AI-enhanced Synchronized Multiparametric ^{18}F -FDG PET/MRI for Accurate Breast Cancer Diagnosis

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Research Article

Keywords: ^{18}F -FDG PET/MRI, breast cancer, artificial intelligence, radiomics

Posted Date: April 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-410600/v1>

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Version of Record: A version of this preprint was published at European Journal of Nuclear Medicine and Molecular Imaging on August 10th, 2021. See the published version at <https://doi.org/10.1007/s00259-021-05492-z>.

Abstract

Purpose: to assess whether a radiomics and machine learning (ML) model combining quantitative parameters and radiomics features extracted from synchronized multiparametric ^{18}F -FDG PET/MRI images can differentiate benign and malignant breast lesions.

Methods: 102 consecutive patients with 120 BI-RADS 0, 4 and 5 breast lesions (101 malignant, 19 benign) detected by ultrasound and/or mammography were prospectively enrolled and underwent hybrid ^{18}F -FDG PET/MRI for diagnostic purposes. Quantitative parameters and radiomics features were extracted from dynamic contrast-enhanced (MTT, VD, PF), diffusion (ADCmean of breast lesions and contralateral breast parenchyma), PET (SUVmax, mean and minimum of breast lesions, SUVmean of uni- and contralateral breast parenchyma) and T2-w images. Different diagnostic models were developed using a fine gaussian support vector machine algorithm and exploring different combinations of quantitative parameters and radiomics features to obtain the highest accuracy in discriminating benign from malignant breast lesions using a 5-fold cross validation. The performance of the best radiomics and ML model was compared with that of expert readers review physician using the McNemar test.

Results: Eight radiomics models were developed. The integrated model combining MTT and ADC with radiomics features extracted from PET and ADC images obtained the highest accuracy for breast cancer diagnosis (AUC 0.983) and was higher (AUC 0.868) yet not significant to expert readers review ($p=0.508$).

Conclusion: A radiomics and ML model combining quantitative parameters and radiomics features extracted from synchronized multiparametric ^{18}F -FDG PET/MRI images can accurately discriminate benign from malignant breast lesions.

Introduction

Breast cancer is the most commonly occurring malignancy in women worldwide, representing 11.6% of newly diagnosed cancer cases in 2018 [1]. Patients' prognosis changes dramatically if breast cancer is diagnosed at early compared to later stages, with a 5-year survival rate ranging from 98–100% to 66–98%, respectively [2]. Despite the many advantages obtained in the field of new surgical approaches and targeted drug development, early diagnosis still represents one of the most effective means to conquer breast cancer. Imaging techniques that are currently used to diagnose breast cancer comprise mammography, ultrasound and MRI [3]. Among these, MRI is the highest sensitive imaging modality for breast cancer detection, through the depiction of neoangiogenesis as a tumor specific feature. A challenge in the broader use of breast MRI are false positive findings leading to unnecessary invasive biopsies in benign tumor causing unnecessary costs and patient anxiety [4]. Other factors that affect MRI specificity are related to image acquisition technique and readers' experience [4].

Carcinogenesis is a complex, multistep process during which cancers develop distinct pathological biological properties- cancer hallmarks- including sustained proliferation, evading growth suppressors and apoptosis, promoting angiogenesis, invasion and metastasis [5]. Advanced imaging techniques including morphologic, functional and metabolic information have been introduced to allow the non-invasive depiction of these pathophysiological processes at cellular level. These novel imaging data can be used for tumor diagnosis and characterization, assessment of the response to specific treatments and prediction of patients' outcome [6].

Synchronized multiparametric ^{18}F -fluoro-2-deoxy-d-glucose (^{18}F -FDG) PET/MRI is a novel imaging technique that combines multiparametric morphologic and functional information from MRI with metabolic information provided by PET offering unique insights into tumor biology to achieve the ultimate goal of precision medicine in oncology [7, 8]. Recent data support the use of ^{18}F -FDG PET/MRI in breast cancer patients for different diagnostic purposes [9, 10]. Initial data using the combination of separately acquired MRI and PET data indicate an improvement in the differentiation of benign and malignant breast lesions [11], but at present the role of synchronized multiparametric ^{18}F -FDG PET/MRI for breast cancer diagnosis has not been fully assessed.

Recently a new paradigm in healthcare has emerged with advances in medical imaging technologies, image analysis and the advent of artificial intelligence (AI) and its application to medical imaging. Radiomics is the extraction of large numbers of quantitative features from standard-of-care medical images using computer algorithms that can be correlated with various data e.g patient characteristics, outcomes and pooled in large-scale analysis to create decision support models [12–14]. Radiomics has the potential to represent “the bridge between medical imaging and personalized medicine” [15].

