PET/CT hybrid imaging vs contrast-enhanced MRI with diffusion-weighted imaging in the diagnosis of liver deposits in patients with breast cancer

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Received 07 June 2020
Revised 28 June 2020
Accepted 20 July 2020
Published 12 September 2020

Journal of Current Medical Research and Practice
2021, 6:415–422

Introduction
Patients with breast cancer often undergo positron emission tomography-computed tomography (PET-CT) examinations for a multitude of reasons, such as staging, localizing metastasis, or early detection of recurrence. Liver deposits may present as incidental findings in such patients with underlying breast cancer. Accurate detection and diagnosis of such lesions may pose a challenge owing to the background activity of the liver.

Objective
The aim was to compare between PET-CT hybrid imaging and contrast-enhanced magnetic resonance imaging with diffusion-weighted imaging (DWI) in their capabilities to detect and/or characterize hepatic lesions encountered in patient with breast cancer, as well as to determine the cutoff values for standard uptake value with apparent diffusion coefficient.

Materials and methods
This study included 45 patient with breast cancer referred with hepatic focal lesions. All patients were females, with an age range of 30–69 years. They all underwent contrast-enhanced PET-CT and contrast-enhanced MRI with DWI. Both examinations were reviewed independently, and the results were either correlated with histopathological results of the lesions or imaging follow-up.

Results
On patient-based analysis, dynamic MRI with DWI has shown superiority over contrast-enhanced PET/CT in detecting and characterization of hepatic metastases, with sensitivity, specificity, and accuracy of 96.4, 100, and 97.7% respectively, compared with 75, 100, and 84.4%, respectively, attributed to PET/CT. Cutoff value of apparent diffusion coefficient value was 1.331×10^{-3} mm^2/s with 98.1% accuracy. SUV_{max} was chosen as the main index, and a cut-off value was determined to be more than 3.84, with an accuracy of 79.14%.

Conclusion
PET/CT showed competitive results in comparison with MRI and might present itself to be a useful tool in detecting and characterizing hepatic focal lesions in patient with breast cancer.

Keywords:
breast cancer, diagnosis, diffusion, liver deposits, MRI, positron emission tomography-computed tomography

J Curr Med Res Pract 6:415–422

2357-0121

Introduction

The liver is the most common site for metastatic blood spread, as hepatic metastatic focal lesions are known to be more common than primary hepatic tumors [1]. Hepatic liver metastases can result from a variety of neoplasms, most commonly from colorectal, breast, or lung cancers, with the liver being one of the most commonly involved organs in patient with breast cancer [2].

Liver metastasis is observed as an ominous sign with severely diminished average survival, in addition to rendering the patient as nonoperable, so chemotherapy becomes the treatment of choice [3].

It is very critical to patient prognosis and management to establish an early method of diagnosis and accurate characterization of liver metastases, as well as assessing therapy response with accuracy and reproducibility. Therefore, adept radiological modality should ensure high sensitivity and specificity, ensure minimal invasiveness, and be able to detect extrahepatic lesions [4].

^{18}F-FDG positron emission tomography-computed tomography (PET/CT) has been established to have high accuracy and sensitivity to detect hepatic metastases. It showed superiority over contrast-enhanced computed

tomography in its ability to detect untreated liver metastases. So adding FDG-PET in the algorithm of detecting hepatic metastasis can have a wide effect on staging and proper selection of patients for resection of liver metastasis [5].

A substantial number of studies have discussed the difference between using diffusion-weighted magnetic resonance imaging (DWI-MRI) and T2-weighted imaging to detect hepatic focal lesions (HFLs). These studies showed much improved HFL detection on DWI sequences. To identify solid HFLs is a challenge owing to the overlapping conventional anatomical appearance, diffusion appearances, and the apparent diffusion coefficient (ADC) values difference between benign and malignant lesions [6]. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a complementary imaging technique to other functional imaging modalities such as PET and MR spectroscopy, where it emphasizes the physiological aspect of the lesion rather than its anatomical appearance. DCE-MRI is complementary to DWI-MRI to provide functional as well as detailed morphological information in the same setting [7].

