histograms and correlation coefficients between D_t , f_p , and standardized uptake value (SUV). Correlations were compared with prognostics from biopsy, metastatic burden from whole-body PET, and treatment history.

Results—SUV|| D_t correlation coefficient significantly distinguished treated (0.11 ± 0.24) from non-treated (-0.33 ± 0.26) patients ($p = 0.005$). SUV|| f_p correlations were on average negative for the whole cohort (-0.17 ± 0.13).

Conclusions—Simultaneously acquired and registered FDG-PET/DWI allowed quantifiable descriptions of breast cancer microenvironments that may provide a framework for monitoring and predicting response to treatment.

Keywords

intravoxel incoherent motion; ^{18}F -fluorodeoxyglucose; positron emission tomography; breast cancer; diffusion; perfusion

Introduction

Breast cancer is often radiologically apparent by a decrease in apparent diffusion coefficient (ADC) compared to surrounding fibroglandular tissue (FGT) on diffusion-weighted MRI (1–4). The addition of intravoxel incoherent motion (IVIM) analysis elaborates on the single component ADC model by adding another term to account for signal loss in a diffusion-weighted sequence due to micro-vascular incoherent blood flow from tumor micro-vessels (5,6). The resulting IVIM bi-exponential model is expressed in three parameters: tissue diffusion (D_t), perfusion fraction (f_p), and pseudo-diffusion (D_p). It has been shown that breast cancer is associated with reduced D_t and higher f_p compared with benign lesions (7–13), as this indicates increased cellularity and vascularity, respectively.

Positron emission tomography (PET) using the tracer ^{18}F -fluorodeoxyglucose (FDG) demarcates enhanced glucose uptake and subsequent phosphorylation, and is widely used clinically for the detection of nodal or distant metastases in breast cancer (14). However, the sensitivity of FDG-PET to the physical tumor microenvironment and its relation to molecular prognostic factors (15,16) is not completely understood. Correlative multi-contrast studies are one route to shedding light on this issue.

T1-weighted MRI of the breast with a gadolinium-based contrast agent offers volumetric millimeter-scale resolution and high signal-to-noise ratio, and is commonly used for breast cancer screening, staging, and assessment of the size of breast cancers (17,18). Moreover, its high resolution and contrast properties make this modality a clear choice for the delineation of lesion boundaries.

The structural and physiological environment of tumors is heterogeneous and different from the surrounding healthy tissue. These differences are a result of irregular angiogenic patterns, cellularity, enhanced metabolism and proliferation of cancer. These heterogeneities in breast and other cancerous lesions can be quantified using FDG-PET (19) and MRI (20–25) by texture analysis, segmentation, and one-dimensional histogram analysis, from which metrics can be derived to serve as biomarkers for tumor type or efficacy of drug delivery and response to chemotherapy.

The respective microstructural and physiologic parameterization available from DWI and FDG-PET can be facilitated by co-registering the image volumes from these modalities. While these modalities can be independently applied and then registered, there is greater uncertainty that local blood flow and metabolism would be unaltered between scans. For instance local hypoxia has been shown to change in a matter of minutes in preclinical

imaging of a glioma line (26). One may expect that flow and nutrient delivery may also see such dynamics. The recent clinical introduction of integrated PET/MR systems (27) enables acquisition of both modalities simultaneously in human subjects and generation of correlated description of a lesion on a voxelwise basis (28).

Taken together the aforementioned imaging modalities offer means to delineate and describe metabolic and structural characteristics of breast cancer. Studies in breast and other cancers have suggested there may be inter-relationships at the group level between measures of diffusion and SUV (29–32), but they are moderate and variable, implying relationships beyond the canonical inverse correlation of ADC and SUV. By studying the complementary information offered by FDG-PET and DWI, there may prove to be analyses that differentiate lesions' diagnoses, prognoses or responsiveness to treatment.

In this study, an integrated PET/MR system was used to assess the inter-metric relationships and intralesional heterogeneity of co-registered IVIM and FDG metrics in breast cancer with the goals of (1) categorizing the observed heterogeneity and (2) comparing IVIM and SUV parametric information with established clinical prognostic factors, presence of metastases, and treatment history.

Methods

Patient Population

In this IRB-approved and HIPAA-compliant study with written informed consent, 21 women (age 25 to 79, average 49 ± 14 years) with histopathologically confirmed breast cancer were imaged over a 1.5 year period (9/18/12–2/21/14) in a simultaneous PET/MR system (details below) with residual FDG from immediately preceding clinical FDG PET/CT. The recruitment criteria for these patients included (a) whole-body PET/MR staging to explore an alternative to PET/CT, (b) clinical MRI of the local breast lesion either for pre-surgical or treatment planning or mid-treatment follow-up, and/or (c) research and development of new diagnostic/prognostic tools from simultaneous PET/MR in the breast cancer population. Five scans showed insufficient fat suppression or other artifact on diffusion-weighted imaging, 1 scan did not include axial post-contrast imaging, and 1 scan featured a lesion with insufficient PET activity for registration. Eleven patients underwent a PET/MR for staging of disease. One patient underwent neoadjuvant chemotherapy. The PET/MR was performed to assess for response to treatment. This patient was scanned twice before and after chemotherapy (6 month interval between scans). In the included cohort (14 patients, 1 imaged twice, aged 25 to 66, average 46 ± 12 years), one index lesion per patient was analyzed exclusively and consisted of 10 invasive ductal carcinoma (IDC) (one scanned twice), 1 IDC/ductal carcinoma in situ (DCIS), and 3 invasive lobular carcinoma (ILC) (one pleomorphic). The patients had a mixture of disease progression with 3 having no progression beyond the index lesion and 11 having nodal involvement or distant metastases at the time of exam. The following prognostic factors were available from standard work-up of surgical or biopsy specimens: Her2/neu, estrogen receptor (ER) and progesterone receptor (PR) level, and proliferation factor (Ki-67) expression. Seven patients received no chemotherapy and eight received chemotherapy prior to imaging. Seven of the 8 treated patients and 5 of the 7 untreated patients were metastatic. Chemotherapy regimens varied

accordingly with the heterogeneity in histology and prognostic factors of the tumor and included hormone therapy and cytotoxic treatment. Results from the whole body PET/MR evaluation (33) or local DCE-MRI (34) of these patients have been recently reported and in some cases provided the metastatic burden assessment considered in the present study.