We hypothesized that an AI-based radiomics model combining quantitative simultaneously acquired ^{18}F -FDG PET/MRI data enables accurate differentiation of benign and malignant breast tumors. Therefore, the aim of our study was to develop and validate a diagnostic AI model using quantitative perfusion, diffusion and metabolic data as well as radiomics features extracted from simultaneous multiparametric ^{18}F -FDG PET/MRI to non-invasively differentiate benign from malignant breast lesions.

Materials And Methods

Patient population

This prospective single-institution study was approved by the institutional review board and written informed consent was obtained from all participants. From June 2016 to July 2020, 154 patients were included in the study and underwent synchronized multiparametric ^{18}F -FDG PET/MRI of the breast for diagnostic purpose. Patients fulfilled the following inclusion criteria: > 18-year-old; not pregnant nor breastfeeding; imaging abnormality (BI-RADS 0, 4/5) on ultrasound and/or mammography (i.e. asymmetries, microcalcifications, architectural distortion, breast mass); no previous treatment; no contraindications to contrast-enhanced MRI. Exclusion criteria were: no histopathology nor follow-up available; incomplete ^{18}F -FDG PET/MRI examinations; ^{18}F -FDG PET/MRI images not suitable for the subsequent quantitative and radiomics analysis (e.g. image artifacts, incomplete dynamic scans). Thus, 102 patients (mean age 50 years, age range 23-82 years) with 120 breast lesions (101 malignant and 19 benign) were finally included in this study. The BI-RADS category distribution of included lesion was: BI-RADS 0 (n=8), BI-RADS 4 (n=16), BI-RADS 5 (n=96). The flow-chart of the patient selection process is illustrated in Figure 1.

Standard of reference

Histology was used as standard of reference for lesions classified as BI-RADS 4 (n=22) / 5 (n=95) at ^{18}F -FDG PET/MRI. In case of a benign histopathological diagnosis at image-guided needle biopsy, the final diagnosis was benign. In case of a high-risk lesion with uncertain potential for malignancy, the final diagnosis was established with open surgery. In patients with malignant lesions the standard of reference was histological analysis of the surgical specimen; in patients who received neoadjuvant treatment, the biopsy results were considered the standard of reference. In three lesions classified as BI-RADS 2 (n=2) or BI-RADS 3 (n=1) at ^{18}F -FDG PET/MRI stable imaging follow-up was available for at least two years.

Multiparametric PET/MRI acquisition protocol

All patients underwent synchronized multiparametric ^{18}F -FDG PET/MRI performed on a Biograph mMR system (Siemens, Germany), an MRI-compatible PET detector integrated with a 3.0 MRI scanner.

Patients fasted at least 5 hours before receiving an intravenous application of 2.5–3.5 MBq/kg bodyweight of 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F -FDG). All measured blood glucose levels were less than 150 mg/dL (8.3 mmol/L) prior the tracer injection. The PET/MRI acquisition started then after an uptake time of 60 min. MRI-based attenuation correction was applied using Dixon-VIBE sequences obtaining in-phase and opposed-phase as well as fat-saturated and water-saturated images. A three-dimensional (3D) acquisition technique was used that offered an axial field of view (FOV) of approximately 26 cm and a transverse FOV of 59 cm with a sensitivity of 13.2 cps/kBq.

The multiparametric MRI was performed using a dedicated 16 channel breast coil (Rapid Biomedical, Germany) and the imaging protocol consisted of the following sequences:

1. Axial T2-weighted sequence, TR/TE= 4820/192 ms, matrix size 640x480, FOV 360 x 360 mm, slice thickness 2.5 mm, gap 3 mm, FA 128°.
2. Diffusion tensor imaging using a 2D diffusion-weighted single-shot spin-echo-prepared echo-planar imaging (EPI) sequence with parallel imaging and fat suppression, TR/TE, 4500/87 ms, matrix 190 × 112, FA 90°, FOV 212 × 360 mm, slice thickness 4 mm, gap 5.2 mm. Diffusion gradients were applied in twelve directions with b values of 0 and 800 s/mm².
3. Dynamic contrast-enhanced (DCE) imaging, obtained before and after intravenous administration of paramagnetic contrast agent (Dotarem: 0.2 ml/kg body weight), at a flow rate of 3.5 ml/s. Five pre-contrast axial T1 Vibe with flip angles of 2°, 10°, 20°, 30° and 40° were first acquired for T1 mapping, followed by axial T1 TWIST dynamic sequences (TR/TE = 4.7/2.46 ms, matrix 448x448, FOV 340x340 mm, slice thickness: 2 mm, no gap, Flip Angle: 15°) with 20 measurements, and temporal resolution of 16.7 s. After MRI update, T1 TWIST DIXON dynamic sequences were acquired (TR/TE = 4.7/1.3 ms, matrix 352x352, FOV 440x440 mm, slice thickness: 2 mm, no gap, Flip Angle: 10.5°) with 23 measurements, and a temporal resolution of 14 s. Subtraction and maximum intensity projection images were then obtained.

