Title: PET/MRI in Breast Cancer

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ABSTRACT

PET/MRI is an emerging imaging technology that allows for the acquisition of multiple MRI parameters simultaneously with PET data. In this review, we'll address the technical requirements of PET/MRI including protocols and tracers, the potential of integrated localized breast PET/MRI exams, and possible applications of whole body PET/MRI in breast cancer patients. Currently, PET/MRI can be performed on sequential and integrated PET/MRI scanners but, as not all practices can access these dedicated machines, several studies look at PET and MRI exams that are performed separately on separate scanners within a short time frame. This practice likely provides similar clinical data, although exact co-localization for iso-voxel analysis, currently performed only in research, is not possible. In PET/MRI, the MRI sequences are flexible and can be customized according to the aim of the exam.   The most commonly used radiotracer is ^{18}F-FDG, however, tracers that image hypoxia and drug targets such as estrogen receptors and HER2 are in development and may increase the utility of PET/MR. For dedicated breast PET/MRI, a potential advantage over standard breast MRI alone may be the complimentary sensitivities of MRI for extent of disease within the breast and PET for axillary and internal mammary nodal metastases. . Moreover, layers of multiparametric MRI and PET metrics derived from the index lesion are being investigated as predictors of response to neoadjuvant therapy. These data may eventually be able to be quantified and mined in a way that furthers radiomics and also precision medicine. Finally, in whole body imaging of breast cancer patients, single institution studies have found that PET/MRI detects more metastases than PET/CT   at about half the radiation dose, although survival benefit has not been shown.

For now, whole body PET/MRI in breast cancer patients may be most relevant for young

patients who may undergo serial surveillance exams.

Keywords: PET/MRI, breast MRI, breast PET/MRI, multi-parametric, response to neoadjuvant

therapy, metastatic breast cancer

INTRODUCTION

Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) have been combined into integrated PET/MR imaging, an imaging tool that acquires both the metabolic data of PET and, most often, the high contrast morphological data of MRI as part of a single exam. Advanced MR techniques such as proton MR spectroscopy (MRS) and diffusion weighted imaging (DWI) can also be run simultaneously with PET acquisition, broadening potential clinical oncologic and research applications.

MRI and PET imaging are both commonly used in breast cancer. PET imaging in breast cancer is most often used in the form of PET/CT with fluorine-18 fludeoxyglucose (^{18}F-FDG) to assess for distant metastatic disease and to look for and monitor recurrent disease (1). Positron Emission Mammography (PEM) is also used in breast imaging, but this system has a higher spatial resolution and smaller field of view than whole body PET imaging and is not currently integrated with MRI for breast imaging (2). As such, PEM is not discussed in this review.

Dynamic contrast enhanced (DCE) MRI is both a morphologic and a functional imaging tool that, in addition to providing morphologic data, depicts areas of increased blood-flow, an early characteristic of breast cancers and an obligate characteristic of biologically relevant breast cancers. DCE MRI is the most sensitive tool for breast cancer screening (3,4) and is also used to assess the extent of disease in patients with known breast cancers and to monitor breast cancers during and after neo-adjuvant therapy (5). Preliminary investigtaions of advanced perfusion, diffusion, spectroscopy, and sodium imaging MR techniques are underway to further

characterize breast cancers. Eventually, these tools may help to match specific imaging characteristics with disease characteristics and behavior (radiomics) and with genetic information (radiogenomics).

Breast MR cannot always differentiate benign from malignant enhancement and cannot identify locally advanced disease in morphologically normal lymph nodes. PET breast imaging has demonstrated increased specificity as compared with MR (6, 7) and high sensitivity for axillary lymph node metastases (8,9). Fusing separate PET and MR breast imaging has been looked at as a means to preserve the sensitivity of MR, decrease false positive exams, and increase axillary nodal metastasis sensitivity (10-13).   This field was limited by the logistic limitations of requiring patients to undergo multiple exams and the technical and temporal limitations of fusing the two exams. Now, however, PET and MR imaging can be acquired simultaneously and co-registered, allowing radiologists to evaluate not only how the combination of exams can improve sensitivity and specificity, but also to put together exams with multiple parameters (eg. PET, DCE MRI, DWI MRI, MRS). With multi-parametric imaging, radiologists can assess layers of parameters voxel-by-voxel, and use this information to characterize tumor heterogeneity and to search for multi-parametric hints at predicting clinical outcomes.

