

Staging performance of whole-body DWI, PET/CT and PET/MRI in invasive ductal carcinoma of the breast

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Abstract. The aim of the present study was to evaluate the performance of whole-body diffusion-weighted imaging (WB-DWI), whole-body positron emission tomography with computed tomography (WB-PET/CT), and whole-body positron emission tomography with magnetic resonance imaging (WB-PET/MRI) in staging patients with untreated invasive ductal carcinoma of the breast. Fifty-one women with newly diagnosed invasive ductal carcinoma of the breast underwent WB-DWI, WB-PET/CT and WB-PET/MRI before treatment. A radiologist and a nuclear medicine physician reviewed in consensus the images from the three modalities and searched for occurrence, number and location of metastases. Final staging, according to each technique, was compared. Pathology and imaging follow-up were used as the reference. WB-DWI, WB-PET/CT and WB-PET/MRI correctly and concordantly staged 33/51 patients: stage IIA in 7 patients, stage IIB in 8 patients, stage IIIC in 4 patients and stage IV in 14 patients. WB-DWI, WB-PET/CT and WB-PET/MRI incorrectly and concordantly staged 1/51 patient as stage IV instead of IIIA. Discordant staging was reported in 17/51 patients. WB-PET/MRI resulted in improved staging when compared to WB-PET/CT (50 correctly staged on WB-PET/MRI

vs. 38 correctly staged on WB-PET/CT; McNemar's test; $P < 0.01$). Comparing the performance of WB-PET/MRI and WB-DWI (43 correct) did not reveal a statistically significant difference (McNemar test, $P = 0.14$). WB-PET/MRI is more accurate in the initial staging of breast cancer than WB-DWI and WB-PET/CT, however, the discrepancies between WB-PET/MRI and WB-DWI were not statistically significant. When available, WB-PET/MRI should be considered for staging patient with invasive ductal breast carcinoma.

Introduction

Imaging plays a pivotal role in the staging and management of breast cancer patients. For instance, breast MRI is used in stage I disease to rule out additional sites of malignancy that might be occult at mammography. Other imaging techniques, such as bone scans, abdominal CT or MR and chest CT are recommended in stage I-II disease in patients with abnormal liver function tests, alkaline phosphatase, bone pain, abnormal physical examination, localized bone pain, or with abdominal or pulmonary symptoms and in stage IIIA disease. PET/CT is considered optional for stage IIIA, stage IV and recurrent disease (1).

Growing evidence suggests that PET/CT may detect distant metastases (sensitivity of 78-100%) over conventional non-metabolic imaging modalities (sensitivity of 37-78.6%) (2). Specifically, a recent meta-analysis showed that the detection of distant metastases increases from 1.2 to 3.3-34.3% if PET/CT is added to conventional imaging for the staging of patients with stage II breast cancer (2).

The use of diffusion-weighted imaging (DWI) MRI has recently increased as a potential alternative to PET/CT for whole-body staging, prognosis and treatment response assess-

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ment of several malignancies, including malignancies of the breast. Some studies suggest comparable performance of DWI to PET in disease staging with the added advantages of lack of radiation, widespread availability and no additional costs over those related to operation of a normal MR scanner (3,4). Other studies have found similar sensitivity of DWI to metabolic imaging at the expense of reduced accuracy (4-8). Therefore in this study we also explored, as described below, the performance of DWI standing alone.

In recent years, PET/MRI has emerged as a new tool with significant clinical potential for the evaluation and management of cancer patients (9-12). PET/MRI allows for improved diagnosis and staging accuracy in a number of primary and metastatic cancers, including lymphoma, head and neck, liver and bone tumors (13-19). Moreover, data suggest that PET/MRI might play a superior role in affecting oncologic management decisions, compared to PET/CT (20,21).

Available data supporting the use of PET/MRI in the evaluation of breast cancer patients remain limited but has been promising (22-25). While primary lesion detection has been previously shown to be equivalent between PET/CT and PET/MRI, PET/MRI might improve detection of metastatic lesions, when compared to PET/CT and might lead to management changes in up to one third of the patients, when compared to initial clinical staging (23,26). Other studies have also shown a role of combining PET and MRI in characterizing tumor pathology and predicting response to therapy (27-30).

The aim of the present study was to compare the staging performance of whole body diffusion-weighted imaging (WB-DWI), whole body positron emission tomography with computed tomography (WB-PET/CT), and whole body positron emission tomography with magnetic resonance imaging (WB-PET/MRI) in staging breast cancer patients with newly diagnosed invasive ductal carcinoma. To the best of our knowledge, this is the first study concurrently assessing the performance of these three modalities in the same patient population.