Materials and methods

In this prospective study, we included 45 patient with breast cancer, all with pathologically proved-breast cancer referred with HFLs. We did not have age/sex criteria; however, we excluded patients with double malignancy in addition to breast cancer. Relevant history and written consent were acquired from patients. This study was approved by the Ethics Committee of National Cancer Institute, Cairo University, and Faculty of Medicine, Asyut University, and all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. All examinations were performed at the National Cancer Institute in Cairo.

Study design

This is an observational prospective study done at the Diagnostic Radiology and Nuclear Medicine units at the National Cancer Institute in Cairo. The study was approved and monitored by the Medical Ethics Committee, Assiut Faculty of Medicine, IRB#16151154. All patients underwent dynamic MRI with diffusion after contrast media injection, as well as PET/CT examination after injection of radioactive 18F-fluorodeoxyglucose.

Protocol for MRI imaging

MRI was performed on a 1.5 T Siemens MR system (Avanto; Siemens Healthcare, Erlangen, Germany). Axial in-phase and opposed-phase gradient-echo T1-weighted, fat-suppressed turbo spin-echo T2-weighted, and half-Fourier acquisition single-shot turbo spin-echo (HASTE) T2-weighted imaging studies of the liver were performed.

DW-MRI was performed using free-breathing, multiple averaging techniques. Four b values were employed (b0, b50, 100, and 400 s/mm^2) to enable accurate ADC values of liver deposits to be calculated. Following IV gadolinium injection, dynamic contrast-enhanced axial T1-weighted MRI was performed in arterial, portovenous, and interstitial phases of contrast enhancement using a volume-interpolated breath-hold examination.

PET/CT was performed on GE PET/CT system (Discovery 610 16-slice; GE Healthcare, Chicago, Illinois, USA). Regarding the breathing patterns during CT acquisition, for PET/CT, the position of the diaphragm should match as closely as possible on the PET emission and the CT transmission images.

Protocol for PET imaging

Emission images are obtained at least 45 min following radiopharmaceutical injection. Emission image acquisition time varies from 2 to 5 min or longer per bed position for body imaging and is based on the administered activity, patient body weight, and the sensitivity of the PET tomography (as determined largely by detector composition and acquisition method).

Semiquantitative estimation of tumor glucose metabolism is done using the standardized uptake value (SUV), which is based on relative lesion radioactivity measured on images corrected for attenuation and normalized for the injected dose and body weight, lean body mass, or body surface area.

Lesion-based analysis

The count of the lesions, as single/multiple, as well as actual counting of lesions on the PACS workstation (ADW) was done. Based on the lesion FDG uptake, metabolic activity was represented as avid or non-avid lesions. Lesion enhancement pattern was assessed as hyper-enhancing or hypo-enhancing with regards to the MRI contrast material. Quantitative analysis was done using maximum standardized uptake value of the lesion (SUV_{max}) for the PET/CT, and as for the DW-MRI image set, mean ADC value is measured on the b = 400 s mm^2 image.

Statistical analysis

The data were statistically described in terms of mean ± SD and analyzed using Student's *t*-test. *P* values less than 0.05 was considered statistically significant. Receiver operating characteristic curves (ROC) are used to represent sensitivity and specificity of MRI and PET/CT performance, as well as cut-off values for ADC and SUV_{max}. All statistical calculations were performed and analyzed using the Statistical Package for the Social Sciences (Version 23; SPSS Inc., Chicago, Illinois, USA) (Fig. 1).

Results

Our study included 45 patients. All were females, with a mean age of 50 years (range: 30–69 years) (Tables 1 and 2).

Histopathology was reported in 15 of the patients and showed that 13 HFLs turned out to be metastases, and two were adenoma.

Follow-up imaging of the patients, by either dynamic MRI with DWI or contrast-enhanced CT, was considered the gold standard to determine the progression, or regression of the lesions, acting as the reference for diagnosis.

Of the 45 patients included in the study, 17 were finally diagnosed as having benign lesions (10 patients with hemangioma, three with regenerating nodules, two with cysts, and two with adenoma), and 28 were diagnosed as having malignant lesions (metastases). According to RECIST, nine patients (40.9%) showed a significant increase in size, whereas 13 other patients showed an insignificant increase.

A total of 17 patients were diagnosed as having benign lesions by both MRI and PET/CT, whereas 20 patients were declared to have malignant lesions by both, unanimously.