TECHNICAL

PET and MR fusion became clinically viable with advances in PET detectors. Traditional PET photomultiplier tubes used in PET/computed tomography (CT) systems are not compatible with the high magnetic fields integral to MR imaging, and photomultiplier tubes are too large to fit

into an MR gantry. The development of MRI-compatible solid state PET detectors facilitated placing PET and MR scanners in the same space. Two non-integrated PET/MRI systems scan patients sequentially, with patients undergoing PET or PET/CT and MRI separately in the same room while the patient's position is unchanged. The sequential PET/CT and MRI system allows for CT-based attenuation correction. Although these systems provide improved co-localization over completely separate MR and PET exams, they do not allow for dynamic imaging on both systems. Integrated, simultaneous PET/MR imaging depends on solid-state semiconductor PET detectors, such as avalanche photodiodes, which are much smaller than conventional PET detectors (14) and can be placed inside an MR gantry. This type of integrated system performs both exams at the same time, providing a shorted exam time for patients, and the opportunity to visualize dynamic processes with both modalities. An integrated system, or any system without CT, requires MR-based attenuation correction, most commonly achieved through a Dixon sequence-based segmentation method (7, 14-16). MR-based attenuation correction for breast and body PET/MRI has been validated (17-24).

Radiotracers

There are only two FDA approved PET radiotracers used in breast cancer imaging, ^{18}F-FDG and Fluorine 18-sodium fluoride (^{18}F-NaF). ^{18}F-FDG images cellular glucose uptake and is highly sensitive for breast cancers and for breast cancer metastases in a wide range of organs (23). ^{18}F-FDG has some limitations including lower sensitivity for lobular breast cancers (25, 26), ductal carcinoma in situ (DCIS) (26), and, as the reconstructed spatial resolution of PET is 5-6mm at full width half maximum (1), for small, sub-centimeter tumors (27). Conversely, ^{18}F-

FDG can show increased uptake in benign breast processes including common entities like fibrocystic changes, fibroadenomas, and fat necrosis (28, 29).

[18]F-NaF is a bone specific radioisotope that has been investigated in breast cancer patients (30, 31). Piccardo et al demonstrated that in the setting of PET/CT, ^{18}F-NaF had a higher sensitivity for osseous metastatic disease than ^{18}F-FDG (100% vs 72%), but that only a negative ^{18}F-FDG PET/CT was predictive of overall survival, suggesting that ^{18}F-FDG activity is more closely linked to biologically active metastatic disease. This study supports the idea that skeletal ^{18}F-FDG uptake principally occurs in breast cancer cells while skeletal ^{18}F-NaF uptake is reflective of bone remodeling and associated blood flow (32).

Targeted treatments are administered for estrogen receptor (ER) positive and human epidermal growth factor receptor 2 (HER2) positive tumors. Although biopsies provide receptor expression information, breast cancers are heterogeneous, and biopsy may not always demonstrate the presence of a receptor that is present. Further, breast cancer receptor expression can change over time and in response to treatment, both in the primary tumor and in metastases. Hormone receptor and HER2 targeted radiotracers (33-37) are being investigated and may eventually allow for non-invasive dynamic, optimized therapy throughout breast cancer treatment. In addition, novel radiotracers targeting hypoxia may be useful in therapeutic planning as hypoxic tumors can undergo mutations that increase resistance to chemotherapy and potentiate metastases (38-40). One such tracer, ^{18}F-Fluoromisonidazole

(^{18}F-FMISO) accumulates in hypoxic cells with nitroreductase enzymes and has been shown to predict clinical resistance to anti-hormone therapy (41).