Image analysis

Two board-certified radiologists with 10 and 6 years of experience in breast imaging independently evaluated MRI data. A nuclear medicine physician with 10 years of experience and a radiologist with 6 years of experience, trained in hybrid imaging under the supervision of a nuclear medicine physician, independently evaluated PET images. Readers were blinded from final histopathological results and previous examinations. To assess the intra-observer reproducibility of PET/MRI quantitative parameter measurements, all lesions were reassessed by the same readers after a wash-out period of four weeks.

Quantitative Data Analysis

Multiparametric MRI

All MR images were imported into an open-source medical image viewer (Horos v.3.3.5) for image visualization and quantitative parameters extraction.

Breast lesions were identified on DCE post-contrast subtracted images and lesion location and size (maximum diameter on DCE post-contrast subtracted images in the axial plane) was recorded.

- For quantitative perfusion analysis, a pixel-by-pixel fast-deconvolution method was applied using the open source MRI perfusion analysis tool UMMPerfusion (Horos plugin) [16]. Arterial input function was selected by drawing a 2D region of interest (ROI) in the right ventricle. Breast lesions were identified and segmented on subtracted images at early post-contrast time points, as soon as the lesion was clearly visible [17]. 2D ROIs were drawn over the enhancing tumor portion, avoiding the inclusion of cystic, hemorrhagic necrotic areas or susceptibility artifacts from biopsy markers, and then pasted on the corresponding quantitative maps to extract mean transit time (MTT), plasma flow (PF) and volume distribution (VD).
- DW images and corresponding quantitative ADC maps were analyzed. In detail, breast lesions were first identified on high b-value DW images; thereafter, 2D ROI were positioned on ADC maps on the qualitatively darkest part of the tumor, using DCE images as a reference to identify contrast-enhanced regions and also avoiding the inclusion of cystic, hemorrhagic necrotic areas or susceptibility artifacts from biopsy markers [18]. Using this approach, ADCmean of primary lesions and as well as of the normal appearing unilateral and contralateral breast parenchyma was calculated.

¹⁸F-FDG PET

For PET quantification, a volumes-of-interest (VOI) was manually drawn around every suspicious breast lesion to acquire their maximum (SUVmax), mean (SUVmean) and minimum (SUVmin) standardized uptake value (SUV) using the Hermes Hybrid

Viewer (Hermes Medical Solutions, Stockholm, Sweden). The VOI was defined using the region grow 3-dimensional approach with a fixed threshold determined to capture PET metabolic tumor volume, but not physiological ^{18}F -FDG uptake in surrounding tissues. For metabolic quantification of non-tumoral unilateral and contralateral breast tissue, a VOI was placed in the normal breast parenchyma to obtain its SUVmean away from the nipple and areola. Examples of ROI placement over breast lesions on DCE-MRI, ADC and PET images for the extraction of quantitative parameters are illustrated in Figure 2.

Radiomics analysis and model development

PET/MRI images were imported to dedicated software (ITK-SNAP v. 3.6.0) [19] for lesion segmentation. A radiologist with 6 years of experience in breast imaging annotated each lesion on DCE, DWI, PET and T2-w images. First, whole breast lesions were segmented on DCE-MRI images using a semi-automated method. The second post-contrast time point was chosen for lesion segmentation, in order to better depict tumor enhancement compared to the surrounding breast parenchyma. The same approach was applied to DWI and PET images. Finally, manual segmentation was performed to annotate breast lesions on T2-w images slice per slice. In all steps, care was taken to avoid the inclusion of cystic/necrotic areas. When a biopsy marker was present, a distance of at least 2 mm was kept. Examples of tumor segmentation analysis is illustrated in Figure 3.

Considering the unbalanced distribution of benign and malignant breast lesions, adaptive synthetic sampling was employed to equalize class sizes [20]. Data for all four image types was initially reduced to 16 gray levels. Radiomics features were calculated using CERR [21]. DCE, T2-w, ADC and PET images were used for radiomics feature extraction. Segmentations performed on DWI images were used for the extraction of radiomics features from ADC images. Considering that T2w and ADC images were not isotropic, feature extraction was performed in a 2D fashion for each slice and then aggregated over the whole lesion (BTW3 as defined by the Image Biomarker Standardisation Initiative) [22]. The LASSO regression was then utilized to determine which radiomics features were of most importance. A maximum of 5 features were selected to avoid overfitting. Diagnostic models were then developed in MATLAB using a fine gaussian support vector machine (SVM), one of the most employed ML classifiers in medical imaging [23] and a 5-fold cross-validation. Data were initially standardized to prevent any particular dependence on an individual parameter. This process was then repeated 1000 times to provide final diagnostic metrics. Analysis was performed for each of the four image types independently and then in various combinations to assess potential improvements in diagnostic accuracy for the discrimination of benign and malignant breast lesion.