Image Acquisition

The subjects were imaged using an integrated 3T PET/MR Biograph mMR (Siemens Healthcare, Erlangen, Germany) using a four channel breast coil (35) (Noras, Würzburg, Germany), and residual FDG from immediately preceding clinical FDG PET/CT. The patients were in the prone position and each patient was bilaterally imaged with a prototype twice-refocused spin echo echo-planar imaging (EPI) axial diffusion weighted imaging (DWI) sequence (TR/TE = 5400/85 ms, matrix 192, 10 slices, bandwidth 1736 Hz/px, 3 averages) with with online eddy-current distortion correction provided by vendor software (36) and spectral attenuated inversion recovery in combination with a slice gradient reversal fat suppression technique at 10 b-values (0, 30, 70, 100, 150, 200, 300, 400, 500, 800 s/mm²) over the entire volume of the lesion. This was followed by injection of gadolinium contrast (Magnevist, Bayer) and a subsequent axial T1-weighted volume interpolated breath-hold examination (VIBE) sequence (T1C+). The T1C+ sequence (TR/TE = 4.7/1.6 ms, matrix 320, 95 slices) used either a standard Cartesian k-space sampling, or a golden-angle radial sparse parallel (GRASP) MRI sequence in either prototype or standardized form, with custom inhouse reconstruction (37). The DWI and T1C+ images were initially reconstructed with voxel sizes of $1.8 \times 1.8 \times 4$ mm and $1 \times 1 \times 1$ mm to 2 mm, respectively.

The FDG-PET acquisition consisted of a single 15 min thorax position starting at the commencement of the local exam and overlapped with the DWI acquisition. The injected activities ranged from 478 to 561 MBq (average 533 MBq) and the start time of PET/MR imaging following injection ranged from approximately 2 to 4 hours (average 2 hours 55 min). Each image was corrected for attenuation using patient specific and breast coil μ -maps (35). The PET images were reconstructed using three-dimensional ordinary Poisson ordered subsets estimation maximization (3D OP-OSEM) (38) with a voxel size of $4.2 \times 4.2 \times 2$ mm.

Image Analysis

Figure 1 illustrates the processing pipeline of this study following acquisition. The T1C+, DWI, and PET volumetric images were imported into FireVoxel (New York University, New York, NY). The entire lesion was segmented in FireVoxel on the T1C+ volume using the contrast enhancement to define the lesion boundaries by a single radiologist blinded to pathology (A.P.) for all lesions. A pixel mask was then generated in the same coordinate frame for later processing. Using FireVoxel, the PET and DWI were independently registered to the T1C+ volume as follows. In both cases, the registration process used a mutual information criterion restricted to a 3D dilated (radius 5 mm) lesion mask segmented on the T1C+. In some cases (1 for DWI, 2 for PET) the segmentation volume itself was used as registration target due to weak contrast in the DWI or PET images. For DWI, a 3D affine transformation with rigid body translation along 3 dimensions and, in order to mitigate image distortion, stretching along the anterior-posterior phase encoding direction, was

performed to align the lesion volume to T1C+. The highest b-value image was used as the target volume and all b-value volumes used the same registration parameters. For PET, a rigid body 3D registration was performed to align the lesion to the T1C+ volume. Since the near-simultaneous acquisition should provide an inherent first-order alignment between the T1C+ and PET/DWI, these registrations served to compensate for uncorrected DWI spatial distortion and any patient movement between the acquisitions of the T1C+ and the other two modalities. The registered images were resampled and interpolated by FireVoxel to match the coordinate frame and matrix dimensions of the T1C+ so that the DWI and PET images were then co-registered with each other via the higher resolution T1-weighted post-contrast image. Finally, the segmented lesion volumes on DWI and PET were cropped and saved for further processing to conserve memory.

The co-registered DWI, PET, and pixel mask volumes were imported into IGOR Pro (version 6.34; WaveMetrics, Lake Oswego, Oregon) and analyzed using in-house custom software. From the DWI, ADC maps were derived for each voxel with monoexponential analysis. Using a bi-exponential model and technique previously described (13), each DWI voxel was fit across all b-values to determine tissue diffusion (D_t), perfusion fraction (f_p), and pseudo-diffusion (D_p) over the contoured lesion as defined by the pixel mask:

$$\frac{S}{S_0} = f_p \exp(-b \cdot D_p) + (1 - f_p) \exp(-b \cdot D_t) \quad (1.1)$$

The raw PET image values were converted to standardized uptake value (SUV) using total body mass, time from injection, and instrumental calibration factors. The correlating voxel SUVs were recorded from the PET data. All regions of the contoured lesion were included in the analysis unless they could not be fit in one of the IVIM parameters. The total number of voxels in the segmented lesion was quantified as a measure of lesion size and computed using the T1C+ voxel volume in cubic centimeters (cc).