Protocol

As for a routine PET/CT exam, the patient is given a radiotracer (typically 555MBq ^{18}F-FDG) intravenous (IV) injection after fasting for at least four hours. The patient then rests for 45 minutes in a dark room. For a breast PET/MRI exam, a dedicated breast coil is used and the patient is positioned prone. MRI sequences are then run simultaneously with the acquisition of PET data and IV gadolinium is administered IV after pre-contrast imaging at the normal weight-based dose. It is recommended that the PET data be collected for at least two minutes, although times from three and a half to 15 minutes have been reported (19, 42-43). MRI sequences can vary, including the sequences recommended by the American College of Radiology (5) or can be customized, for example to include abbreviated breast MRI sequences (a single pre- and post-contrast T1-weighted image set) and/or DWI, and MRS.

Whole body PET/MR imaging uses the same radiotracer (typically ^{18}F-FDG) dose, fasting time, and resting time. The exam, however, is performed with supine positioning and head and body matrix coils. The exam is split into stations, such as head, neck, chest, abdomen, pelvis, and thighs, and can be acquired either from caudal to cranial or the reverse. These stations can then be combined into a single image set as part of post-processing. PET data should be acquired for at least 2 minutes per station (or for the entire duration of MR imaging at each station) The authors scan from the thighs through the vertex, with a gadolinium injection during

the abdomen station to see contrast in the liver and to facilitate post-contrast evaluation of the brain. In breast cancer patients, dynamic contrast-enhanced (DCE) MRI has been shown to best detect breast and brain lesions, DWI has outperformed DCE MRI for liver and bone metastases, and PET has had high sensitivity for lymph node metastases (44). Suggested sequences are listed in Table 1.

INDEX LESION EVALUATION

Benign vs. Malignant

DCE breast MRI has a high sensitivity, reported at up to 100% (3,4) and a positive predictive value above 35% (45). PET/CT is not routinely performed for breast cancer detection because is it not adequately sensitive (46-50), especially for lobular cancers (48) and for cancers less than 1cm (50). Authors have investigated whether combining DCE MRI and PET data in the breast can improve the diagnostic accuracy for breast cancer (6, 7, 11) but have found that the addition of PET often decreases the sensitivity of DCE-MRI.

In a study of 101 benign and malignant breast lesions, Botsikas et al compared DCE MRI with qualitative and quantitative ^{18}F-FDG PET/MRI and reported areas under the curve (AUC) of 0.9558, 0.8347, and 0.8855 with MRI, qualitative, and quantitative ^{18}F-FDG PET/MRI (6). Although the specificity of DCE MRI improved from 67% to 100%, the authors did not recommend adding PET to MRI because of the compromised sensitivity (6). Similarly, adding PET to DCE MRI data decreased sensitivity from 93% to 88% in a study of 58 breast lesions by Heusner et al (7).

However, Bitencourt et al showed that when multiple MR parameters are included in a PET/MR evaluation, 100% sensitivity could be achieved (46). In this study, the authors evaluated 38 lesions, 29 of which were malignant, with DCE MRI, DWI, and ^{18}F-FDG PET. A lesion had to meet one of three criteria: a washout curve on DCE MRI, ADC_{min} <1.00 × 10 mm/s, or ^{18}F-FDG uptake above background. The specificity in this study was 55% (46). In another multi-parametric study, Pinker et al included four parameters- PET DCE MRI, DWI and 1hydrogen-MRS, in their evaluation of 78 indeterminate or suspicious breast lesions (51). While the authors demonstrated that combining all 4 parameters would have reduced unnecessary biopsies by 50% as compared with DCE MRI alone, this extensive exam may not be clinically practical. Figure 1 shows an example of multi-parametric imaging of a triple negative breast cancer. In an investigation of advanced perfusion, Jena et al. performed a feasibility study, looking at whether the pharmacokinetic DCE-MRI parameters K_{trans} (a volume transfer coefficient reflecting vascular permeability), K_{ep} (a flux rate constant), and V_e (an extracellular volume ratio) from a high resolution breast MRI protocol on an integrated [^{18}F]FDG PET/MRI system could separate benign and malignant lesions as well as those same metrics obtained from a stand-alone 3T scanner (52). The authors showed sensitivities of 98.6%, 82.9%, and 98.6% for K_{trans}, K_{ep}, and v_e for detecting breast cancers, and accuracies of 94.50%, 79.82% and 87.16% for these same variables (52). These results are improved over their earlier work on a stand-alone 3T MRI (53), suggesting advanced DCE MRI metrics obtained on an integrated scanner are valid.