Materials and methods

Study design and patient enrollment. A retrospective HIPAA-compliant study was approved by the institutional review board. Informed consent, that included the possibility of subsequent usage of imaging and clinical data for imaging research purposes, was obtained from patients before undergoing same day PET/MRI and PET/CT. Inclusion criteria consisted of: i) new, untreated biopsy-proven invasive ductal carcinoma of the breast; ii) female; iii) 18 years of age or older; iv) clinical contrast enhanced (CE) PET/CT study; v) same day CE-PET/MRI study; and vi) availability of pathology or at least two-years imaging follow-up. Patients were excluded if they met any of the following criteria: i) pregnancy; ii) blood glucose >140 mg/dl; iii) contraindication to MR imaging; and iv) inclusion in previous PET/MRI studies.

Imaging protocols

PET/CT imaging. PET/CT images were acquired ~1 h following FDG administration, mean FDG activity of 4.44 MBq/kg of body weight. Whole body images were acquired using a 64-detector row PET/CT scanner (Gemini TF; Philips

Medical Systems, Best, The Netherlands) with time-of-flight capability. Automatic attenuation correction was performed using attenuation correction maps generated from CT imaging. Both non-contrast and contrast-enhanced CT images were collected. Iopamidol (Iopamiro 370; Bracco Imaging, Milan, Italy) was injected intravenously using a power injector at a rate of 2 ml/sec with a dose of 80 ml in patients weighing <80 kg; and a dose of 100 ml in patients weighing >80 kg. Bolus care function was used to acquire diagnostic quality arterial phase images of the upper abdomen, portal venous phase images of the whole body and delayed phase of the abdomen and pelvis.

PET/MRI imaging. PET/MRI images were acquired using a Biograph mMR imager (Siemens Healthcare, Erlangen, Germany) with a 16-channel head and neck surface coil and three or four 12-channel body coils, depending on the patient's height. The coils were combined to form a whole-body coil using total imaging matrix technology. PET/MRI images were collected ~1.5 h following FDG injection. The following MRI sequences were obtained concurrently with PET: axial DWI (b-values 50, 400 and 800 s/mm²), coronal short tau inversion recovery (STIR), coronal T1-weighted Dixon, axial T2 weighted half Fourier acquired single-shot turbo spin echo (HASTE). Contrast enhanced-axial and coronal T1-weighted fat saturated (VIBE, volume interpolated breath-hold examination) images were acquired after PET completion. PET attenuation correction was performed using the two-point Dixon sequence. For contrast-enhanced MR imaging, 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma, Berlin, Germany) was injected at a rate of 3 ml/sec followed by the same volume of saline at the same rate, using a power injector. The total time of PET/MRI imaging was ~1 h.

Image post-processing. PET/CT image post-processing was performed using a dedicated workstation (Extended Brilliance Workstation Philips). Post-processing of PET/MRI images was done using a Syngovia workstation (Siemens Healthcare). Image post-processing consisted of image co-registration and fusion. Images were archived using the IDS7 image archiving and communication system (Sectra, Linköping, Sweden).

Image interpretation. WB-PET/CT, WB-DWI standing alone, WB-PET/MRI that also included DWI and ADC maps, were randomly presented and evaluated separately, at least 6 weeks apart, in consensus by a radiologist (OAC) with 17 years of experience in MR and 5 years in nuclear medicine and a nuclear medicine physician (AS) with 33 years of experience in nuclear medicine and 20 years in MR. Specifically, they searched for the occurrence, number and location of metastatic lesions and recorded for each patient the disease stage, based on each modality (WB-PET/CT, WB-DWI and WB-PET/MRI) according to the TNM staging (31). A combination of biopsy, surgical pathology and 24-month follow-up data were used to define the ground truth pathologic disease stage for each patient. Readers were blinded to the final clinical/pathologic stage. Studies for an individual patient were considered to be concordant if the stage derived from all three imaging modalities were in agreement, otherwise it was considered discordant. A modality stage was defined correct if in agreement with the