Clinical ^{18}F -FDG PET/MRI Interpretation

DCE-MRI was assessed according to the BI-RADS V Edition lexicon [24]. A BI-RADS category from 2 to 5 was assigned to each lesion. BI-RADS scores were then dichotomized as follows: 2-3= benign and 4-5=malignant. Subsequently, ADC values were calculated for each lesion, as described above. An ADC value of $1.3 \times 10^{-3} \text{ mm}^2/\text{sec}$ was used as diagnostic threshold for defining benignity and malignancy, as suggested by the EUSOBI consensus statement on diffusion weighted imaging [18]. Lesions showing ADC values equal to or greater than $1.3 \times 10^{-3} \text{ mm}^2/\text{sec}$ were classified as benign, while lesions with ADC values lower than $1.3 \times 10^{-3} \text{ mm}^2/\text{sec}$ were classified as malignant. On PET a lesion was classified as benign if it did not show ^{18}F -FDG uptake higher than the above background activity; conversely, a lesion showing ^{18}F -FDG uptake greater than the surrounding parenchyma was classified as malignant [25]. To achieve a final diagnosis, the following criteria were applied for the combined DCE-MRI, DWI and PET evaluation:

- A lesion was classified as malignant if at least two among DCE-MRI, DWI and PET or all of them were positive for malignancy.
- A lesion was classified as benign if at least two among DCE-MRI, DWI and PET or all of them were negative for malignancy

Statistical analysis

Intra and interobserver reproducibility of quantitative parameter measurements was assessed using the intraclass correlation coefficient (ICC) analysis. The agreement was rated as follows: poor with ICC <0.5, moderate when comprised between 0.5 and 0.75, good when ranging between 0.75 – 0.90, and excellent when greater than 0.90 [26]. Kolmogorov-Smirnov test was

performed to assess whether quantitative parameters were distributed normally. Accordingly, independent t test or Mann-Whitney U test were used to compare quantitative parameters between benign and malignant breast lesions. Diagnostic accuracy, sensitivity, specificity, positive and negative likelihood ratio of radiologists and nuclear medicine physician in classifying breast lesions were also calculated. ROC curves of BI-RADS score as well as significant quantitative DWI, perfusion and PET parameters for breast cancer diagnosis were also calculated. Differences in terms of performance among the different radiomics models and between the best performing radiomics model and clinical interpretation were assessed using Mc Nemar test. A p value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using SPSS, released 2017, Version 25.0. Armonk, NY: IBM Corp and MedCalc 18 (MedCalc software bvba).

Results

Patient population

Of the 120 included breast lesions, 101 (84%) were malignant and 19 (16%) benign. Histological features of included breast lesions are reported in Tables 1 and 2.

Table 1
Histological features of included malignant breast lesions.

Histological Diagnosis	N.	%
Apocrine carcinoma	1	1
DCIS	3	3
IDC	79	78
ILC	7	7
IDC + ILC	3	3
Papillary carcinoma	2	2
Invasive tubular carcinoma	1	1
Lymphoma	1	1
Malignant phylloid tumor	2	2
Mucinous carcinoma	1	1
Metaplastic carcinoma	1	1
Total	101	100
Tumor Grade		
G1	7	7
G2	35	36
G3	56	57
Total	98	100
Molecular subtype		
Luminal A	10	10
Luminal B	51	52
HER2 +	12	12
Triple Negative	25	26
Total	98	100

Note: DCIS= ductal carcinoma in situ; IDC= invasive ductal carcinoma; ILC= invasive lobular carcinoma

Table 2
Final diagnosis of included benign breast lesions.

Diagnosis	N.	%	Standard of reference
Sclerosing adenosis	1	5	Histology
FAH	2	11	Histology
Fibroadenoma	6	31	Histology
Fibrocystic parenchyma	1	5	Histology
Epithelial duct proliferation	2	11	Histology
Mastitis	1	5	Histology
Papilloma	2	11	Histology
PASH	1	5	Histology
BI-RADS 2 findings*	3	16	Follow-up.
Total	19	100	

Note: FAH= fibroadenomatous hyperplasia; PASH= pseudoangiomatous stromal hyperplasia; Follow-up= clinical and instrumental follow-up. * confirmed as benign during the follow-up

Breast carcinomas showed significantly higher maximum diameter (28.5 vs 10.68 mm, $p = 0.035$) and SUVmax (6.22 vs 3.09, $p = 0.003$) as well as lower ADCmean (9.23 vs 1.42×10^{-3} mm²/sec, $p < 0.001$) and MTT (77.17 vs 118.90 sec, $p < 0.001$) than benign breast lesions. Mean values of quantitative parameters in both benign and malignant breast lesions with corresponding significance levels are reported in Supplementary Materials S1. ICC values of all quantitative parameters including intra and inter-observer reproducibility are shown in Supplementary Materials S2. Intra and inter-observer reproducibility of quantitative parameters measurement ranged from moderate to excellent.