Relationships between PET/MR metrics and clinical features

Advanced MRI can provide several perfusion and diffusion metrics which have been looked at, together with PET metrics, in efforts to predict clinical features through imaging analyses. Although some authors have seen correlations between PET and MR metrics, as described below, these correlations are not uniform between studies.

Metastatic disease, Ki67

Margolis et al. evaluated perfusion data K_{trans}, K_{ep}, and V_e, and ^{18}F-FDG PET data standardized uptake value (SUV) and metabolic tumor volume (MTV) in breast cancer patients with and without metastases (54). In this study, K_{trans} and SUV_{max} correlated positively with metastatic disease whereas k_{ep} correlated negatively. Similarly, tumors with higher levels of Ki67, a marker for cell proliferation, showed a significantly greater K_{trans} compared to tumors with lower levels of Ki67 (54). Data like these suggest the potential for K_{trans} and SUV_{max} to suggest patients in whom whole body imaging should be performed to assess for metastatic disease.

Tumor markers

Catalano et al investigated whether ^{18}F-FDG PET/MR could differentiate between histological phenotypes of breast cancer in 21 patients with invasive ductal carcinoma (IDC) (55). The authors found that estrogen receptor (ER) and progesterone receptor (PR) negative tumors had higher SUV_{max} and k_{ep} than ER or PR positive tumors; that HER2 negative tumors had higher apparent diffusion coeffieient (ADC)$_{mean}$, k_{ep}, and SUV_{max} values; and that tumors with lower levels of Ki67 showed lower ADC$_{mean}$, but not greater k_{trans}, as seen in the Margolis study (54). PET/MR markers correlated with immunohistochemical (IHC) phenotype in 62%, a promising beginning (55).

Survival

An et al. looked at 67 women with breast cancer with DCE MRI and ^{18}F-FDG PET performed separately and demonstrated an inverse relationship between SUV_{max} and V_e and, notably, a negative correlation between metabolic heterogeneity and survival (56). These same authors also found a positive correlation between SUV_{max} and K_{ep} in non-triple negative breast cancers (TNBC), but not in TNBC (57).

SUV_{max} and ADC

High SUV_{max} is a marker for tumors with high concentrations of glucose uptake and has been positively correlated with many clinical factors including tumor grade (58-61), stage (58), size (58-61), ER negativity (58-62), PR negativity (58, 62), HER2 positivity (58, 59), TNBC (50, 61), higher Ki67 (50, 58, 62), and axillary lymph node positivity (58-61). SUVmax has also been correlated inversely with both progression free survival and overall survival (60). High levels of restricted diffusion are a marker for malignancy and generate low ADC values. Correlations between ADC values and clinical factors appear less replicable than those between SUVs and clinical markers. For example, ADC has been inversely correlated with ER positivity (61), HER2 negativity (60, 61), tumor size, Ki67 expression, histologic subtype, the presence of axillary metastases and TNM staging (58). However, in a study by Karan et al. of 70 women with breast cancer, no correlations between ADC median and many of these metrics (size, grade, lymph node status, ER status, HER2 status) were seen (59). Several authors have investigated whether SUVmax and ADC are inversely related and have obtained mixed results (50, 58-61), suggesting

that these markers reflect two separate and not necessarily related properties of breast cancers.

LOCO-REGIONAL STAGING

Loco-regional staging of breast cancer includes primary tumor size, assessment of multi-focality, and detection of nodal disease in the axillae and internal mammary (IM) chains. Accurate loco-regional staging is important for surgical and oncologic planning as well as post-treatment surveillance.