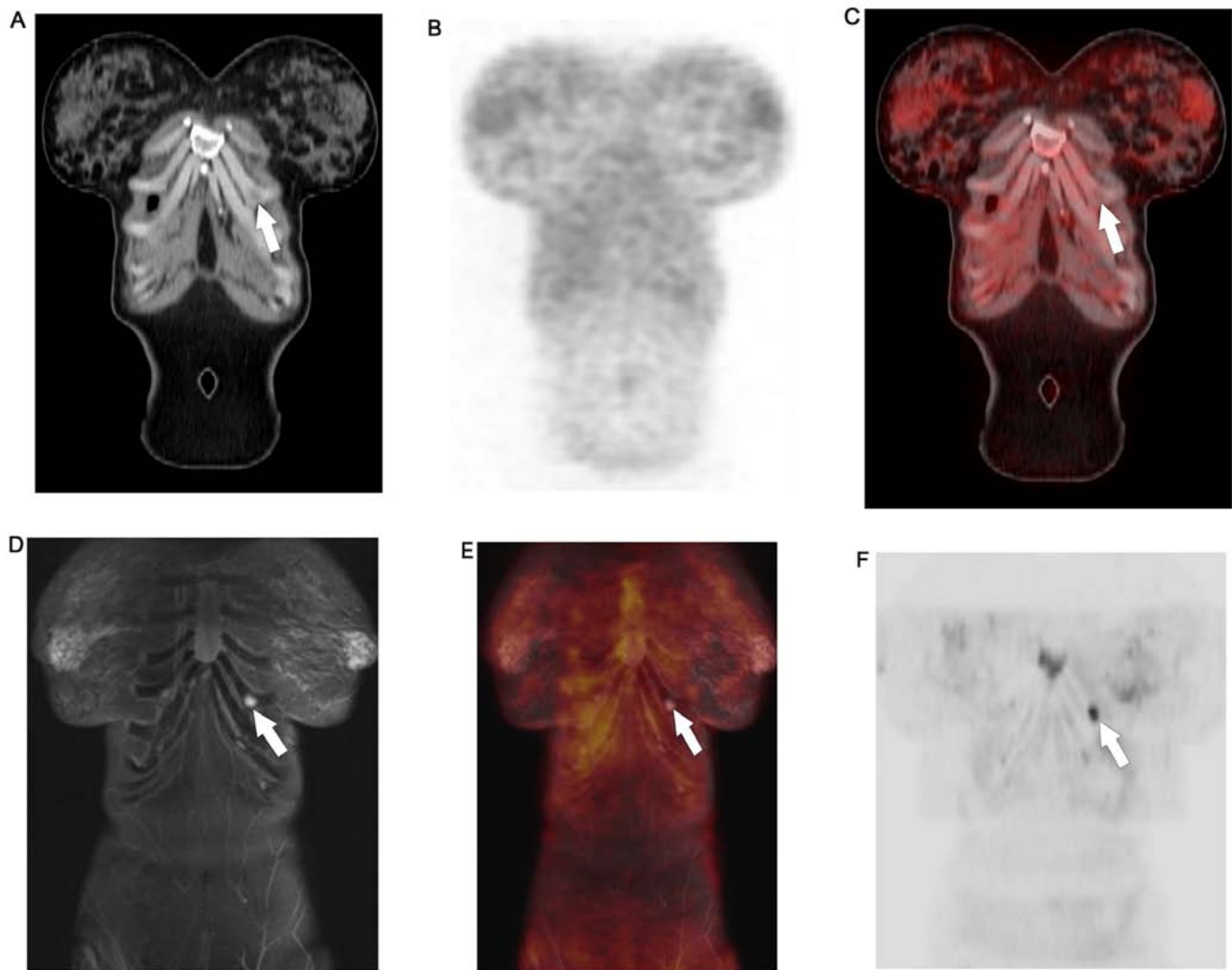


Figure 1. A 63-year-old female with stage IIB breast cancer. Coronal images from CT (A), PET (B), fused PET/CT (C), short tau inversion recovery (STIR) (D), fused PET/STIR (E), and inverted gray scale coronal DWI (F). This patient was correctly staged by PET/CT and PET/MRI, but misclassified as stage IV by DWI (arrow) due to a cartilaginous island in a left anterior rib that retained high signal intensity on the 800-b-value diffusion-weighted images. The lesion did not exhibit increased uptake on PET and did not demonstrate aggressive tumor features on CT or MR anatomic imaging.

clinical/pathological stage, otherwise it was considered incorrect.

Standard of reference. Pathology served as primary standard of reference. In the case of non-availability of pathology, imaging follow-up, lasting at least two years, served as secondary standard of reference.