For the registered data, two-dimensional (2D) histograms were generated in IGOR Pro for all lesion voxels with $0.01 < \text{ADC}$, $D_t < 3 \mu\text{m}^2/\text{ms}$, $0 < f_p < 0.75$, and $0.01 < D_p < 100 \mu\text{m}^2/\text{ms}$, in each lesion by using 100 bins over a range of SUVs from zero to 10% larger than the SUV maximum and 100 bins over the aforementioned ranges of ADC and IVIM parameters. One-dimensional histogram mean, maximum, minimum, standard deviation, skewness, and kurtosis values were also determined for each metric as previously described (13).

The qualitative behavior of the 2D histograms of SUV vs. D_t and SUV vs. f_p were inspected. Secondly, the Pearson correlation coefficients (R) of cross-plots of the two metric pairs with each lesion voxel contributing one point were calculated. Lesions were plotted based on their R between SUV || D_t and between SUV || f_p .

Statistics

Pearson correlation coefficients (R) were calculated between SUV and the diffusion metrics using IGOR Pro for each lesion. For comparison of imaging metrics and prognostic factors

(ER, PR, Her2/neu, and Ki-67), both group comparisons and correlations were performed. Pearson correlation coefficients between 1D histogram metrics or cross-correlation coefficients and prognostic factor values were determined. Student's t-tests were performed for each imaging metric between groups defined by binary classifications of each prognostic factor, metastatic status, and treatment status. For prognostic factors, positivity was defined as >10% ER, PR, or Ki-67 expression, and Her2/neu > +1. Significance was considered $p < 0.05$ for this study. Statistical Package for the Social Sciences (SPSS) (version 20; SPSS, Chicago, IL) was used for statistical calculations unless otherwise noted.

Results

The image registration pipeline illustrated in Figure 1 was successful for 15 malignant lesions evaluated in this study (94% of those with complete artifact-free datasets). The segmented lesion volumes ranged from 1.2 to 34.9 cc, with a mean volume of 9.9 ± 9.3 cc. Table 1 shows the 1D histogram metrics from ADC, IVIM, and SUV parameters across the whole lesion group. The prognostic factor groupings in this cohort, defined as in Statistics section, were: ER (12/15 positive), PR (7/15 positive), Her2/neu (6/15 positive), and Ki-67 (8/12 positive of patients with available data). Multiple feature prognostic distribution was as follows. ER+/PR+/Her2+: 1 treated/1 untreated; ER+/PR+/Her2-: 3 treated/2 untreated; ER-/PR-/Her2-: 0 treated, 3 untreated; ER+/PR-/Her2+: 4 treated/0 untreated; ER+/PR-/Her2-: 1 untreated.

The 2D histograms showed varying relationships with SUV against the IVIM parameters across the different lesions, 6 of which can be seen in Figures 1 and 2, with correlation coefficients for all lesions summarized in Table 2 and illustrated in Figure 3. The appearance of SUV against ADC and D_t was in many cases a negative trend of varying strength and the Pearson R values reflect this with a mean value for all imaged lesions of -0.16 for $SUV \parallel ADC$ and -0.10 for $SUV \parallel D_t$. $SUV \parallel f_p$ correlations showed a negative trend with a mean R of -0.17 for all lesions. $SUV \parallel D_p$ exhibited heterogeneous trends with lesions showing positive, negative, or no correlation with an overall correlation of -0.02 . When stratified by treatment status, significant differences in $SUV \parallel D_t$ and $SUV \parallel ADC$ correlations were observed between treated and untreated lesions (Table 2 and Figure 3), with untreated lesions displaying a more negative correlation. The patient scanned both before and after treatment is also indicated in Figure 2, showing a clear change in $SUV \parallel D_t$ correlation. Larger lesions tended to show $SUV \parallel f_p$ correlations closer to 0 than smaller masses, which displayed negative correlation coefficients.

Table 3 shows results of group comparison and correlation analysis between imaging metrics and prognostic factors/clinical status. ADC metrics showed significant correlation with Ki-67 expression, with average ADC negatively correlating and skewness/kurtosis positively correlating. Pseudodiffusion D_p metrics showed opposite correlation trends with Ki-67 compared to ADC. Average, maximum, and standard deviation of SUV correlated negatively with hormone (ER/PR) expression. Maximum f_p , and SUV kurtosis correlated positively with lesion size. D_p skewness and standard deviation showed significant differences between patients with and without metastases. For 2D correlation metrics, $SUV \parallel ADC$ and $SUV \parallel D_t$ R values correlated positively with ER and Her2/neu expression levels. $SUV \parallel f_p$ R values

correlated positively with lesion size. Finally, $SUV||ADC$ and $SUV||D_t$ R-values showed significant differentiation of treated and non-treated patients.

Discussion

The one-dimensional histogram parameters showed the expected reduction of tissue diffusion compared with ADC when the two-compartment model is incorporated. The relative standard deviations of D_p (22%) and f_p (30%) compared with D_t (22%) for the malignant lesions are comparable or smaller than literature reports in larger cohorts (8,10,11,13). The correlations observed between prognostic factors and 1D IVIM or SUV histogram metrics aligned with findings in breast cancer patient groups (13,39–41). The negative correlation between ADC and proliferation index Ki-67 is consistent with the inverse relation of cell density and ADC. The negative correlation of SUV with hormonal receptor (ER/PR) expression has also been previously described (42). Generally, by individual IVIM or SUV metrics, this group represents lesions of similar malignancy that are not significantly different from each other. As indicated in Table 3, no single parameter from IVIM or PET significantly distinguished treated from nontreated lesions. The next level analysis (2D correlations of IVIM and SUV) was performed to further characterize their individuality.

