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Tumor metabolism and perfusion ratio assessed by 18F-FDG PET/CT and DCE-MRI in breast cancer patients: Correlation with tumor subtype and histologic prognostic factors

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ABSTRACT

Objective: Our purpose was to evaluate whether breast cancer with high metabolic–perfusion ratio would be associated with poor histopathologic prognostic factors and whether triple negative breast cancer (TNBC) would show high metabolic–perfusion ratio compared to non-triple negative breast cancer (non-TNBC).

Methods: From March 2011 to November 2011, 67 females with invasive ductal carcinoma of breast who underwent both MRI and 18F-FDG PET/CT were included. Perfusion parameters including Ktrans, Kep and Ve were acquired from Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Metabolic parameters including the standardized uptake value (SUV) and volumetric metabolic parameters including metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were obtained from F-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT).

Results: In non-TNBC, SUVmax was significantly correlated with Kep ($\rho = 0.298$, $p = 0.036$) and Ve ($\rho = -0.286$, $p = 0.044$). In TNBC, there was no significant correlation between all perfusion and metabolic parameters. Compared to non-TNBC, higher SUVmax (10.2 vs 5.3, $p < 0.001$), higher SUVmax/Ktrans (56.02 vs 20.3, $p < 0.001$), higher MTV50/Ktrans (7.8 vs 16.54, $p < 0.001$), higher TLG50/Ktrans (36.49 vs 12.3, $p < 0.001$), higher TLG50/Ve (91.34 vs 27.1 $p = 0.022$) were significantly correlated with TNBC. Lower Ktrans (0.17 vs 0.29, $p = 0.017$) and lower Ve (0.29 vs 0.41, $p = 0.011$) were also significantly associated TNBC.

Conclusion: While several perfusion parameters and metabolic parameters were correlated in non-TNBC, they were not correlated in TNBC. TNBC showed higher metabolic–perfusion ratios compared to non-TNBC.

1. Introduction

Angiogenesis is the formation of new tumor supplying vessels from a preexisting vasculature. It is crucial for the tumor growth and distant metastasis via the penetration of cancer cells into the blood circulation. Vascular endothelial growth factor (VEGF), platelet-derived endothelial cell growth factor, and basic fibroblast growth factor, produced by tumor cells induce neovascularization [1]. Unlike normal blood vessels, tumor supplying vessels are functionally and structurally abnormal showing tortuous, dilated and saccular morphology.

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is available to assess vascular characteristics of tumor masses. DCE perfusion MRI could evaluate tumor angiogenesis because neoangiogenesis may increase blood flow and vascular permeability in the tumor tissues [2,3]. Three perfusion parameters are usually used for pharmacokinetic modeling in breast cancer imaging; forward volume transfer constant (Ktrans, expressed as min^{-1}), reverse volume transfer constant (Kep, expressed as min^{-1}) and extravascular extracellular space volume per unit volume of tissue (Ve). Higher perfusion parameters of tumors indicate neoangiogenesis including the recruitment and development of arteriovenous shunts, dilated capillary beds and hyper-permeable vessels.

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F-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) measures functional and metabolic properties and is valuable in the assessment of breast cancer [4,5]. The most frequently derived parameters from FDG PET/CT are the standardized uptake value (SUV) and volumetric metabolic parameters including metabolic tumor volume (MTV) and total lesion glycolysis (TLG) [6,7]. Although blood flow and vessel permeability play important roles for intracellular FDG uptake, previous study reported that there was no correlation between perfusion parameters derived from MRI and SUV derived from FDG PET imaging [8].

Our hypothesis was that breast cancers with high metabolic–perfusion ratio would be associated with poor histopathologic prognostic factors. Furthermore, triple negative breast cancer (TNBC) will also show high metabolic–perfusion ratio compared to non-triple negative breast cancer (non-TNBC).

2. Materials and methods

2.1. Patients

This retrospective study was approved by our Institutional Review Board (IRB) with waiver of any need for informed consent. From March 2011 to November 2011, 67 females with invasive ductal carcinoma of breast who underwent both MRI and FDG PET/CT were included. The intervals between MRI and PET/CT ranged from 0 to 9 (median, 2 days). 64 patients (95.5%) underwent surgical treatment including 23 patients who underwent neoadjuvant chemotherapy prior to surgery. The remaining three patients with advanced-stage disease underwent chemotherapy and radiation therapy without surgery.

2.2. MRI techniques

All MR examinations were performed using 1.5 T system (Signa HDxt; General Electric Medical Systems, Milwaukee, WI) with a dedicated breast coil (8-channel HD breast array, General Electric Medical Systems).