Statistical analysis. The three methods (WB-PET/CT, WB-DWI and WB-PETMR) were compared pairwise using the McNemar's test, with Bonferroni adjustment for multiple comparisons.

Results

Patient demographics. A total of 191 patients with non-treated ductal invasive breast cancer underwent same-day PET/CT and PET/MRI imaging between February 2012 and December 2015. One hundred and forty patients were excluded for the following reasons: 63 for having been included in previous

PET/MRI studies with possibility of patient recall by the readers and 77 for absence of follow-up or pathology confirmation. Therefore, the final population consisted of 51 patients. The average age of study participants was 53 years with a standard deviation of 14 years (age range, 20-71 years). Final disease stage was IIA in 8 patients, IIB in 12, IIIA in 4, IIIC in 7 and stage IV in 20 patients.

Staging by standard of reference. Pathology served as standard of reference for 42 patients: 31 patients with stages II and III, 6 patients with oligometastatic stage IV, 5 patients with polymetastatic stage IV.

Follow-up imaging lasting ≥ 24 months served as standard of reference for 9 patients with polymetastatic stage IV.

Final staging was stage IIA 1 patient; stage IIB 12 patients; stage IIC 7 patients; stage IIIA 4 patients; stage IIIC 7 patients; and stage IV 20 patients.

Classification concordance. Thirty-three patients (65%) were correctly and concordantly staged by WB-PET/CT, WB-DWI

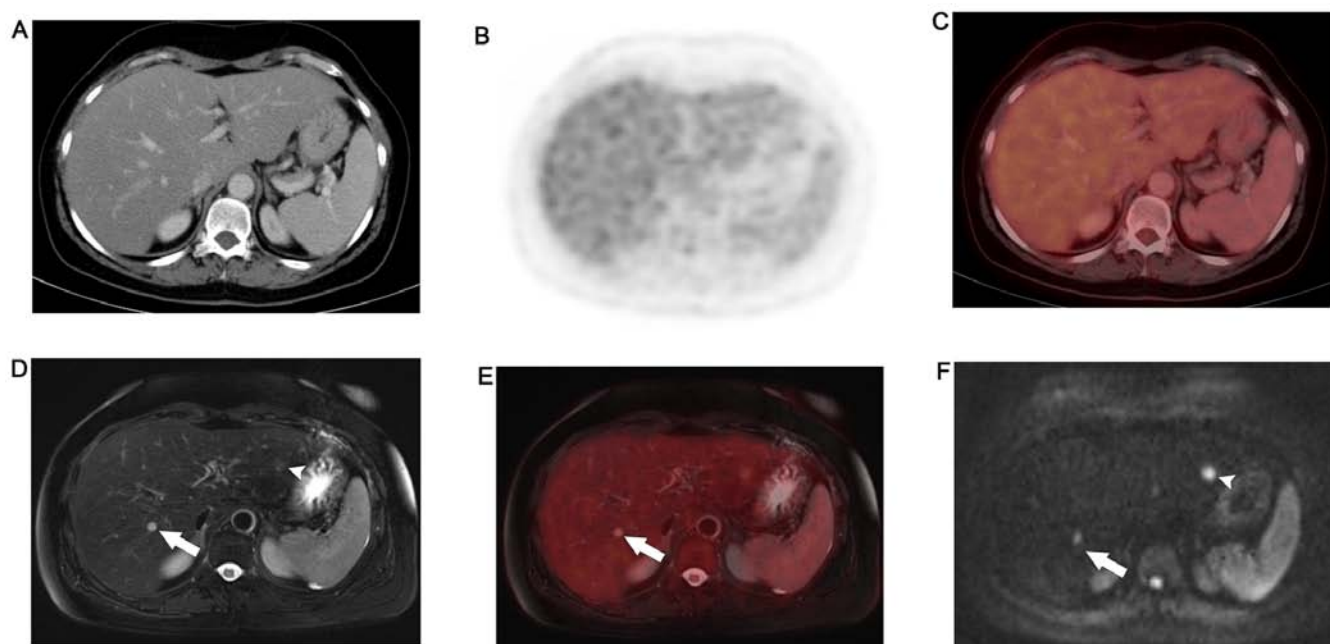


Figure 2. A 47-year-old female with stage IV breast cancer. Axial images from CT (A), PET (B), fused PET/CT (C), T2 weighted fat saturated FSE (D), fused PET/T2w fast spin echo (FSE) (E) and axial DWI (F). The metastasis in the right lobe of the liver (arrows) was not detected by PET/CT but identified on the T2 weighted fat saturated FSE acquisition and DWI. DWI disclosed also a second lesion (arrowhead) in the left lobe of the liver that was less evident in (D) and invisible on PET/CT.