The 2D histogram analysis reveals relationships between SUV, diffusion, and perfusion fraction that are not revealed in analysis of means or other 1D histogram metrics. Regarding the $SUV||D_t$ correlation, we observe that slightly over half of the lesions display the ‘canonical’ negative intralesion correlation between SUV and D_t that is often observed at the group level (29–32). These lesions tended to be treatment-naïve, and so displayed timepoints of an uninterrupted growth process in its early stages, retaining a strong link between cell density and glucose metabolism. The limiting asymptotic appearance of SUV against diffusion in many lesions suggests some areas have reached a maximal cellular packing as predicted in integrated logistic growth and diffusion models (43). This also compares favorably with Byun *et al.* (30) who demonstrated only a weak negative correlation ($r > -0.3$) between maximum SUV and mean or minimum ADC using sequential FDG-PET and DWI in women with IDC, though that study used a whole lesion analysis for maximum SUV and a single representative slice for ADC. In the treated lesions, all of which received some form of cytotoxic chemotherapy, the $SUV||D_t$ correlations were near 0 or positive, arising either from a maximally packed cell density for all SUVs or a heterogeneous mixture of necrosis, apoptosis, or fibroglandular or adipose tissue. All of these scenarios reflect a departure from the early growth model in which cell density is proportional to glucose metabolism.

Regarding the $SUV||f_p$ intralesional correlations, there are again some universalities and some group variabilities. Figure 3 illustrates that most lesions display a negative correlation; examples in Figure 2 reveal different histogram patterns surrounding this negative trend but most show higher SUVs occurring at smaller perfusion fraction (f_p) levels. Avril *et al.* (15) posited that beyond a certain cellularity, uptake of glucose in breast cancer no longer correlates with the numerical density of tumor cells but inversely correlates with microvascular density. Using this combined with saturated cellularity as an endpoint for terminal lesion growth, the diffusion-perfusion-metabolic correlations show that lesions

having stronger limiting diffusion value and greater negative correlation of SUV with f_p are more advanced in their development. Conversely, another trend that is illustrated in Figure 3 and reflected in the significant correlations shown in Table 3 is that larger lesions tend to have weaker negative or positive $SUV||f_p$ correlations compared with smaller lesions. As shown in the example in Figure 2b, this may reflect the likelihood that a larger heterogeneous lesion, from either prolonged growth or treatment effect, is more likely to include both vascular/FDG avid areas and normal/necrotic/avascular areas, weakening the negative correlation between vascularity and glucose metabolism. Finally, regardless of whether $SUV||f_p$ is a more variable signature than $SUV||D_t$ in breast cancer cohorts, the IVIM separation of microvascular (f_p , D_p) from microstructural (D_t) metrics provides a more accurate view of their relationships with glucose consumption.

The differences between the lesion correlation signatures may have therapeutic implications. The high rate of glycolysis in cancer is thought to confer a robustness to harsh environments and resistance to therapy via hypoxia and acidosis (44). The highest SUVs of many lesions in this study show the lowest perfusions in the lesion, suggesting that the regions with less vascular supply are those that are metabolically most active and most robust. In contrast, a few lesions show approximately equal or greater perfusion at their highest SUVs compared with their lowest, and so may be less conditioned to hypoxic/acidic environments in their most glucose avid regions. The simultaneous PET/MR platform and analysis of intratumoral correlations may reveal signatures of tumor growth and viability patterns related to treatment efficacy that would escape a routine average metric quantification. The 2D space shown in Figure 3 defines a framework by which early and subtle effects of treatment can be monitored and perhaps inform management strategies. This approach may have further applications with other PET tracers such as ^{18}F -fluorothymidine (FLT), which probes cellular proliferation.

Several limitations exist in this pilot study, including possible error in co-registration, differences in point-spread function between imaging modalities, and the heterogeneity and limited size of the population. No multiple comparisons corrections were performed in the statistical analysis of this pilot cohort, and not all findings here would be robust to such a correction. The results herein are therefore best seen as uncovering new metrics of cancer characterization and motivating future studies to more deeply investigate their diagnostic performance in comparison with known biomarkers (e.g. ADC, SUV). In the treated patients, we did not separately consider particular chemotherapy regimens or timing between treatment and scan time in this study. The timing of the study was not controlled to monitor early response to therapy, which may have impacted the lack of treatment differentiation by conventional DWI and PET metrics. The evaluation of patients following their clinical PET/CT led to longer than standard uptake times, which may have influenced SUVs. The simultaneously acquired T1C+, DWI and PET data should not require additional registration but for the uncorrected spatial distortions caused by the inhomogeneity in the static magnetic field and patient movement over the course of the scan (due to the T1C+ being acquired after the DWI/PET). The reduced contrast and anatomical resolution of the PET and DWI combined with the spatial nonlinearities of the latter would preclude a high quality registration between the two modalities themselves without field-map or reversed phase encoding corrections not included in these acquisitions (45). By introducing T1C+ imaging,

improved lesion visualization and PET/DWI registration was achieved at the expense of requiring a third contrast (enhancement).

The difference in point-spread-functions and voxel sizes between the PET, DWI, and T1C+ introduces uncertainty into the parametric maps and subsequent analyses. The partial volume effect on the SUV in PET relative to higher resolution modalities is well known (46). This blurring will increase the uncertainty along the vertical axis of the 2D histograms, as well as reduce volume contributions of isolated groups that are comparable to or smaller than the size of the point-spread of the original PET. The matrix resampling of the DWI and PET to the finer dimensions of the T1C+ gives an artificial increase in resolution that is isotropic to all voxels within a given lesion, and also smooth the raw images as part of the matrix resampling. This may introduce error in parameter fitting if the diffusion weighted voxel intensities vary over short length scales. We have not investigated the effects of each of these registration/interpolation workflow steps on the output metrics in detail in the present work. Yet despite these uncertainties, the results indicate coherent regions of heterogeneous metrics within the lesions that would be otherwise unobservable using whole lesion averages.