Radiomics models

One hundred and one features were extracted in six classes (22 first order, 26 based on gray-level co-occurrence matrices, 16 based on run length matrices, 16 based on size zone matrices, 16 based on neighborhood gray level dependence matrices, and five based on neighborhood gray tone difference matrices) from DCE, ADC, T2-w and PET images, respectively. Eight radiomics models were developed to predict breast cancer diagnosis, based on different combinations of multiparametric ¹⁸F-FDG PET/MRI images. Radiomics models with corresponding selected radiomics features are reported in Table 3. Firstly, a radiomics model based on quantitative parameters alone was built. ADCmean of breast lesions, MTT and SUVmax were selected by the LASSO regression and used by the SVM classifier, obtaining an AUC of 0.981 for correctly classifying breast lesions.

Table 3
Selected features/quantitative parameters for each radiomics model.

Radiomics model	Selected features/quantitative parameters
ADCr	ADC – minimum (FO)
	coefficient of dispersion (FO)
	zln (SZM)
	difference variance (GLCM)
	inverse difference moment (GLCM)
DCE	auto correlation (FO)
	strength (NGTDM)
	busyness (NGTDM)
	standard deviation (FO)
	szlgle (SZM).
PET	inverse difference moment normalized (GLCM)
	glv (NGLDM)
	first information correlation (GLCM)
	lzlgle (SZM)
	skewness (FO)
T2-w	glv (SZM)
	skewness (FO)
	glv (NGLDM)
	kurtosis (FO)
	correlation (GLCM)
ADCr, DCE	minimum (FO ADC)
	strength (NGTDM DCE)
	zp (SZM ADC)
	rln (RLM ADC)
	coefficient of dispersion (FO ADC)
ADCr, DCE, PET	minimum (FO ADC)
	lzlgle (SZM PET)
	difference variance (GLCM ADC)
	auto correlation (GLCM DCE)
	hgce (NGLDM PET)
ADCr, DCE, PET + ADCmean, MTT, SUVmax	lzlgle (SZM PET)
	minimum (FO ADC)
	zln (SZM PET)

Radiomics model	Selected features/quantitative parameters
	MTT
	ADCt

Note: ADCr= radiomics features extracted from ADC maps; ADCmean=apparent diffusion coefficient mean of breast lesions; DCE=radiomics features extracted from dynamic contrast-enhanced images; PET= radiomics features extracted from positron emission tomography images; T2-w= radiomics features extracted from T2-weighted images; MTT=mean transit time; SUV= standard uptake value; FO= first order parameter; GLCM – gray level cooccurrence matrix-based parameter; NGLDM – neighborhood gray level dependence matrix-based parameter; NGTDM – neighborhood gray tone difference matrix-based parameter; RLM – run length matrix-based parameter; SZM – size zone matrix-based parameter; glv – gray level variance; hgce – high gray level count emphasis; lzlgle – large zone low gray level emphasis; rln – run length non-uniformity; szlgle – small zone low gray level emphasis; zln – zone size non-uniformity; zp – zone percentage.

Thereafter, the accuracy of diagnostic models based on radiomics features extracted from individual DCE, T2w, ADC and PET images was explored. Among these models, the best performance in discriminating benign from malignant breast lesions was obtained by SVM classifier using features extracted from ADC images (AUC 0.937). The model based on T2-w features performed worse with AUC of 0.793. Based on these findings, two radiomics models were built combining 1) radiomics features extracted from ADC maps and DCE images; and 2) radiomics features extracted from ADC, DCE and PET images. Of these, the latter showed the best performance for breast cancer diagnosis (AUC 0.969). Finally, an integrated model combining quantitative parameters and radiomics features extracted from DCE, PET images and ADC maps was built. MTT and ADCmean of breast lesions and radiomics features extracted from ADC maps and PET images were selected by the LASSO regression. This model obtained the highest accuracy in discriminating benign from malignant breast lesions with an AUC of 0.983. A summary of all radiomics models with corresponding accuracy metrics, including AUROC, diagnostic accuracy, sensitivity, specificity, positive and negative likelihood ratio is reported in Table 4.

Table 4
Summary of developed radiomics models with corresponding accuracy metrics.