Table I. Classification concordance.

Standard of reference	Concordant staging (34/51 patients)	Discordant staging (17/51 patients)
Stage IIA	-	1 (2%)
Stage IIB	8 (16%)	4 (8%)
Stage IIC	7 (14%)	-
Stage IIIA	-	4 (8%)
Stage IIIC	4 (8%)	3 (6%)
Stage IV	14 (27%)	6 (12%)

and WB-PET/MRI: 7 patients with stage IIA, 8 patients with stage IIB, 4 patients with stage IIIC and 14 patients with stage IV disease (Table I and Fig. 1).

One stage IIIA patient was incorrectly and concordantly miss-staged as IV by all modalities (Table II). Discordant staging was reported in 17 patients (33%): 1 patient with stage IIA, 4 patients with stage IIB, 4 patients with stage IIIA, 3 patients with stage IIIC and 6 patients with stage IV disease (Tables I-II and Fig. 2).

Staging misclassification by imaging modality. To assess the performance of each imaging modality in staging newly diagnosed breast cancer, the occurrence of staging misclassification was determined for each examination: WB-DWI miss-staged 8 patients, WB-PET/CT miss-staged 13 patients and WB-PET/MRI miss-staged 1 patient.

WB-PET/MR detected FDG avid lung metastases and left liver lobe metastases that were not appreciated on WB-DWI.

Moreover, it ascertained the benign nature of lesions that, due to T2 shine-through, retained high signal on high b-values DWI.

WB-PET/MRI identified non-FDG avid permeative bony metastases and sub-centimeter hepatic metastases that were not appreciated on WB-PET/CT. Details are provided in Table III.

Staging performance of WB-PET/CT, WB-DWI and WB-PET/MRI. The staging accuracy of WB-PET/CT was 75%, of WB-DWI was 84% and of WB-PET/MRI was 98% (Table III). WB-PET/MRI vs. WB-PET/CT differ significantly in their agreement with the true stage, with adjusted P-value of 0.005. On the other hand, the differences between WB-PET/MR and WB-DWI ($P=0.14$) and between WB-PET/CT and WB-DWI ($P=0.27$) were not statistically significant.

Discussion

In the present study, we assessed the performance of whole body diffusion-weighted imaging (WB-DWI), whole body positron emission tomography with computed tomography (WB-PET/CT), and whole body positron emission tomography with magnetic resonance imaging (WB-PET/MRI) in patients with untreated invasive ductal breast cancer. All three modalities correctly staged the cancer in 64% of patients. In the patients with discordant staging among the imaging modalities, our results show superior staging accuracy of WB-PET/MRI in staging metastatic disease, when compared to the other modalities being assessed.

In particular, when compared to WB-DWI alone, PET/MR performed better both in detecting FDG avid lung metastases

Table II. Staging misclassification by imaging modality.

Standard of reference	WB-DWI	Reason for discrepancy	WB-PET/CT	Reason for discrepancy	WB-PET/MR	Reason for discrepancy	Combined modalities
Stage IIA	-		1 (stage IV)	Sclerosed hepatic hemangioma miss-interpreted as metastasis (1 pt)	-		1
Stage IIB	1 pt (stage IV)	Cartilaginous island miss-interpreted as metastasis (1 pt)	3 pts (stage IIA)	Lack of detection of level I/II lymphadenopathy (3 pts)			4
Stage IIIA	2 pts (stage IV)	Benign red bone marrow miss-interpreted as metastases (2 pt)	3 pts (stage IIB, IV)	Benign red bone marrow miss-interpreted as metastasis (1 pt) Lack of identification of internal mammary lymphadenopathy (2 pt)	1 pt (stage IV)	Benign red bone marrow miss-interpreted as metastasis (1 pt)	4
Stage IIIC	-		3 pts (stage IIA, IV)	Lack of detection of infraclavicular lymphadenopathy (2 pts). Non-regional lymph nodes miss-interpreted as malignant (1 pt)	-		3
Stage IV	5 pts (stages IIB, IIIA, IIIC)	Lack of detection of metastases in the liver (2 pts), lung (2 pts) and peritoneum (1 pt)	3 pts (stage IIB, IIIA)	Lack of detection of metastases in the liver (2 pts), bones (1 pt)	-		6
Total misclassified	8 pts WB-DWI		13 pts WB-PET/CT		1 pt WB-PET/MR		18 pts

WB, whole body; DWI, diffusion weighted imaging; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; pt, patient.