Conclusions

This proof-of-concept study has yielded descriptions of correlations between SUV, D_t , and f_p in breast cancer using a straightforward method. Through co-registration of FDG-PET and DWI of images and resulting histogram/correlation analysis new insights into the metabolically and structurally heterogeneous tumor environment were achieved. This simultaneously acquired parametric approach supports future studies with more controlled recruitment criteria and timing to assess lesion behavior between diffusion and PET metrics, and their relationship to established clinical biomarkers and treatment response.

Acknowledgments

We would like to acknowledge Dr. James Babb for statistical guidance and Ms. Joon Lee for support in clinical coordination. This work was supported under the rubric of the Center for Advanced Imaging Innovation and Research (CAI2R, www.cai2r.net), a NIBIB Biomedical Technology Resource Center (NIH P41 EB017183).

References

1. Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, Mahankali S, Gao JH. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. *Journal of magnetic resonance imaging*. 2002; 16(2):172–178. [PubMed: 12203765]
2. Inoue K, Kozawa E, Mizukoshi W, Tanaka J, Saeki T, Sakurai T, Kimura F. Usefulness of diffusion-weighted imaging of breast tumors: quantitative and visual assessment. *Japanese journal of radiology*. 2011; 29(6):429–436. [PubMed: 21786099]
3. Partridge SC, Mullins CD, Kurland BF, Allain MD, DeMartini WB, Eby PR, Lehman CD. Apparent diffusion coefficient values for discriminating benign and malignant breast MRI lesions: effects of lesion type and size. *AJR American journal of roentgenology*. 2010; 194(6):1664–1673. [PubMed: 20489111]
4. Rubesova E, Grell AS, De Maertelaer V, Metens T, Chao SL, Lemort M. Quantitative diffusion imaging in breast cancer: a clinical prospective study. *Journal of magnetic resonance imaging : JMIR*. 2006; 24(2):319–324. [PubMed: 16786565]

5. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology*. 1986; 161(2):401–407. [PubMed: 3763909]
6. Iima M, Le Bihan D. Clinical Intravoxel Incoherent Motion and Diffusion MR Imaging: Past, Present, and Future. *Radiology*. 2016; 278(1):13–32. [PubMed: 26690990]
7. Suo S, Lin N, Wang H, Zhang L, Wang R, Zhang S, Hua J, Xu J. Intravoxel incoherent motion diffusion-weighted MR imaging of breast cancer at 3.0 tesla: Comparison of different curve-fitting methods. *Journal of magnetic resonance imaging : JMRI*. 2015; 42(2):362–370. [PubMed: 25407944]
8. Iima M, Yano K, Kataoka M, Umehana M, Murata K, Kanao S, Togashi K, Le Bihan D. Quantitative non-Gaussian diffusion and intravoxel incoherent motion magnetic resonance imaging: differentiation of malignant and benign breast lesions. *Invest Radiol*. 2015; 50(4):205–211. [PubMed: 25260092]
9. Dijkstra H, Dorrius MD, Wielema M, Jaspers K, Pijnappel RM, Oudkerk M, Sijens PE. Semi-automated quantitative intravoxel incoherent motion analysis and its implementation in breast diffusion-weighted imaging. *Journal of magnetic resonance imaging : JMRI*. 2016; 43(5):1122–1131. [PubMed: 26558851]
10. Bokacheva L, Kaplan JB, Giri DD, Patil S, Gnanasigamani M, Nyman CG, Deasy JO, Morris EA, Thakur SB. Intravoxel incoherent motion diffusion-weighted MRI at 3.0 T differentiates malignant breast lesions from benign lesions and breast parenchyma. *Journal of magnetic resonance imaging : JMRI*. 2014; 40(4):813–823. [PubMed: 24273096]
11. Liu C, Liang C, Liu Z, Zhang S, Huang B. Intravoxel incoherent motion (IVIM) in evaluation of breast lesions: comparison with conventional DWI. *Eur J Radiol*. 2013; 82(12):e782–789. [PubMed: 24034833]
12. Sigmund EE, Cho GY, Kim S, Finn M, Moccaldi M, Jensen JH, Sodickson DK, Goldberg JD, Formenti S, Moy L. Intravoxel incoherent motion imaging of tumor microenvironment in locally advanced breast cancer. *Magn Reson Med*. 2011; 65(5):1437–1447. [PubMed: 21287591]
13. Cho GY, Moy L, Kim SG, Baete SH, Moccaldi M, Babb JS, Sodickson DK, Sigmund EE. Evaluation of breast cancer using intravoxel incoherent motion (IVIM) histogram analysis: comparison with malignant status, histological subtype, and molecular prognostic factors. *Eur Radiol*. 2016; 26(8):2547–2558. [PubMed: 26615557]
14. Crippa F, Agresti R, Seregni E, Greco M, Pascali C, Boggi A, Chiesa C, Sanctis VD, Delledonne V, Salvadori B. Prospective evaluation of fluorine-18-FDG PET in presurgical staging of the axilla in breast cancer. *Journal of Nuclear Medicine*. 1998; 39(1):4–8. [PubMed: 9443729]
15. Avril N, Menzel M, Dose J, Schelling M, Weber W, Jänicke F, Nathrath W, Schwaiger M. Glucose metabolism of breast cancer assessed by 18F-FDG PET: histologic and immunohistochemical tissue analysis. *Journal of Nuclear Medicine*. 2001; 42(1):9–16. [PubMed: 11197987]
16. Groheux D, Giachetti S, Moretti J-L, Porcher R, Espié M, Lehmann-Che J, de Roquancourt A, Hamy A-S, Cuvier C, Vercellino L. Correlation of high 18F-FDG uptake to clinical, pathological and biological prognostic factors in breast cancer. *European journal of nuclear medicine and molecular imaging*. 2011; 38(3):426–435. [PubMed: 21057787]
17. Partridge SC, Gibbs JE, Lu Y, Esserman LJ, Tripathy D, Wolverton DS, Rugo HS, Hwang ES, Ewing CA, Hylton NM. MRI measurements of breast tumor volume predict response to neoadjuvant chemotherapy and recurrence-free survival. *AJR American journal of roentgenology*. 2005; 184(6):1774–1781. [PubMed: 15908529]
18. Dietzel M, Baltzer PA, Vag T, Groschel T, Gajda M, Camara O, Kaiser WA. Magnetic resonance mammography of invasive lobular versus ductal carcinoma: systematic comparison of 811 patients reveals high diagnostic accuracy irrespective of typing. *Journal of computer assisted tomography*. 2010; 34(4):587–595. [PubMed: 20657229]
19. Soussan M, Orlhac F, Boubaya M, Zelek L, Ziou M, Eder V, Buvat I. Relationship between Tumor Heterogeneity Measured on FDG-PET/CT and Pathological Prognostic Factors in Invasive Breast Cancer. *Plos One*. 2014; 9(4)
20. Holli K, Laaperi AL, Harrison L, Luukkaala T, Toivonen T, Ryymin P, Dastidar P, Soimakallio S, Eskola H. Characterization of breast cancer types by texture analysis of magnetic resonance images. *Academic radiology*. 2010; 17(2):135–141. [PubMed: 19945302]

