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Assessment of aggressiveness of breast cancer using simultaneous 18F-FDG-PET and DCE-MRI: preliminary observation

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Abstract

Purpose—To investigate the feasibility of using simultaneous breast MRI and PET to assess the synergy of MR pharmacokinetic and fluorine-18 fluorodeoxyglucose (18F-FDG) uptake data to characterize tumor aggressiveness in terms of metastatic burden and Ki67 status.

Methods—Twelve consecutive patients underwent breast and whole body PET/MRI. During the MR scan, PET events were simultaneously accumulated. MR contrast kinetic model parametric maps were computed using the extended Tofts model, including the volume transfer constant between blood plasma and the interstitial space (K^{trans}), the transfer constant from the interstitial space to the blood plasma (k_{ep}), and the plasmatic volume fraction (V_p).

Results—Patients with systemic metastases had a significantly lower k_{ep} compared to those with local disease (0.45 vs 0.99 min⁻¹, $p=0.011$). Metastatic burden correlated positively with K^{trans} and standardized uptake value (SUV), and negatively with k_{ep} . Ki67 positive tumors had a significantly greater K^{trans} compared to Ki67 negative tumors (0.29 vs 0.45 min⁻¹, $p=0.03$). A negative correlation was found between metabolic tumor volume and transfer constant (K^{trans} or K_{ep}).

Conclusion—These preliminary results suggest that MR pharmacokinetic parameters and FDG-PET may aid in the assessment of tumor aggressiveness and metastatic potential. Future studies are warranted with a larger cohort to further assess the role of pharmacokinetic modeling in simultaneous PET/MRI imaging.

Keywords

FDG-PET; dynamic contrast enhanced MRI; breast cancer; metastatic burden; Ki67

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Introduction

The development of systemic, hematogenous metastatic disease has been one of the main causes of breast cancer mortality. The presence of lymph-node metastasis, large size of primary tumor, and loss of histopathological differentiation are the prognostic markers of breast cancer metastasis currently used in the management of breast cancer patients [1], but with limited accuracy. Even lymphovascular invasion and the presence of regional lymph node metastases do not always correlate with subsequent distant spread [2].

It has been suggested that metastasis is a late, acquired event in tumorigenesis [3]. Particularly, tumor metastatic potential is closely linked to tumor microenvironment and cancer cell survivability. A harsh microenvironment exhibiting characteristics such as hypoxia, acidosis, ischemia, nutritional deprivation, or cytotoxic effect of radiation therapy or chemotherapy is known to promote tumor malignancy and metastasis [4–6]. Noninvasive or minimally invasive measurement of such tumor microenvironment and tumor characteristics may lead to accurate prediction of tumor metastatic potential and facilitate individualized cancer management. However, there is no established imaging marker for breast cancer metastatic potential to date.

Imaging of tumor glucose metabolism with ^{18}F -Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET) has gained widespread use to study the aggressiveness of tumor and overall prognosis of the patients [7, 8]. FDG uptake has also been correlated with the expression of HIF-1 α [9] and was found significantly increased in the primary Ewing sarcoma family of tumors with distant metastasis [10]. On the other hand, it has been also reported that it remains challenging for ^{18}F -FDG PET to reliably differentiate chronically hypoxic from normoxic tumors [11] or malignant lesions from benign inflammatory processes [12].

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) has emerged as one of most promising methods for assessing tumor microcirculation environment [13–16] and for providing complimentary information to ^{18}F -FDG-PET in terms of assessing tumor metastatic potential [17]. FDG-PET has high sensitivity (92–100%) to detect metastatic lymph nodes, but with mixed specificity (77 – 93%) [18, 19]. In contrast, a meta-analysis of 43 papers on application of DCE-MRI for lymph node assessment found that DCE-MRI has higher specificity (87%) than sensitivity (72%) [20]. The combination of PET and MRI has been shown to be a promising approach and lends the opportunity to observe tumor biology in vivo [21, 22]. However, the synergistic potential of FDG-PET and DCE-MRI for assessing aggressiveness and metastatic potential of the primary tumors has not been investigated.