Regarding the final results of imaging follow-up (Gold standard), PET/CT was shown to have a sensitivity, specificity, and accuracy of 75, 100, and 84.4%, respectively, whereas MRI showed sensitivity, specificity, and accuracy of 96.4, 100, and 97.7%, respectively.

The cutoff value of ADC value (Fig. 2) was found to be 1.331, and showed sensitivity, specificity, and accuracy of 94.1, 96.4, and 98.1%, respectively. However, the cutoff value of SUV_{max} was found to be 3.84 and showed sensitivity, specificity, and accuracy of 64.3, 94, and 79.14%, respectively (Fig. 3).

Discussion

PET/CT application in patient with breast cancer has usually been confined to detection of extra-axillary involvement and distant metastasis, as its role in characterizing the primary tumor itself showed no superiority to other standard methods [8].

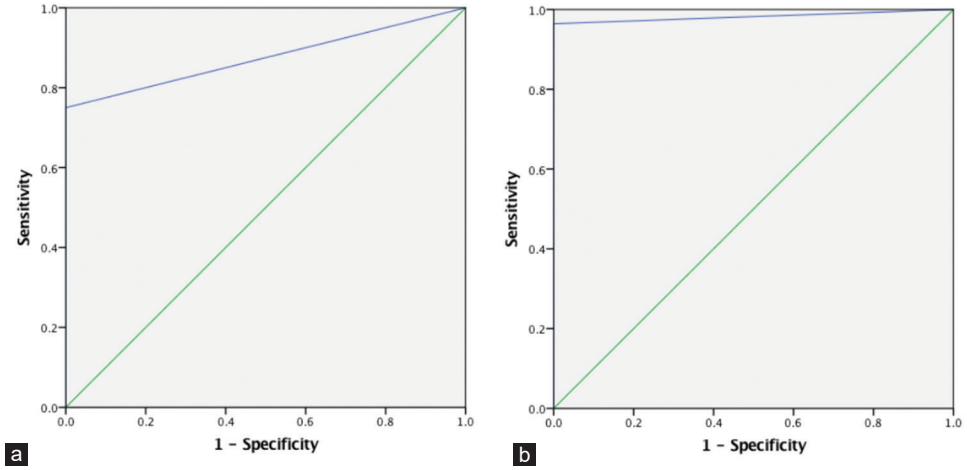
However, for the overall patient management, ^{18}F-FDG-PET/CT has the added advantage over MRI and CT of providing functional and molecular as well as anatomic information [9].

The liver is one of the commonest sites of metastatic spread from breast cancer, and the detection of

Table 1 Age of patients

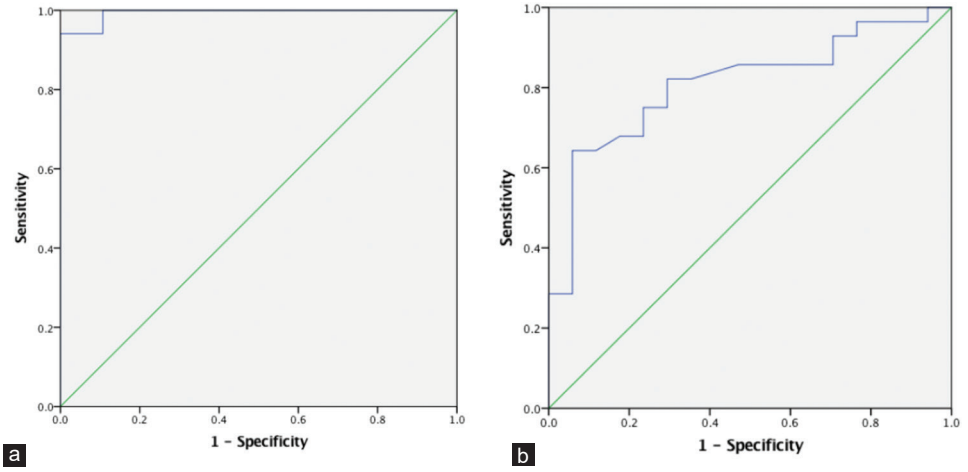
Age (years)	*n*=35 [*n* (%)]
<50	20 (44.4)
≥50	25 (55.6)
Mean±SD (range)	48.63±10.45 (30.0-69.0)