21. Teruel JR, Heldahl MG, Goa PE, Pickles M, Lundgren S, Bathen TF, Gibbs P. Dynamic contrast-enhanced MRI texture analysis for pretreatment prediction of clinical and pathological response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. *NMR in biomedicine*. 2014; 27(8):887–896. [PubMed: 24840393]
22. Ahmed A, Gibbs P, Pickles M, Turnbull L. Texture analysis in assessment and prediction of chemotherapy response in breast cancer. *Journal of magnetic resonance imaging : JMRI*. 2013; 38(1):89–101. [PubMed: 23238914]
23. Yankeelov TE, Lepage M, Chakravarthy A, Broome EE, Niermann KJ, Kelley MC, Meszoely I, Mayer IA, Herman CR, McManus K, Price RR, Gore JC. Integration of quantitative DCE-MRI and ADC mapping to monitor treatment response in human breast cancer: initial results. *Magnetic resonance imaging*. 2007; 25(1):1–13. [PubMed: 17222711]
24. Hirano M, Satake H, Ishigaki S, Ikeda M, Kawai H, Naganawa S. Diffusion-Weighted Imaging of Breast Masses: Comparison of Diagnostic Performance Using Various Apparent Diffusion Coefficient Parameters. *Am J Roentgenol*. 2012; 198(3):717–722. [PubMed: 22358015]
25. Ungersma SE, Pacheco G, Ho C, Yee SF, Ross J, van Bruggen N, Peale FV Jr, Ross S, Carano RA. Vessel imaging with viable tumor analysis for quantification of tumor angiogenesis. *Magn Reson Med*. 2010; 63(6):1637–1647. [PubMed: 20512867]
26. Cardenas-Navia LI, Mace D, Richardson RA, Wilson DF, Shan S, Dewhirst MW. The pervasive presence of fluctuating oxygenation in tumors. *Cancer Res*. 2008; 68(14):5812–5819. [PubMed: 18632635]
27. Drzezga A, Souvatzoglou M, Eiber M, Beer AJ, Fürst S, Martinez-Möller A, Nekolla SG, Ziegler S, Ganter C, Rummeny EJ. First clinical experience with integrated whole-body PET/MR: comparison to PET/CT in patients with oncologic diagnoses. *Journal of Nuclear Medicine*. 2012; 53(6):845–855. [PubMed: 22534830]
28. Schmidt H, Brendle C, Schraml C, Martirosian P, Bezrukov I, Hetzel J, Muller M, Sauter A, Claussen CD, Pfannenbergl C, Schwenzer NF. Correlation of simultaneously acquired diffusion-weighted imaging and 2-deoxy-[18F] fluoro-2-D-glucose positron emission tomography of pulmonary lesions in a dedicated whole-body magnetic resonance/positron emission tomography system. *Invest Radiol*. 2013; 48(5):247–255. [PubMed: 23519008]
29. Ho K-C, Lin G, Wang J-J, Lai C-H, Chang C-J, Yen T-C. Correlation of apparent diffusion coefficients measured by 3T diffusion-weighted MRI and SUV from FDG PET/CT in primary cervical cancer. *European journal of nuclear medicine and molecular imaging*. 2009; 36(2):200–208. [PubMed: 18779960]
30. Byun BH, Noh WC, Lim I, Lee SS, Cho AR, Park JA, Kim KM, Kim HA, Kim EK, Kim BI, Choi CW, Lim SM. A new method for apparent diffusion coefficient measurement using sequential (18)F-FDG PET and MRI: correlation with histological grade of invasive ductal carcinoma of the breast. *Annals of nuclear medicine*. 2013; 27(8):720–728. [PubMed: 23700260]
31. Schwenzer NF, Schmidt H, Gatidis S, Brendle C, Muller M, Konigsrainer I, Claussen CD, Pfannenbergl AC, Schraml C. Measurement of apparent diffusion coefficient with simultaneous MR/positron emission tomography in patients with peritoneal carcinomatosis: comparison with 18F-FDG-PET. *Journal of magnetic resonance imaging : JMRI*. 2014; 40(5):1121–1128. [PubMed: 24923481]
32. Baba S, Isoda T, Maruoka Y, Kitamura Y, Sasaki M, Yoshida T, Honda H. Diagnostic and prognostic value of pretreatment SUV in 18F-FDG/PET in breast cancer: comparison with apparent diffusion coefficient from diffusion-weighted MR imaging. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2014; 55(5):736–742.
33. Melsaether AN, Raad RA, Pujara AC, Ponzo FD, Pysarenko KM, Jhaveri K, Babb JS, Sigmund EE, Kim SG, Moy LA. Comparison of Whole-Body F FDG PET/MR Imaging and Whole-Body F FDG PET/CT in Terms of Lesion Detection and Radiation Dose in Patients with Breast Cancer. *Radiology*. 2016:151155.
34. Margolis NE, Moy L, Sigmund EE, Freed M, McKellop J, Melsaether AN, Kim SG. Assessment of Aggressiveness of Breast Cancer Using Simultaneous 18F-FDG-PET and DCE-MRI: Preliminary Observation. *Clin Nucl Med*. 2016; 41(8):e355–361. [PubMed: 27187730]
35. Aklan B, Paulus DH, Wenkel E, Braun H, Navalpakkam BK, Ziegler S, Geppert C, Sigmund EE, Melsaether A, Quick HH. Toward simultaneous PET/MR breast imaging: systematic evaluation