Images	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Accuracy	AUROC
ADCr	90.7 (83.8–93.8)	87.4 (79.4–93.1)	7.20 (4.29–11.92)	0.11 (0.05–0.19)	89.0 (84.1–93.1)	0.937 (0.901–0.973)
DCE	77.5 (67.8–85.0)	89.5 (81.7–94.6)	7.38 (4.33–14.33)	0.25 (0.18–0.36)	83.5 (77.5–88.2)	0.889 (0.841–0.937)
PET	79.4 (73.3–89.1)	83.9 (74.9–90.1)	4.93 (3.18–8.01)	0.25 (0.17–0.36)	81.7 (77.0–87.8)	0.898 (0.844–0.941)
T2-w	67.7 (57.3–76.3)	77.2 (68.4–85.3)	2.97 (2.03–4.39)	0.42 (0.31–0.57)	72.4 (65.9–78.6)	0.793 (0.732–0.855)
ADCr DCE	88.9 (81.4–94.4)	83.1 (74.9–90.1)	5.26 (3.45–8.30)	0.13 (0.07–0.23)	86.0 (80.8–90.7)	0.934 (0.901–0.968)
ADCr DCE PET	94.9 (88.8–98.4)	83.2 (74.9–90.1)	5.65 (3.69–8.82)	0.06 (0.03–0.14)	89.0 (84.1–93.1)	0.969 (0.947–0.990)
ADCmean MTT SUVmax	94.5 (87.5–97.8)	91.8 (85.3–96.6)	11.52 (6.22–23.61)	0.06 (0.02–0.13)	93.2 (88.8–96.2)	0.981 (0.966–0.996)
ADCr DCE PET + ADCmean MTT SUVmax	95.3 (88.8–98.4)	94.3 (87.6–97.8)	16.72 (7.43–35.16)	0.05 (0.02–0.12)	94.8 (90.5–97.3)	0.983 (0.962–1.000)

Note: AUROC= area under the receiver operating characteristic curve; ADCr= radiomics features extracted from ADC maps; ADCmean=apparent diffusion coefficient of breast lesion; DCE=radiomics features extracted from dynamic contrast-enhanced images; PET= radiomics features extracted from positron emission tomography images; T2-w= radiomics features extracted from T2-weighted images; MTT=mean transit time; SUV= standard uptake value.

At McNemar test (Table 5), the performance of the integrated model combining quantitative parameters and radiomics features was higher, but not significantly different from that of the other radiomics models ($p > 0.069$) .

Table 5
Results of the McNemar test for the comparison of AUC values of the developed radiomics models.

Radiomics model	ADC	DCE	PET	T2	ADCr/DCE	ADCr/DCE/PET	ADCmean/MTT/SUVmax
DCE	0.178						
PET	0.068	0.720					
T2-w	< 0.001	0.020	0.062				
ADCr/DCE	0.480	0.609	0.321	0.003			
ADCr/DCE/PET	1.000	0.178	0.068	< 0.001	0.480		
ADCmean/MTT/SUVmax	0.243	0.009	0.002	< 0.001	0.045	0.243	
ADCr DCE PET + ADCmean MTT SUVmax	0.082	0.002	< 0.001	< 0.001	0.010	0.082	0.689

Note: DCE=dynamic contrast enhanced; ADC=apparent diffusion coefficient; PET=positron emission tomography; ADCr=radiomics features extracted from ADC maps; MTT=mean transit time; SUV=standardized uptake value

Clinical Interpretation ¹⁸F-FDG PET/MRI

The distribution of BI-RADS descriptors, ADC values and PET findings in the study population is reported in Supplementary Materials S3. Clinical Interpretation achieved a diagnostic accuracy of 0.958 (0.905–0.986), sensitivity and specificity of 100% (96% – 100%) and 73.7% (49% – 91%), positive and negative likelihood ratio, NPV of 3.80 (1.79–8.06) and 0 in differentiating benign from malignant breast lesions.

All radiomics models but the one based on T2w-radiomics features achieved greater AUCs than clinical interpretation of ¹⁸F-FDG PET/MRI. However, this difference was not significant ($p = 0.508$). ROC curves of BI-RADS scores along with significant quantitative DWI (ADCmean), perfusion (MTT) and PET (SUVmax) for differentiating benign from malignant breast lesions are illustrated in Supplementary Materials S4.

Discussion

At present, no studies have been published on synchronized AI- ¹⁸F-FDG PET/MRI for breast cancer diagnosis. The aim of this study was to investigate whether an AI-based radiomics model combining quantitative simultaneously acquired ¹⁸F-FDG PET/MRI data enables accurate differentiation of benign and malignant breast tumors. A model including both quantitative parameters and radiomics features can accurately discriminate benign from malignant breast lesions. Our results indicate that AI-enhanced functional and metabolic breast imaging showed an excellent performance, higher than expert readers, thus having the potential to assist human readers in correctly classifying suspicious breast lesions and obviate unnecessary invasive breast procedures.

While DCE-MRI is undisputedly the most sensitive test for breast cancer detection with a pooled sensitivity of 99% [27], there is still room for improvement in diagnostic accuracy due to overlap in imaging features of benign and malignant breast tumors, interpretation-influencing physiological factors such background parenchymal enhancement and last but not least human detection or interpretation error [28].