Figure 1



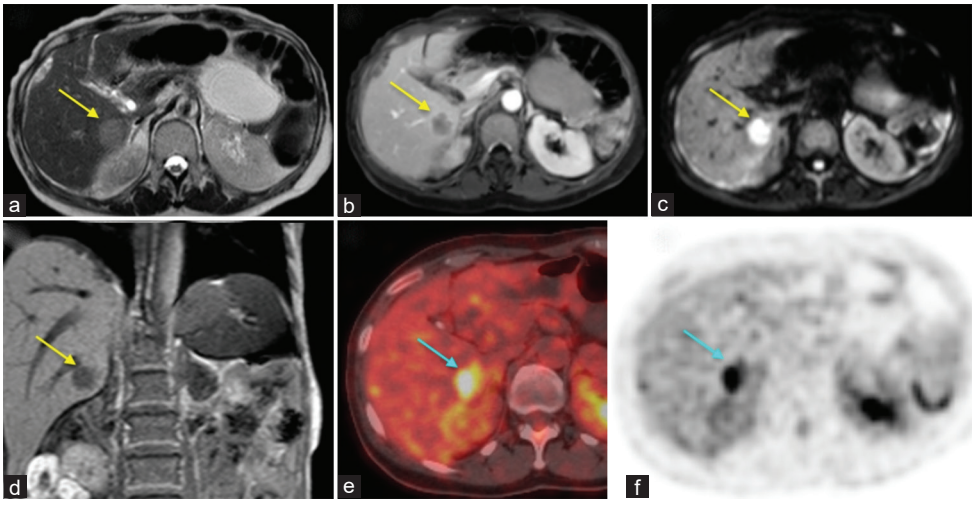
Receiver operating characteristic curve showing sensitivity and specificity of PET/CT (a) and MRI (b). PET-CT, positron emission tomography-computed tomography

Figure 2



Receiver operating characteristic curve showing cutoff value of ADC (a) and SUVmax (b). ADC, apparent diffusion coefficient.

Figure 3



A female patient who underwent right mastectomy presented with hepatic focal lesion (a) Precontrast MRI coronal T1WI shows hypointense lesion at segment VI (SIX) of the liver. (b) Axial postcontrast T1WI showed ring enhancement around a hypo-enhancing lesion. (c) DWI showed restriction at b value 50. (d) DWI showed persistent restriction at b value 400, with mean ADC of 0.56 mm2/s (yellow arrow). (e) Axial hybrid fused PET/CT showing avidity of the same lesion with high SUV uptake (WITH SUVma × 8.8). (f) Attenuated-corrected PET only image confirming activity in the same lesion (light blue arrow). ADC, apparent diffusion coefficient; DWI; PET, positron emission tomography

liver metastases in the diagnostic process is crucial owing to its effect on morbidity and mortality of the patients [10].

With its inherent high soft-tissue contrast, MRI has been found to be the most sensitive technique for the detection of liver metastases. With contrast-enhanced studies, liver lesions show MRI enhancement patterns similar to those obtained with contrast-enhanced CT [4].

Our study included 45 patients, where all were females, with a mean age of 50 years, with a wide range of 30–69 years. In all patients, the diagnosis of breast cancer has been established histopathologically.

This study is similar to a study by Salem and colleagues in 2015; they included 35 patients with indeterminate HFLs, where they compared hybrid techniques of PET/CT and PET/MRI. Moreover, they did not designate breast cancer as the sole primary malignancy, and so they had a much larger diversity of sexes, with 20% females and 80% males, compared with our (100% female), with a different range of age (40–71 years).

Contrast-enhanced (dynamic) MRI with DWI and PET/CT hybrid imaging were performed for all patients. However, the final diagnosis was based on histopathology in 15 patients (13 metastases and two adenomas), as well as using sequential various imaging modalities (including PET/CT, CT, and MRI) in follow-up imaging. A total of 17 patients were finally diagnosed with benign liver focal lesions, whereas 28 were malignant (28 patients were finally diagnosed

with metastases, eight patients had hemangiomas, three patients with regenerating nodules, two patients with cysts, and two patients with adenomas).