- and integration of a radiofrequency breast coil. *Med Phys*. 2013; 40(2):024301. [PubMed: 23387782]
36. Feiweier, T., Huwer, S., Kim, TH., Porter, DA., Speckner, T. Siemens Aktiengesellschaft, assignee. Method and magnetic resonance system to reduce distortions in diffusion imaging patent US 8508226 B2. Sep 13. 2013
37. Feng L, Grimm R, Block KT, Chandarana H, Kim S, Xu J, Axel L, Sodickson DK, Otazo R. Golden-angle radial sparse parallel MRI: Combination of compressed sensing, parallel imaging, and golden-angle radial sampling for fast and flexible dynamic volumetric MRI. *Magn Reson Med*. 2014; 72(3):707–717. [PubMed: 24142845]
38. Comtat C, Bataille F, Michel C, Jones JP, Sibomana M, Janeiro L, Trebossen R. OSEM-3D reconstruction strategies for the ECAT HRRT. *Ieee Nucl Sci Conf R*. 2004:3492–3496.
39. Choi SY, Chang YW, Park HJ, Kim HJ, Hong SS, Seo DY. Correlation of the apparent diffusion coefficient values on diffusion-weighted imaging with prognostic factors for breast cancer. *Br J Radiol*. 2012; 85(1016):e474–479. [PubMed: 22128125]
40. Jeh SK, Kim SH, Kim HS, Kang BJ, Jeong SH, Yim HW, Song BJ. Correlation of the Apparent Diffusion Coefficient Value and Dynamic Magnetic Resonance Imaging Findings With Prognostic Factors in Invasive Ductal Carcinoma. *Journal of Magnetic Resonance Imaging*. 2011; 33(1):102–109. [PubMed: 21182127]
41. Kamitani T, Matsuo Y, Yabuuchi H, Fujita N, Nagao M, Jinnouchi M, Yonezawa M, Yamasaki Y, Tokunaga E, Kubo M, Yamamoto H, Yoshiura T, Honda H. Correlations between apparent diffusion coefficient values and prognostic factors of breast cancer. *Magn Reson Med Sci*. 2013; 12(3):193–199. [PubMed: 23857151]
42. Nakajo M, Kajiya Y, Kaneko T, Kaneko Y, Takasaki T, Tani A, Ueno M, Koriyama C. FDG PET/CT and diffusion-weighted imaging for breast cancer: prognostic value of maximum standardized uptake values and apparent diffusion coefficient values of the primary lesion. *Eur J Nucl Med Mol Imaging*. 2010; 37(11):2011–2020. [PubMed: 20607535]
43. Atuegwu NC, Arlinghaus LR, Li X, Welch EB, Chakravarthy BA, Gore JC, Yankeelov TE. Integration of diffusion-weighted MRI data and a simple mathematical model to predict breast tumor cellularity during neoadjuvant chemotherapy. *Magn Reson Med*. 2011; 66(6):1689–1696. [PubMed: 21956404]
44. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? *Nature reviews Cancer*. 2004; 4(11):891–899. [PubMed: 15516961]
45. Teruel JR, Fjosne HE, Ostlie A, Holland D, Dale AM, Bathen TF, Goa PE. Inhomogeneous static magnetic field-induced distortion correction applied to diffusion weighted MRI of the breast at 3T. *Magn Reson Med*. 2015; 74(4):1138–1144. [PubMed: 25323982]
46. Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor imaging. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2007; 48(6):932–945.

Figure 1.

Image processing workflow for the present study. Diffusion-weighted images (DWI), T1-weighted post contrast images (T1C+), and FDG-PET images are acquired in the MR/PET protocol. Lesions are segmented on T1C+ volumes, which guides separate registration/resampling processes aligning DWI and PET volumes to T1C+ space. Lesion voxels are extracted, and IVIM fitting on DWI and SUV calibration on PET images are performed. Finally, voxelwise 2D histograms are constructed for each diffusion parameter's correlation with SUV.