To compensate for these limitations, additional functional and metabolic imaging techniques such as DWI, perfusion and PET have been developed that provide insights of tumor biology and thus improve diagnostic accuracy. Several studies have shown the incremental diagnostic value of these individual parameters [29, 30] particularly their combined application as

multiparametric MRI or PET/MRI has been shown to improve diagnostic accuracy for breast cancer detection and characterization [11, 31].

Our findings also indicate that different functional and metabolic imaging techniques enable the non-invasive simultaneous depiction of oncogenic processes such as induction of neoangiogenesis, metabolic reprogramming and sustained proliferation. In our study the clinical interpretation of ^{18}F -FDG PET/MRI showed a good diagnostic accuracy with an AUC 0.868 for breast cancer diagnosis, and these findings are in line with previous studies [11, 31, 32].

To fully leverage the wealth of information provided by synchronized multiparametric ^{18}F -FDG PET/MRI we aimed to develop and validate a diagnostic AI model using quantitative perfusion, diffusion and metabolic data as well as radiomics features to non-invasively differentiate benign from malignant breast lesions.

The AI-model with the best diagnostic accuracy was based both on radiomics features extracted from ADC and PET images as well as quantitative DCE (MTT) and DWI (ADCmean) information of breast lesions and achieved an accuracy, sensitivity and specificity of 94.8%, 95.3 and 94.3%, respectively. This indicates that to enable a most accurate breast cancer detection information on tumor cellularity, metabolism and permeability is desirable.

It is worth noting that the model based on quantitative parameters only (i.e. ADC, MTT and SUVmax) also showed a good performance (accuracy: 93.2%).

Although the multiparametric ^{18}F -FDG PET/MRI AI-based radiomics model performed best, the performance was not statistically different from the clinical interpretation by expert readers. It has to be noted that while clinical interpretation achieved similar sensitivities (95.3% vs 100%), the multiparametric ^{18}F -FDG PET/MRI AI-based radiomics model achieved a higher specificity (94.3% vs 73.7%) highlighting the potential to reduce false positive findings and obviate unnecessary breast biopsies in benign breast tumors [29].

Several studies have been published on the use of AI applied to MRI for breast cancer diagnosis, mainly aiming at increasing its relatively low specificity, compared to the high sensitivity, with accuracy values ranging from 0.728 to 0.920 [33–37]. Similar to our work, the group of Zhang et al. also explored the possibility to improve the accuracy of the ML classifier combining radiomics features extracted from both morphological and functional contrast-enhanced and diffusion kurtosis MRI images of 207 histologically proven breast lesions. They found that the model based on radiomics features from T2-w, DKI and quantitative DCE pharmacokinetic parameter maps had the best discriminatory ability for benign and malignant breast lesions (AUC = 0.921) [33]. Radiomics coupled to machine learning analysis applied to DCE-MRI, including both radiomics features and clinical data, also proved to be accurate in the characterization of < 1 cm breast lesions in ninety-six high-risk BRCA mutation carriers, with a diagnostic accuracy of 81.5%, significantly higher than qualitative morphological assessment with BI-RADS classification (AUC 53.4%) [37]. The usefulness of a multiparametric MRI approach was explored in a recent study by Tsarouchi et al. [38]. DCE-MRI and DWI images of 85 breast lesions were analyzed for the extraction of first order and texture features for the assessment of image heterogeneity and breast cancer diagnosis. Random forest resulted as the best performing algorithm (accuracy 91.67%), combining both DCE-MRI and DWI parameters in a multiparametric assessment [38].

Regarding PET imaging, the role of this functional technique has been explored in breast cancer mainly for prognostic/therapeutic purposes, particularly in the early prediction of the response to neoadjuvant chemotherapy [39–41]. In a recently published study, the usefulness of radiomics and ML applied to PET/CT to differentiate breast carcinoma from lymphoma was investigated in a small number of lesions (19 breast lymphoma and 25 breast cancer lesions) [42]. Different predictive models were built using combinations of clinical data, quantitative parameters (SUV), radiomics features (first and second order parameters extracted from both PET and CT images) and CT images. Models based on clinical data, SUV and PET radiomics features as well as on clinical data and CT radiomics features resulted as the most accurate ones with AUC of 0.806 and 0.759 in the validation cohort, respectively [42]. In an experimental study by Vogl et al. conducted on 34 breast lesions, a computer-aided segmentation and diagnosis (CAD) system was developed for automated lesion segmentation and classification (benign vs malignant) using separately acquired MRI and ^{18}F -FDG PET/CT images [43]. The CAD system

achieved a Dice similarity coefficient of 0.665 for lesion segmentation and AUC of 0.978 for breast cancer diagnosis. While PET and DWI features were found to improved DCE-MRI segmentation performance, such improvement was not observed for lesion characterization[43].