Tumor Size and Multi-focality

While PET/MRI appears to outperform PET/CT, PET/MRI does not appear to offer benefit over the current standard, MRI alone, in assessing tumor size or multi-focality, the presence of at least one additional malignant focus less than 5 cm from the index lesion. Multifocality is associated with an increased likelihood of nodal disease (64) and may be associated with an increased risk of recurrence after lumpectomy (65). A study by Grueneisen et al. of PET/MRI versus PET/CT and MRI alone in 49 patients with 50 breast cancers demonstrated that PET/MRI and MRI alone correctly identified the T-stage of breast cancers a significantly higher number of times than PET/CT [41/50 (82%) PET/MRI and MRI alone vs 34/50 (68%) PET/CT; $p < 0.05$] (8). In the same study by Grueneisen et al., PET/MRI and MRI alone correctly identified multifocal/multicentric disease in 8/9 patients, compared with 5/9 by PET/CT. Similar to Grueneisen et al., Goorts et al. found that PET/MRI and MRI alone were equivalent for assessing breast tumor size and multifocality in 40 patients with breast cancer (66).

Two additional studies demonstrated MRI to be more sensitive than PET/CT for the detection of multifocal breast cancer, while PET/CT demonstrated higher specificity. Jung et al. compared the two modalities among 105 biopsy-proven breast cancers. MRI detected all 105 primary tumors, while PET/CT identified 85/105 (81.0%) primary tumors. Additional foci of malignancy were present in the same breast in 25 cases at surgical pathology. The authors reported that the sensitivity of MRI for detecting these ipsilateral lesions was significantly higher than PET/CT ($p \leq 0.001$), while the specificity of PET/CT was superior to that of MRI ($p \leq 0.008$) (48). A similar study by Ergul et al. reported that in 24 patients with early-stage breast cancer, the sensitivity and specificity of PET/CT and MRI for the detection of multifocality were 67% versus 78% and 100% versus 53%, respectively (9). Finally, in comparing PET imaging alone versus MRI alone, Taneja et al. identified multifocal/multicentric disease in 21/36 patients. MRI detected a significantly higher number of satellite lesions compared with PET (35 versus 17, $p = 0.001$); however, 4 MRI-detected satellite lesions proved to be false positives at pathology (43).

Axillary and Internal Mammary Lymph Nodes

In contrast to tumor size and extent, most, but not all, studies indicate that PET-based imaging is more sensitive than MRI for the detection of axillary metastases and limited studies show PET and MRI have similar sensitivity for internal mammary nodes. In Grueneisen et al.'s cohort of 49 patients, 18 patients had axillary disease. The sensitivity for axillary nodal status was 78% for PET/CT, 78% for PET/MRI, and 67% for MRI alone; these differences were not statistically significant, likely due to the relatively small number of patients. PET/CT also demonstrated a slightly superior specificity of 94% for axillary disease, compared with 90% for PET/MRI and 87%

for MRI alone (8). Among the 24 patients in Ergul et al.'s series, 15 patients had axillary involvement diagnosed by axillary lymph node dissection. The sensitivity of PET/CT for axillary metastasis was 67%, compared with 47% for MRI. The specificity of PET/CT for axillary nodal disease was also higher than MRI, 89% versus 78%, respectively (9). Notably, the CT portion of PET/CT appears critical to the sensitivity of staging the axilla using PET: without CT, the sensitivity of PET alone for the presence of axillary metastasis has been reported at 60% by Taneja et al. compared with 93.3 % for MRI alone. The specificity of both PET alone and MRI alone for axillary metastases was 91% in this study (43). Botsikas et al. evaluated the performance of PET/MRI versus MRI alone for the detection of axillary, IM, and supraclavicular lymph nodes, and reported combined results in 58 patients with breast cancer. Contrary to the studies described previously, MRI alone demonstrated increased sensitivity of 88% versus 79% for PET/MRI, although this difference was not statistically significant. Specificity was also not significantly different, reported as 98% for MRI and 100% for PET/MRI (6).

Regarding changing axillary nodal status, Goorts et al. reported 1 case of axillary down-staging and 1 case of axillary up-staging by PET/MRI compared with conventional imaging (66). One study evaluated the impact of dedicated axillary PET/MRI on axillary nodal status in 12 patients with clinically positive axillary nodal disease. In this study, axillary PET/MRI changed nodal status in 40% of patients compared with ultrasound, in 40% of patients compared with contrast-enhanced MRI, and in 22% of patients compared with PET/CT (67).