Fat suppressed T2-weighted fast spin-echo sagittal images were also obtained first. The following image parameters were used: 3616/98.8; flip angle, 90°; image matrix, 320 × 256; field of view, 320 mm × 320 mm; section thickness, 3.0 mm; section gap, 0 mm.

For the baseline T1 calculation, pre-contrast transverse 3D gradient-echo images were obtained using flip angle of 3° and 12° and the following parameters: TR/TE = 3.62/1.78msec, FOV = 280 mm, matrix 200 × 200, number of slices = 40, slice thickness = 2 mm (interpolated), no gap, receiver bandwidth = 50 kHz. DCE-MRIs were obtained using a 3D fast spoiled gradient-echo (SPGR) sequence with parallel imaging acceleration through the entire breast using flip angle of 20° and same parameters with pre-contrast image. In total, 42 phases of images with a temporal resolution of 11 s were obtained before, during and after contrast injection.

Gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany) was injected into an antecubital vein using an automated injector at a dose of 0.1 mmol/kg of body weight and at a rate of 3 mL/s, followed by a 20-mL saline flush for all patients.

2.3. MRI analysis

For the kinetic curve analysis, we used the Functool Software (GE Medical Systems). Post-processing of the high temporal resolution images was done using VizPack software (General Electric Medical Systems). The arterial input function (AIF) was measured in the aortic arch or in the highest level of scanned aorta, if the aortic arch is not scanned. Several ROIs for AIF were positioned in the center of aortic lumen and an ROI showing the highest maximal peak enhancement and fastest peak arrival time was selected as a single representative AIF. For the measurement of perfusion parameters of the tumor, ROI was drawn manually around the tumor margins on three consecutive axial sections including the center of tumor mass. Care was taken to exclude adjacent soft tissues and blood vessels. The ROIs of the tumor did not include central, poorly enhanced, low-attenuated areas, which were considered to be areas of necrosis. The mean value of the parameters within the ROIs was automatically calculated and displayed and we took the highest mean value. All MR images were reviewed by two radiologists of 6 and 12 years of experience in interpreting breast imaging in consensus. The enhancement kinetics from each pixel was measured throughout the scan time and fitted with two compartment model by Tofts et al. [9,10].

2.4. FDG PET/CT technique and image analysis

After fasting for at least 6 h, each patient received 5 MBq/kg FDG intravenously. The blood glucose level at the time of injection was <150 mg/dL in all patients. Patients were instructed to rest comfortably for 60 min and to urinate prior to scanning. Whole-body PET/CT images were obtained using a Discovery ST scanner (GE Healthcare, Milwaukee, WI). Seven-to-eight frames (3 min/frame) of emission PET data were acquired in the three-dimensional mode after obtaining a non-contrast CT scan from the base of the skull to the upper thigh (120 kV; 30–100 mA in the AutomA mode; section width = 3.75 mm). Emission PET images were reconstructed using an iterative method (ordered-subsets expectation maximization with two iterations and 20 subsets, field of view = 600 mm, slice thickness = 3.27 mm) and attenuation-corrected by reference to the non-contrast CT image.

A nuclear medicine specialist with 10 years of PET experience reviewed all FDG PET/CT images on a dedicated workstation (GE Advantage Workstation 4.4). Volumetric metabolic parameters were obtained using the Volume Viewer software. The volumetric region of interest (VOI) was carefully placed over the breast lesion exhibiting elevated FDG activity, compared to normal tissue, to avoid overlap with adjacent FDG-avid structures and areas exhibiting physiological uptake. A threshold of 50% SUVmax was used to delineate the MTV. All SUVs were estimated based on injected dose and body weight, and the SUVmax, SUVmean, and MTV of each lesion were calculated automatically. TLG was calculated by multiplying the SUVmean by the MTV.

2.5. Histological evaluation

Surgical specimens from the areas of the macroscopic tumor were serially sliced at 5-mm intervals, prepared as paraffin-embedded sections, and stained with hematoxylin–eosin.

After the size assessment, the specimens were evaluated according to the following histopathologic features: histological type of carcinoma; Black's nuclear grade (NG, 1 – poorly differentiated, 2 – moderately differentiated, and 3 – well differentiated), modified Bloom-Richardson's histological grade (HG, 1 – well differentiated, 2 – moderately differentiated, and 3 – poorly differentiated); presence of estrogen receptor (ER) and progesterone receptor (PR); expression of HER2. The overall stage of cancer was classified according to the American Joint Committee on Cancer TNM staging of breast cancer. For dichotomous dependent variables, grouping for comparisons occurred according to NG (high [grade 1] vs. low [grade 2 and 3]) and HG (low [grade 1 and2] vs. high [grade 3]). Tumor subtype was classified into TNBC and non-TNBC. All specimens were reviewed by a pathologist with 17 years of experience.

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