Figure 2.

Example 2D IVIM/PET histograms for several breast lesions included in this study. (a) (invasive ductal carcinoma), (b) (invasive ductal/ductal carcinoma in situ hybrid) and (c) (invasive ductal carcinoma) are untreated lesions, while (d) (invasive lobular carcinoma) and (e) (invasive ductal carcinoma) are treated lesions. Co-registered T1C+/DWI and T1C+/PET fusions are shown with highlighted segmented lesion areas, along with 2D histograms for SUV vs. ADC, D_t , f_p , and D_p . The SUV||ADC and SUV|| D_t histograms display a range of correlations from negative (untreated) to positive (treated); SUV|| f_p histograms are more varied but negative correlations predominate.

Figure 3.

Pearson correlations between f_p and D_t against SUV for all lesions. Symbols are color-coded for treatment status (Non-Tx or Tx) and symbol size is proportional to square root of lesion volume. Examples shown in Figure 1 (1) and Figure 2 (a-e) are labelled. Results from the patient scanned pre-treatment (*) and post-treatment (†) are indicated. Untreated and treated lesions show significantly different $SUV||D_t$ correlations, with untreated lesions displaying more significantly negative correlations relationships. Larger lesions have $SUV||f_p$ correlations closer to 0, while smaller lesions display negative $SUV||f_p$ correlations.

Table 1

ADC, IVIM, and PET Metrics from 1D histogram analysis. ADC indicates apparent diffusion coefficient; D_t , tissue diffusion; f_p , perfusion fraction; D_p , pseudo-diffusion; SUV, standard uptake value; avg, average of sample; SD, standard deviation over group; St. Dev., standard deviation of histogram; Max, maximum; min, minimum.

	ADC ^a		D_t^a		f_p		D_p^a		SUV	
	Avg	SD	Avg	SD	Avg	SD	Avg	SD	Avg	SD
Avg ^b	1.41	0.29	1.25	0.27	0.10	0.03	20.6	4.6	3.88	4.46
Max	2.79	0.27	2.45	0.33	0.62	0.18	99.4	0.60	9.2	10.4
Min	0.21	0.27	0.11	0.16	0.00	0.00	0.07	0.10	0.41	0.47
St. dev.	0.42	0.09	0.39	0.09	0.09	0.04	16.3	3.7	1.94	2.31
Skewness	0.22	0.72	0.13	0.73	1.19	0.46	2.20	0.73	0.56	0.45
Kurtosis	0.68	1.70	0.59	1.66	2.20	2.42	6.41	5.06	-0.08	1.24

^a ADC, D_t and D_p values are in $\mu\text{m}^2/\text{ms}$

^b $N = 15$

Table 2

Pearson correlation coefficients between IVIM and SUV metrics. (*) indicates significant difference between treated and untreated subgroups (p-values given in right column for this group comparison).

Correlation	All lesions (N=15)	Untreated (N=7)	Treated (N=8)	p
SUV ADC	-0.16 ± 0.31	$-0.39 \pm 0.24^*$	$0.04 \pm 0.19^*$	0.003
SUV D_t	-0.10 ± 0.33	$-0.33 \pm 0.26^*$	$0.11 \pm 0.24^*$	0.005
SUV f_p	-0.17 ± 0.13	-0.18 ± 0.15	-0.16 ± 0.12	0.798
SUV D_p	-0.02 ± 0.12	0.03 ± 0.15	-0.06 ± 0.06	0.211

Table 3

Correlations between IVIM/PET metrics and clinical factors. Bold values indicate significant Pearson correlations between continuous metric values (p-value, plain text). Asterisks (*) indicate significant differences between (+/-) groups for each marker (p-value, *italics*).

	ER	PR	Her2	KI-67	Size	Mets	Chemo
ADC	Max		-0.611 0.016	-0.651 0.022 <i>0.045*</i>			
	Avg	<i>0.019*</i>		-0.618 0.032			
	skew	<i>0.048*</i>		0.621 0.031			
	kurt			0.615 0.033			
	St.dev.			-0.596 0.041			
D _t	Max		-0.751 0.001				
	Avg	<i>0.024*</i>		-0.590 0.043			
	skew	-0.517 0.049					
	stdev	<i>0.036*</i>					
f _p	Max				0.600 0.018		
	skew	0.665 0.007 <i>0.006*</i>					
	kurt	0.690 0.004 <i>0.031*</i>					
	Avg			0.652 0.022			
D _p	St. dev.			0.731 0.007 <i>0.000*</i>		<i>0.000*</i>	
	skew			-0.617 0.033			

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

		ER	PR	Her2	Ki-67	Size	Mets	Chemo
	kurt				-0.662 0.019 <i>0.027*</i>		<i>0.011*</i>	
SUV	Max	-0.536 0.039 <i>0.036*</i>	-0.538 0.039 <i>0.036*</i>					
	Avg	-0.529 0.042 <i>0.033*</i>	-0.534 0.040 <i>0.033*</i>					
	St. dev.	-0.582 0.023 <i>0.019*</i>	-0.558 0.031 <i>0.026*</i>					
	kurt	0.016*	0.585 0.022			0.541 0.037		
R(SUV ADC)		0.617 0.014 <i>0.033*</i>		0.605 0.017 <i>0.006*</i>				<i>0.003*</i>
R(SUV D ₁)		0.593 0.020		0.588 0.021 <i>0.009*</i>				<i>0.005*</i>
R(SUV f _p)						0.663 0.007		