Hence, the purpose of this study was to investigate the feasibility of using simultaneous breast MRI and PET to assess the synergy of MR pharmacokinetic and FDG uptake data to characterize tumor aggressiveness in terms of Ki67 expression and metastatic burden.

Patients and Methods

Patient Population

In this HIPAA compliant, local institutional review board (IRB) approved prospective study, 20 consecutive patients with breast cancer (age range 24.7–78.5, mean 49.4, all female) underwent simultaneous MR and PET scans between September 2012 and December 2013. Written informed consent was received from all participants. Eight breast cancer patients were excluded since they were scanned with different imaging protocols than the one described below during this period. The remaining 12 patients who underwent the imaging protocol described below during this time period were included (age range 24.7–65.8 years, mean age 49.3 years, all female). The clinical indication for all 12 patients was staging in newly diagnosed breast cancer.

Tumor pathology and immunohistochemistry were obtained from the electronic medical record for each patient. The following prognostic factors were gathered: human epidermal growth factor receptor-2 (HER-2), estrogen receptor (ER) and progesterone receptor (PR) status, and proliferation factor (Ki67). Ki67 expression less than 30% was considered negative [23]. No patients presented Ki67 expression between 20% and 30% in this study. Information regarding metastases was recorded from the whole body PET/MR and PET/CT scans as well as surgical pathology and biopsy results.

Image Acquisition

Simultaneous breast PET/MR imaging was performed after a clinical PET/CT with a single FDG injection. Following PET/CT, patients were transferred to a nearby facility for PET/MR. Breast PET/MR was followed by a whole body simultaneous PET/MR scan. The subjects were imaged using an integrated 3 T MR-PET Biograph mMR (Siemens AG, Erlangen, Germany) using a four channel breast coil (Noras, Würzburg, Germany). The patients were immobilized in the prone position. Bilateral breast DCE-MRI exam was performed using a prototype radial stack-of-stars three-dimensional (3D) spoiled gradient echo pulse sequence with golden-angle spoke ordering. All partitions in the slice direction corresponding to one radial angle were acquired sequentially before rotating to the next angle. Frequency-selective fat suppression was used after each partition loop and 60 initial calibration lines were acquired to estimate system-dependent gradient-delay errors [24]. Relevant imaging parameters were: axial slab orientation, FOV=280×280×256 mm³, FA=10 degrees, and TR/TE=3.6/1.7 ms. A total of 1680 radial spokes were acquired during free breathing to cover the whole breast. Two-fold readout oversampling (512 sample points/spoke) was used to avoid spurious aliasing along each spoke. The reconstructed image matrix size was 256×256×128. The image reconstruction with a high temporal resolution (5 s/frame) was achieved using the Golden-angle RAdial Sparse Parallel (GRASP) MRI method [25, 26]. The total acquisition time was 8 min. After baseline acquisition of 2 min, a single dose of gadopentetate dimeglumine (Magnevist, Bayer) at 0.1 mM/kg body weight was injected at 2 ml/s into an antecubital vein while the scan continued for another 6 min.

During the MR scan, PET events were simultaneously accumulated. The FDG-PET acquisition consisted of a single 15 min thorax bed position starting at the commencement of

the local exam. The mean injected activities were 478 to 561 MBq (mean 533 MBq) and time of MR-PET imaging following injection ranged from 125 to 234 min (mean 176 min). Each image was corrected for attenuation using patient specific T1-Dixon-based attenuation correction and breast coil μ -maps [27]. The PET images were reconstructed with a voxel size of $4.2 \times 4.2 \times 2 \text{ mm}^3$. The raw PET image values were converted to standardized uptake value (SUV) using total body mass, time from injection, and instrumental calibration factors as per standard reconstruction.