In their study, the diagnosis was confirmed by pathology in 13/35 patients (37%) and by clinical and radiological follow-up in 22/35 (63%). The pathology revealed HCC in 11 patients, lymphoma in one patient, and benign pathology in one patient. Overall, 22 patients were categorized as follows: malignant as 17 patients and benign as 5.

The classification of malignant lesions was based on evidence of disease progression in all 22 patients (Table 3).

Dynamic MRI with DWI has shown superiority over contrast-enhanced PET/CT, with sensitivity, specificity, and accuracy of 96.4, 100, and 97.7% respectively, compared with sensitivity, specificity, and accuracy of 75, 100, and 84.4%, respectively, for PET/CT. MRI and PET/CT had the same specificity in detection and characterization of hepatic metastases, whereas differed majorly in accuracy (97.7 and 84.4% of respectively); this is mostly attributed to the higher spatial resolution of MRI in general and the better soft-tissue contrast in comparison with PET/Ce-CT. Moreover, MRI uses DWI as well as the dynamic technique, which easily differentiate between malignant and benign lesions, thereby increasing the accuracy.

In comparison with the present study, the study done by Salem and colleagues in 2015, reported that PET/CT had sensitivity, sensitivity, and accuracy of 94, 75, and 90%, respectively, in detecting HFLs, with higher sensitivity (75%) and accuracy (84.4%) and much less specificity (100%) than ours. We notice that with regards to the few studies that have investigated the sensitivity of PET/CT in the detection of liver metastases, they reported values between 61 and 97%. Thereby, the sensitivity of PET/CT in our study falls within the reported rates [11].

In their study, the low sensitivity (68%) of PET alone in detecting HFL may be explained in part owing to that most of the included HFL were HCC. PET/Ce-CT using dedicated contrast-enhanced CT raised the sensitivity to 94%. Several studies have shown that the fusion of PET data with CT improves not only the sensitivity of PET but also its specificity [12].

The advantage of PET/CT over PET alone can be attributed to the fact that CT compensates for the low anatomic resolution of PET and the difficulty in lesion's localization as well as improving the diagnostic accuracy of nonspecific lesions with increased^{18}F-FDG uptake [13].

Table 2 PET/CT and MRI findings and lesion diagnoses

PET/CT findings			MRI findings		
Classification	Patients	Percentage	Classification	Patients	Percentage
Benign	24	53	Benign	18	40
Malignant	21	47	Malignant	27	60
FDG avidity	Patients	%	Qualitative DWI	Patients	%
Avid	18	40	Facilitated	15	33
None-avid	27	60	Restricted	30	67
Number of lesions	Patients	%	Dynamic Pattern	Patients	%
Single	27	60	Hyper-enhancing	17	38
Multiple	18	40	Hypo-enhancing	28	62
Diagnosis	Patients	%	Number of lesions	Patients	%
Metastasis	21	46.7	Single	21	47
Hemangioma	12	31.1	Multiple	24	53
Adenoma	4	8.9%	MRI diagnosis	Patients	%
Cyst	2	4.4%	Metastasis	27	60
Indeterminate	2	4.4%	Hemangioma	10	22.2
Regeneration nodule	2	4.4%	Adenoma	3	6.7

DWI, diffusion-weighted imaging; PET-CT, positron emission tomography-computed tomography.

Table 3 On patient-based analysis, sensitivity, specificity, PPV, NPV, and accuracy for Ce-MRI+DWI and PET/Ce-CT, in all patients

	FN	FP	TN	TP	Sensitivity	Specificity	PPV	NPV	ACC
Ce-MRI+DWI	1	0	17	27	96.4%	100%	100%	94.4	97.7%
PET/Ce-CT	7	0	17	21	75%	100%	100%	70.8	84.4%

ACC, accuracy; Ce-MRI+DWI, contrast-enhanced magnetic resonance imaging with diffusion-weighted imaging; FN, false negative; FP, false-positive; NPV, negative predictive value; PET/Ce-CT, positron emission tomography with contrast-enhanced computed tomography; PPV, positive predictive value; TN, true negative; TP, true positive.