Table III. Staging performance of the assessed imaging modalities.

	Patients correctly staged (n=51)	Accuracy
WB-PET/CT	38	75%
WB-DWI	43	84%
WB-PET/MRI	50	98%

WB, whole body; DWI, diffusion weighted imaging; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging.

and left liver lobe metastases, and in ruling out malignancy in the case of T2 shine-through retention of signal in some benign lesions. This was the result of the combined information from FDG uptake and the entire setting of MR sequences of our protocol. However, these differences were not statistically significant.

Moreover, since FDG-PET is the same in both WB-PET/CT and WB-PET/MRI, the improved staging performance of WB-PET/MR is likely due to the higher sensitivity of MRI in detecting non-FDG avid lesions, as we found in the case of permeative bony and sub-centimeter hepatic metastases.

The role of PET/MRI in breast cancer staging is under investigation. A study examining the performance of PET/MRI in 36 patients with breast cancer reported correlation of standardized uptake values as measured on PET/MRI and PET/CT in primary and metastatic cancerous lesions (22). Another study in 36 patients with breast cancer showed superior performance of PET/MRI in detecting metastatic lesions, when compared to PET (23). Furthermore, PET/MRI changed management decisions in one third of the patients being studied, when compared to the initial clinical staging (23). Our results add to the existing body of literature by providing new evidence that PET/MRI outperforms PET/CT and DWI in staging patients with breast cancer.

PET/MRI has been shown to add complementary metabolic information to prostate and gynecologic MR imaging, improving the diagnosis and management of prostate and gynecologic cancer patients (32-37). Similarly, PET/MRI accurately staged 28 patients with lymphoma, when compared to PET/CT (15). Other studies have also shown superior performance of PET/MRI in diagnosing primary head and neck, bone and soft tissue lesions and for detecting metastatic disease in the brain, liver and bone (15-18,26). A recent study provided evidence that PET/MRI contributes to the clinical management of cancer patients more often than PET/CT (20).

Early and appropriate staging of breast cancer is especially important in the management of patients with this disease. Available data suggest longer survival and improved quality of life with early detection of metastatic disease (38-40). Our data suggest that PET/MRI is well-positioned to aid in the staging of breast cancer patients at the time of their initial diagnosis. PET/MRI performed particularly well in accurately staging advanced disease, where a higher proportion of discordant staging was reported by other modalities in this study

(stage IIIA and higher). PET/MRI might have the potential to play a critical role in affecting treatment decisions and management in this patient population.

The present study has several limitations, including the small number of patients and the potential selection bias introduced by enrolling only untreated ductal invasive breast cancers. These results might not be applicable to other breast cancer subtypes or to treated patients. A larger study would be needed to validate our findings. In this study, the availability of multiple MR sequences combined with PET helped compensate for the limitations intrinsic to stand-alone sequences. For example, DWI helped in detecting liver lesions, and PET was useful in assessing sub-centimeter metastases in the liver and in lymph nodes.

An additional limitation might have been related to the delta time with PET/CT, acquired ~60 min after FDG injection and PET/MRI, acquired ~90 min after FDG injection. Our longer incubation time for PET/MR is explained by the legal and IRB requirements that mandated us to acquire PET/MR after a standard of care PET-CT obtained at 60 min after FDG injection, before being allowed to acquire any PET-MR study. Although delayed PET acquisitions might demonstrate lower background activity and improved lesion visibility, there is no consensus if this translates into improved accuracy (41-43). However, it is unlikely that this might have influenced the FDG uptake obtained by PET/MR. The PET/MR reconstruction software automatically corrects for incubation time for each bed position. Moreover, several studies have demonstrated comparable performance between PET/CT and subsequently acquired PET/MR as quantified by SUV measurements (22,44,45).

Finally, in the present study, the guidelines of the European Association of Nuclear Medicine (46) were used to dictate image acquisition protocols based on local clinical standards.

In conclusion, PET/MRI outperforms PET/CT and is more accurate in staging untreated patients with invasive ductal carcinoma. PET/MRI has the potential to affect clinical decision making and management of breast cancer patients, and should be considered in the initial staging of this disease.

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