Image Post-Processing and Analysis

MR contrast kinetic model parametric maps were computed using the extended Tofts model (Olea Sphere, version 2.2, Olea Medical, La Ciotat, France), which requires a reference arterial input function (AIF). This latter was manually selected in the aorta at the level of the right pulmonary artery or the axillary artery. A representative example of DCE-MRI data is shown in Figure 1. Regions of interest (ROI) were drawn by a single operator who was blinded to the patient's history. The ROI included the maximally enhancing portion of the tumor based on the area under the curve computed color map. The ROI was drawn on a single slice (area under the curve computed color map superimposed on a post contrast T1 weighted image). ROIs were automatically propagated on additional computed color maps, including the volume transfer constant between blood plasma and the interstitial environment (K^{trans}), the transfer constant from the interstitial environment to the blood plasma (K_{ep}), and the plasma volume fraction (V_p). For each patient, multiple parameters were collected from these ROIs including mean and standard deviation (SD).

PET/MRI post-processing and analysis was performed using a fusion viewer (MIMviewer, version 5.4, MIM Software Inc.). This fusion viewer coregistered MRI and PET data. Maximum and mean standard uptake values (SUV) were measured in the same region of interest chosen for DCE-MRI data analysis. In addition, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were measured using the same software. This single slice was visually confirmed to be the same slice and anatomic location in which DCE parameters were measured on the DCE-MRI data. All image analysis was performed by a radiologist specializing in breast imaging with 6 years of experience.

Data Analysis and Statistics

Statistical analysis for comparisons of MR contrast kinetic data, PET metabolic data, and immunohistochemical data was performed using unpaired *t*-test and Pearson's correlation analysis. For each MR and PET measures, differences between the three groups with different metastatic burdens were evaluated using ANOVA (analysis of variance) with post-hoc Tukey's multiple comparisons test. All statistical tests were conducted at the two-sided 5% significance level using GraphPad Prism version 6.00 (GraphPad Software, La Jolla, CA, USA).

Results

The study population comprised 12 women, ages 24–65 (mean 49), 9 with invasive ductal carcinoma (IDC), 1 with adenocarcinoma, and 2 with invasive lobular carcinoma (ILC). Additional patient and tumor characteristics are described in Table 1.

The post-contrast DCE-MRI pharmacokinetic parameter color maps and PET image show the feasibility of generating DCE-MRI pharmacokinetic modeling data and FDG-PET uptake data to characterize malignant lesions (Fig.2). Whole body imaging performed after the local breast exam shows the presence of axillary (Fig.3A) and distant metastases (Fig. 3B). These examples demonstrate that the MR images are helpful in delineating the anatomical locations with the focal increased FDG uptake, which is difficult to assess on FDG-PET images alone.

Figure 4 shows comparison of PET/MRI parameters with metastatic burden. Groups were defined comprising between patients with local disease, defined as no metastasis and axillary metastasis alone, to those with systemic (distant) metastases, and parameter correlations vs. this ordinal definition of burden were considered. There was a statistically significant negative correlation between decreasing k_{ep} and increasing metastatic burden ($r = -0.59$, $p = 0.042$). Positive correlations, although not statistically significant, were seen between the parameters except k_{ep} and increasing metastatic burden. A significant difference among the metastatic burden groups was found in terms of k_{ep} ($p = 0.047$) and MTV ($p = 0.025$). For both k_{ep} and MTV, post- hoc Tukey's multiple comparisons test indicated that there was a significant difference only between the axillary and systemic metastasis groups.

The scatter plot of k_{ep} and MTV of the primary tumor shows separation of patients with no metastasis, axillary or systemic metastases, although the statistical significance could not be tested due to the small sample size (Fig.4). There was a significant negative correlation between k_{ep} and MTV ($r = -0.66$, $p = 0.02$), but none with any other PET measures. K^{trans} did not show any significant correlation with any of PET measures ($p > 0.05$). Group pairwise comparisons were also made between patients with local disease, defined as no metastasis and axillary metastasis alone, to those with systemic (distant) metastases. Patients with systemic metastases had a significantly lower k_{ep} compared to those with local disease (0.45 vs 0.88 min^{-1} , $p = 0.01$) and higher MTV (27.95 vs 6.56 , $p = 0.01$) (Table 2).