A similar paper by Donati and colleagues in 2015 showed 76% sensitivity of PET/CT in detecting liver metastases; however, their study did not implement contrast-enhanced scans. We, as well, showed superior indices for MRI over PET/CT in detecting and characterizing hepatic lesions (Table 4).

In our lesion-based analysis, we divided the lesions into two groups: lesions less than 2 cm and lesions more than 2 cm. Accordingly, we determined the results of the whole sum of lesions, which was found to be 119 lesions, and of them 29 were benign, whereas 90 were malignant lesions. Contrast-enhanced MRI with diffusion showed sensitivity, specificity, and accuracy of 98.8, 100, and 99% respectively, whereas PET/CT showed slightly lower indices, with 92.2% sensitivity, specificity of 100%, and accuracy of 94%, which complies with the findings of PET/CT done in the study by Salem and colleagues, whereas our contrast-enhanced MRI with diffusion indices were slightly higher, as they recorded sensitivity, specificity, and accuracy of 94, 99, and 94% respectively, mostly owing to their much larger inclusion criteria, as their study included different kinds of primary neoplasms involved, as well as the inclusion of a double primary malignancy, which is not the case in our study, which is confined to breast cancer being the sole primary neoplasm, as well as excluding double primary, which in turn excludes HCC and CCC, and others (Table 5).

Lesions measuring less than 2 cm were far less in number than lesions more than 2 cm, and showed lower indices with regards to both contrast-enhanced MRI with diffusion and PET/CT, with the former showing sensitivity, specificity, and accuracy of 91, 100, and 95%, respectively, and the latter showing sensitivity, specificity, and accuracy of 74, 100, and 87.5%, respectively. However, our classification of lesions does not comply with that in the study by Salem and colleagues, as they divided the lesions into three groups: lesions less than 1 cm, lesions 1–2 cm, and lesions more than 2 (Table 6).

However, for lesions measuring more than 2 cm, contrast-enhanced MRI with diffusion showed identical results to our gold standard (imaging follow-up), as well as the same size-group, as in the study by Salem and colleagues PET/CT indices were slightly lower than MRI with sensitivity, specificity, and accuracy of 95.6, 100, and 96% respectively, and these indices go along very closely with those in the same size-group as in the study by Salem and colleagues.

The mean ADC values of our focal lesions ranged from 0.32 to 2.69 × 10^{-3} mm^2/s with mean 1.3 × 10^{-3} mm^2/s, and according to the literature, ADC value of liver metastases is in the range of 0.94-2.8569 × 10^{-3} mm^2/s [14].

We determined a cutoff value of 1.331 × 10^{-3} mm^2/s between malignant and benign lesions, with 98.1% accuracy, which is similar to a study done by Jahic and colleagues, which provided a cut-off value of 1.341 × 10^{-3} mm^2/s. Taouli and Koh reported the results of various studies in which the value of ADC cut-off ranged from 1.47 to 1.63 × 10^{-3} mm^2/s, which

Table 4 On lesion-based analysis, sensitivity, specificity, PPV, NPV and accuracy for Ce-MRI+DWI and PET/Ce-CT, in all 119 hepatic focal lesions

	FN	FP	TN	TP	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)
Ce-MRI+DWI	1	0	29	89	98.8	100	100	96.6	99
PET/Ce-CT	7	0	29	83	92.2	100	100	80.5	94

ACC, accuracy; DWI, diffusion-weighted imaging; FN, false negative; FP, false-positive; NPV, negative predictive value; PET/Ce-CT, positron emission tomography with contrast-enhanced computed tomography; PPV, positive predictive value; TN, true negative; TP, true positive.

Table 5 On lesion-based analysis, sensitivity, specificity, PPV, NPV, and accuracy for Ce-MRI+DWI and PET/Ce-CT, in all 40 hepatic focal lesions measuring less than 2 cm

	FN	FP	TN	TP	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)
Ce-MRI+DWI	2	0	18	20	91	100	100	90	95
PET/Ce-CT	5	0	18	17	74	100	100	78	87.5

DWI, diffusion-weighted imaging; FN, false negative; FP, false-positive; NPV, negative predictive value; PET/Ce-CT, positron emission tomography with contrast-enhanced computed tomography; PPV, positive predictive value; TN, true negative; TP, true positive.