Limitations of our study have to be acknowledged. Firstly, our study is limited by the small sample size and the unbalanced distribution of benign and malignant breast lesions, with relevant implications for specificity. To overcome the limitation of the relatively small sample size, especially regarding benign lesions, we opted for performing an internal 5-fold cross validation which is proven to be robust in such cases [44]. The unbalanced distribution of benign and malignant tumors is related to this study being conducted at a single tertiary care cancer centre and the inclusion of BI-RADS 0, 4–5 lesions with a clinical indication for performing a breast ^{18}F -FDG PET/MRI. We addressed this limitation by using a well-established adaptive synthetic sampling to balance the two classes. Another limitation is the lack of external validation of the proposed AI-model, which may limit generalizability. To date there is only a limited number of centers world-wide that have clinical synchronized PET/MRI scanners and perform clinical breast imaging and the collaboration with a different institution to validate our models is in development. Furthermore, two dynamic sequences were used before and after MRI update. However, acquisition parameters were kept similar and AI techniques are meant to be applied to images acquired with different acquisition protocols; indeed, this issue did not affect the good accuracy of the ML classifier. Finally, several cases had to be excluded from the analysis as at least one among DCE-MRI, DWI or PET images was not suitable for the extraction of quantitative parameters or for the radiomic analysis, in order not to impair data's reliability. Despite this stringent exclusion criterion, and also considering the limited access to such an advanced imaging technique, an adequate number of breast lesions was finally included which allowed the achievement of a good performance in the AI discrimination task.

In conclusion, a synchronized multiparametric ^{18}F -FDG PET/MRI AI-based radiomics model allows accurate differentiation of benign and malignant breast lesions with a performance comparable to that of expert readers. Initial data indicate that AI-enhanced functional and metabolic breast imaging has the potential to improve breast cancer diagnosis while simultaneously reducing the number of biopsies without missing cancers.

Larger multi-center studies are planned to validate the multiparametric ^{18}F -FDG PET/MRI AI-based radiomics model. Our results indicate that AI-enhanced functional and metabolic breast imaging showed an excellent performance, higher than expert readers, thus having the potential to assist human readers in correctly classifying suspicious breast lesions and obviate unnecessary invasive breast procedures.

Declarations

Funding: This study received funding from H2020 - Research and Innovation Framework Programme PHC-11-2015 # 667211-2, Jubiläumsfonds of the Austrian National Bank # Nr. 18207, and Nr. 17186 the NIH/NCI Cancer Center Support Grant (P30 CA008748), the Breast Cancer Research Foundation and Susan G. Komen.

Conflicts of Interest

Financial Interests:

Katja Pinker received payment for activities not related to the present article including lectures and service on speakers bureaus and for travel/accommodations/meeting expenses unrelated to activities listed from the European Society of Breast Imaging (MRI educational course, annual scientific meeting), the IDKD 2019 (educational course), and Siemens Healthineers.

T. Helbich received payment for activities not related to the present article including lectures and service on speakers bureaus and for travel/accommodations/meeting expenses unrelated to activities listed from the European Society of Breast Imaging, the IDKD 2019 (educational course), and Siemens Healthineers, Guerbet, Novomed.

Pascal Baltzer received payment for activities not related to the present article including lectures and service on speakers bureaus and for travel/accommodations/meeting expenses from the European Society of Breast Imaging (MRI educational

course, annual scientific meeting) and Siemens Healthineers.

Paola Clauser received payment for activities not related to the present article including lectures and service on speakers bureaus and for travel/accommodations/meeting expenses from the European Society of Breast Imaging (MRI educational course, annual scientific meeting) and Siemens Healthineers.

Non-financial interests: none

Acknowledgment: Valeria Romeo was supported by the Bracco Fellowship, an initiative of the European School of Radiology (ESOR) in partnership with the European Society of Radiology (ESR)

Availability of data and material: the datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability: not applicable

Ethics approval: the study was approved by the institutional review board (Medical University of Vienna) and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards

Consent to participate: informed consent was obtained from all individual participants included in the study.

Consent for publication: The authors affirm that human research participants provided informed consent for publication of the images in Figures 2 and 3.

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Figures

Figure 1

Flow-chart of the patient selection process. Pts= patients; US=ultrasound; MG=mammography

Figure 2

ROI placement over breast lesions on DCE-MRI, ADC and PET images for the extraction of quantitative parameters.

Figure 3

Example of tumor segmentation in a 62-year-old patient with a stage IV invasive ductal carcinoma (G3, Luminal B) of the right breast. 3D ROIs were drawn over breast lesions on DCE-MRI (A), T2-w (B), DWI (C) and PET (D) images using a semi-automated method.

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