PET/MRI parameters were also compared with Ki67 expression. Ki67 positive tumors had a significantly higher K^{trans} compared to Ki67 negative tumors (0.29 vs 0.45 min^{-1} , $p = 0.0295$) (Fig.5, Table 2). Ki67 positive tumors tended to have higher k_{ep} , and lower SUV (max and mean), MTV and TLG compared to Ki67 negative tumors, although these data did not reach statistical significance.

Discussion

The preliminary observation from this study demonstrates a successful clinical use of simultaneous PET/MR to assess tumor microcirculation environmental parameters and metabolic activity. Our finding of lower k_{ep} in the tumors of patients with systemic metastases compared to local disease may reflect increased cellularity of these tumors.

However, the k_{ep} may be confounded by an increased extravascular- extracellular space in the setting of edema [28]. Other studies have shown that K^{trans} is a more relevant measure of capillary permeability than the k_{ep} [29].

The data from our study showed significantly higher K^{trans} in Ki67 positive tumors. This observation is in line with prior literature demonstrating a significantly higher K^{trans} and k_{ep} in Ki67 positive tumors compared to Ki67 negative breast cancers; these remained statistically significant at both 5% and 15% Ki67 expression cutoffs [30]. The significantly higher K^{trans} seen among Ki67 positive tumors compared to Ki67 negative tumors may reflect the more aggressive biology of Ki67 positive tumors which may require increased plasma flow and vascular permeability [31].

MTV and TLG measured by ^{18}F -FDG PET have been compared with the treatment outcomes in patients with various neoplasms, such as breast cancer [32], pancreatic cancer [33], and head and neck cancer [34]. They found that MTV and TLG are significant predictors of recurrence free survival and overall survival, which is in line with our observation that patients with Ki67 positive tumors and/or systemic metastases have higher MTV and TLG. Our data suggest possible clustering of patients by metastatic burden, using a combination of k_{ep} and MTV, and by tumor Ki67 status, using a combination of K^{trans} and MTV, highlights the potential multi-parametric utility of PET/MRI. Future studies with a larger cohort are warranted to further investigate the statistical significance of these preliminary findings and the potential synergy of PET/MRI parameters for tumor aggressiveness characterization.

Prior studies have demonstrated relationships between multiparametric PET/MRI data and tumor characteristics [35, 36]. For instance, non-triple negative breast cancers showed significant correlations between metabolic and vascularity parameters, namely a positive correlation of SUV_{max} with k_{ep} and V_e , whereas triple negative tumors did not [35]. Moreover, the combination of quantitative metabolic and vascularity data from PET and MRI have been shown to correlate with breast tumor subtype and histologic grade [35].

Whereas in our study no statistically significant correlation was seen overall between either k_{ep} or K^{trans} and SUV_{max} , a previous study of rectal cancer patient did demonstrate a significant positive correlation between k_{ep} and SUV_{max} [37]. However, in a study of colorectal liver metastases, no association was seen between vascular parameters (k_{ep} , V_e , and K^{trans}) and glucose metabolism [38], which is concordant with our study. Confounding variables, such as tumor subtype, may account for these discrepancies. For instance, triple negative breast cancers have been shown to demonstrate a higher SUV_{max} / K^{trans} ratio compared to non-triple negative breast cancers [35]. Further studies with a larger cohort are required to further evaluate relationships between vascularity, metabolic activity, and tumor subtypes, which can in turn serve as imaging biomarkers for tumor biology and aggressiveness.