Table 6 On lesion-based analysis; sensitivity, specificity, PPV, NPV, and accuracy for Ce-MRI+DWI and PET/Ce-CT, in all 79 hepatic focal lesions measuring more than 2 cm

	FN	FP	TN	TP	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ACC (%)
Ce-MRI+DWI	0	0	10	69	100	100	100	100	100
PET/Ce-CT	3	0	10	66	95.6	100	100	77	96

DWI, diffusion-weighted imaging; FN, false negative; FP, false-positive; NPV, negative predictive value; PET/Ce-CT, positron emission tomography with contrast-enhanced computed tomography; PPV, positive predictive value; TN, true negative; TP, true positive.

can be used for optimal differentiation of benign from malignant lesions. Cut-off ADC value that we reported from 1.331×10^{-3} mm^2/s is slightly lower than the average of the aforementioned study but higher than the one of Cieszanowski and colleagues, which was 1.25×10^{-3} mm^2/s. Filipe and colleagues used the cut-off value of 1.43×10^{-3} mm^2/s when differentiating benign from malignant lesions and have concluded that the ADC value of malignant lesions is significantly lower compared with benign lesions. Testa *et al.* [15] obtained the results that showed a statistically significant difference between benign and malignant lesions with the cutoff value of 1.2×10^{-3} mm^2/s, and the accuracy of 71%.

Several possible reasons explain these differences, including the use of different hardware, the lack of standardized protocols for image acquisition (using different *b* values), different methods for calculating ADC, and different population of patients. The growing use and importance of DWI will certainly with future development contribute to uniformity of parameters for image acquisition.

As for SUV quantification, the ROC curves and AUC of SUV_{ratio} (to the liver) in all patients were plotted, and ROC analysis showed that the optimal cut-off value in all patients was 1.449 for SUV_{ratio} and 0.725 for AUC, with an accuracy of 78.3% It should be noted that the physiologic liver uptake of FDG is quite variable and the SUV value can change depending on a series of variables such as the injected activity, the time elapsing from the dose injection to the acquisition time, and so on. Consequently, we selected SUV_{ratio} as a criterion, preferring it to SUV_{max}, SUV_{mean}, and SUV_{ratio} of the lesion to the mediastinum. However, in our study, analysis of SUV_{ratio} (to the liver) was not compared with the age group of patients, as in the study by Xia *et al.* [16], where they reported different cut-off values or SUV_{ratio} in different age groups, as ROC analysis showed that the optimal cut-off value in all patients, younger group, middle-aged group, and elderly group was 1.25, 1.17, 1.45, and 1.25 for SUV_{ratio}, and 0.856, 0.962, 0.650, 0.973 for AUC.

One false-negative result was found by MRI examination, where the lesion was diagnosed as adenoma and was found to be metastases by follow-up imaging owing to an increase in size.

Seven false-positive results were found by PET/CT examination. It has long been recognized that active benign pathological conditions, such as inflammatory and infective processes, may also show increased accumulation of ^{18}F-FDG. This is largely owing to the enhanced glycolytic metabolism that accompanies inflammatory cellular infiltrates, incorporating activated macrophages, monocytes, and polymorphonuclear cells, which are all actively involved in the recruitment, activation, and healing phases of tissue inflammation [17].

Our study is not free of limitations, starting with a limited number of patients. There was not enough histopathological sample of every liver lesion. We tried to overcome this drawback by using a reference standard taking different parameters into account, including all available imaging tools, histopathology (when available), and imaging follow-up. Moreover, PET/CT comprised a whole-body protocol; however, a few patients could not undergo contrast-enhanced study owing to raised renal chemistry and previously reported hypersensitivity.

Conclusion

Despite its limitations, our study positively demonstrates the high potential of PET/CT, as even in the current setting, PET/CT showed competitive results in comparison with MRI. ^{18}F-FDG-PET/CT might present itself to be a useful tool in detecting and characterizing HFLs in patient with breast cancer.

Recommendations

For the confirmation and augmentation of the present results, larger studies are needed.

Acknowledgements

The authors would like to acknowledge the Departments of Nuclear Medicine and Diagnostic Radiology at National Cancer Institute in Cairo for their support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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