Quantitative measures of pharmacokinetics and metabolic activity may translate to parameters for assessment of prognosis and treatment response. For instance, in a study of breast cancer patients, greater decreases in SUV_{max} and MRslope (initial slope of the

enhancement curve) after the first cycle of neoadjuvant chemotherapy are associated with improved disease free survival [39]. The combination of PET and MRI data in the aforementioned study performed better than the individual modalities alone in predicting treatment response [39].

A strength of our study is the simultaneous PET/MRI acquisition. Previous studies have examined the relationships between breast tumor pharmacokinetics and metabolic activity, however these studies involved separately acquired PET/CT and MRI images [35]. A principal advantage of simultaneous acquisition is patient comfort, as the time and claustrophobia induced by separate examinations may be poorly tolerated [40]. Another important feature is the physiological equivalence for all considered imaging contrasts given the absence of interscan delay. The anatomic positioning is aligned during MRI and PET acquisition, which facilitates the precise anatomic correlation of FDG uptake on PET with the multiparametric data of DCE MRI. Differences in patient positioning during PET/CT and MRI examinations may alter the quantitative results of these imaging modalities. Whole body PET/MRI not only facilitates quantitative tumor characterization, it also allows for confident detection of primary breast cancer, satellite lesions, and distant metastases while at the same time decreasing radiation dose to the patient compared to PET/CT [41–43]. When PET/MR was performed after PET/CT with a single injection, there were strong correlations between SUV values from PET/CT and PET/MRI in breast cancer metastases [44]. The superior soft tissue contrast of MRI, with the metabolic information from PET, has been hypothesized to increase the detection of metastases to the brain, bone marrow and the liver [45].

Limitations of this study include the small sample size, by virtue of the novel nature of this imaging protocol and recently available platform. Measurement of the maximally enhancing portion of the tumor may give different results than the whole tumor, as seen in other studies [28]. However, according to Hayes et al, focusing on so-called hot spots is higher in accuracy than using a whole tumor ROI [46]. Furthermore, it is difficult to choose ROI in nonmass enhancement as there is normal intervening tissue within the lesion. As the PET/MR was performed after a clinical PET/CT, the time from FDG injection to scan was longer than 2 hours. Future studies need to be conducted with a shorter uptake time more similar to the clinical standard to investigate whether the findings in the present study can also be seen at the earlier phase.

In conclusion, the combination of MR pharmacokinetic analysis and FDG-PET may aid in the prediction of tumor aggressiveness and metastatic potential, as represented by the Ki67 expression and metastatic burden. This may help in treatment planning and monitoring response. Future studies are warranted with a larger cohort to assess the statistical significance of our observations and further assess the role of pharmacokinetic modeling in simultaneous PET/MR imaging.

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Figure 1. 42 year old woman with invasive lobular carcinoma (ILC) of right breast. **A.** A representative GRASP DCE-MRI image at 330 seconds into the dynamic scan. **B.** Time-intensity curves measured from the aorta (thick line without markers) and the region of interest shown in A (thin line with circles). These examples demonstrate that GRASP can provide dynamic images with a high temporal resolution without sacrificing the spatial resolution.

Figure 2. 39 year old woman with ER, PR, and HER2 positive right breast invasive ductal carcinoma. Left top to bottom: PET axial attenuation corrected / MRI GRASP axial subtraction fusion, PET axial attenuation corrected, and MRI GRASP axial subtraction images. Right top to bottom: K^{trans} , k_{ep} , and V_p color maps superimposed on MRI GRASP axial images. Color bar ranges are represented as follows: K^{trans} , $-0.09 - 0.25 \text{ min}^{-1}$; k_{ep} , $0.06 - 2.61 \text{ min}^{-1}$; and V_p , $0 - 1.24\%$. Regions of interest have been drawn over the enhancing area of the tumor as depicted by the axial GRASP images sequences.

Figure 3.

Representative cases. Whole body PET maximum intensity projection (MIP) images are shown along with PET/MRI fusion images in color. **A.** 39 year old female with ER, PR, and HER2 positive right breast invasive ductal carcinoma (same patient as Fig.1). Whole body PET and PET/MRI coronal radial VIBE fusion images demonstrate a 3.3cm right breast mass (short arrow). Focal increased uptake in the right axilla is suspicious for metastatic lymph node (long arrow). MR fusion images delineate the anatomical correlate for the focal increased uptake, which is difficult to assess on PET images alone. **B.** 65 year old female with left breast ER and PR positive, HER2 and Ki67 negative invasive lobular cancer, moderately differentiated. Whole body PET MIP image demonstrates increased uptake in the left upper breast (short arrow), as well as bony metastases including a right rib metastasis (long arrow). PET/MRI T1 weighted fusion coronal image demonstrates 7 cm left breast nonmass enhancement (short arrow) and the right rib metastasis (long arrow).

Figure 4. Correlation of MR contrast kinetic parameters and metabolic activity parameters with metastatic burden. The p-values from the correlations are shown for individual plots. The numbers in parentheses are the p-values from the ANOVA test for differences among the three groups with different metastatic burdens.

Figure 5. Comparison of MR contrast kinetic parameters and metabolic activity parameters with tumor aggressiveness (Ki67 expression). The p-values shown in each plots are for the two-tailed t-tests of imaging measures between Ki67 positive and negative tumors.

Table 1

Patient and tumor characteristics.

Patient	Age	Size (cm)*	Pathological Type	ER	PR	Ki67	HER2	Metastases at Time of Exam
1	41.2	4.4	ILC	+	-	-	Equivocal	Systemic
2	60.9	0.5	IDC	N/A	N/A	N/A	N/A	None
3	39.1	2.9	IDC	+	+	N/A	+	Axillary
4	60.6	4.9	IDC/DCIS	+	+	-	+	None
5	29.1	1.7	IDC/DCIS	+	+	+	+	Axillary
6	40.1	6.6	IDC/DCIS	+	+	-	Equivocal	Axillary
7	62.6	1.1	IDC/DCIS	+	-	+	-	Systemic
8	58.1	3.2	Adenocarcinoma	+	+	-	-	Systemic
9	56.6	2.3	IDC	+	+	+	-	Axillary
10	53.3	5.4 & 2.7	IDC	+	-	+	Equivocal	Axillary
11	24.7	2.7	IDC	+	-	-	-	Axillary
12	65.8	7	ILC	+	+	-	-	Systemic
mean	49.3	3.4						

* Size - maximum size of tumor on T1-weighted MRI

N/A - Not available

Table 2

Stratification of pharmacokinetic and metabolic data (mean $\pm$ standard deviation) with tumor characteristics. Local for metastatic burden represents the cases with no metastases and axillary lymph node metastases.

	Ki67 Expression		
	Ki67–	Ki67+	p value
K^{trans} (min^{-1})	0.29 ± 0.08	0.45 ± 0.11	0.03
k_{ep} (min^{-1})	0.61 ± 0.10	0.30 ± 0.19	0.16
v_p	0.08 ± 0.04	0.05 ± 0.04	0.59
SUV_{max}	8.64 ± 8.77	5.21 ± 3.03	0.48
SUV_{mean}	5.14 ± 4.45	3.21 ± 2.17	0.45
MTV	22.06 ± 6.16	6.86 ± 4.94	0.12
TLG	115.9 ± 71.45	21.83 ± 12.29	0.33
	Metastatic Burden		
	Local	Systemic	p value
K^{trans} (min^{-1})	0.37 ± 0.14	0.34 ± 0.07	0.75
k_{ep} (min^{-1})	0.88 ± 0.25	0.45 ± 0.12	0.01
v_p	0.04 ± 0.01	0.12 ± 0.05	0.05
SUV_{max}	4.62 ± 4.66	10.19 ± 9.12	0.18
SUV_{mean}	3.05 ± 2.98	5.60 ± 4.41	0.25
MTV	6.56 ± 2.65	27.95 ± 7.96	0.01
TLG	18.58 ± 7.12	160.7 ± 103.6	0.07