In addition to staging the axilla, cross-sectional imaging affords evaluation of the IM chains. The identification of IM adenopathy is important as this finding is associated with a poorer prognosis and may warrant more aggressive treatment (68, 69). While MRI is increasingly performed to assess the extent of disease following a new diagnosis of breast cancer (70), few studies have evaluated the performance of MRI for the detection of IM metastasis, let alone compared MRI with PET-based imaging in this context. In 1999, Kinoshita et al. reported a sensitivity of 93.3% and a specificity of 89.3% among 43 MRI-detected IM nodes in 16 patients (71). In the above-mentioned study of 40 patients by Goorts et al., PET/MRI detected 1 abnormal IM node not initially seen on MRI alone and increased diagnostic confidence in 3 other cases of IM metastases (66). Jochelson et al. compared the prevalence of IM adenopathy identified by MRI with that by PET/CT. MRI detected IM disease in 14/90 (16%) patients, versus 13/90 (14%) patients by PET/CT (p = 0.317) (69). The similar performance between PET/CT and MRI for IM nodes and the superiority of PET/CT over MRI for axillary nodes suggest a role for PET in the complete loco-regional staging of breast cancer.

NEO-ADJUVANT THERAPY

Predicting breast cancer response to chemotherapy is a field of particular interest for PET/MRI. With the emerging field of radiomics, large volumes of quantitative features can be pulled from both PET and MR images and converted into data (72). These data can be mined and shared and, over time, may lead to discovery of certain PET/MR radiomic signatures that can help determine optimal therapies for individual breast cancers, such as which drugs will be most effective and whether to begin treatment with chemotherapy or surgery. . Such signatures can

be automatically derived from images, as demonstrated by Drukker et al, who, in a study of 143 women who underwent breast cancer treatment, showed that a near completely automatically extracted data point called most enhancing tumor volume (METV) predicted recurrence with similar accuracy to a semi-manual method published by Hylton et al (73, 74). Below are examples of investigations into the clinical relevance of several PET- and MRI- based metrics that could eventually contribute to radiomics.

Response prediction

Cho et al performed ^{18}F-FDG PET/MRI in 26 breast cancer patients before and after the first round of chemotherapy and evaluated qualitative MRI parameters as well as quantitative PET and MRI parameters (75). While the qualitative MRI parameters were not found to be different between pathologic complete responders and pathologic non-complete responders, reductions in total lesion glycolysis (TLG) and signal enhancement ratio (SER) were different between the two groups. Separately, the specificity (for pathologic complete response) of $TLG_{30\%}$ was 100% and of SER was 71.4% and the sensitivity for predicting pathologic non complete response was 63.2% and 84.2%, respectively. Highlighting the synergistic potential or PET and MRI, the combined sensitivity was 100% and specificity was 71.4%.

Wang et al also investigated the synergy between PET and MRI parameters in predicting response to chemotherapy (76). In their study of 14 women with breast cancer, women underwent scanning before and after the first or second cycle of treatment. They found that % change in SUV_{max},TLG, and peak enhancement ratio (PER) predicted response (AUC 0.898, 0.878, and 0.837) and that combined PET and MRI metrics % change SUV_{max}/% change ADC_{min} and % change TLG/% change ADC_{min} had even higher AUC for differentiating pathologic

complete responders from pathologic non-complete responders (AUC 0.976 and 0.905) (77).

In a study of 93 breast cancer patients, Pengel et al. demonstrated that combined PET/MR

metrics in concert with clinical data yielded the best accuracy (77). While age, breast cancer

subtype, % change in SUV_{max} and % change in largest tumor diameter on MRI predicted near

pCR, breast cancer subtype together with changes in SUV_{max} and tumor diameter provided the

highest AUC (0.90) (78). An et al. also showed that combining data, in this case, DWI or DCE-

MRI with PET, led improvement, here in NPV and specificity (78). An example of pre- and post-

chemotherapy imaging is shown in Figure 2.

Lim et al. looked at changes in PET and MR metrics in response to therapy to predict disease

free survival found that patients who met cutoffs for (lesser) declines in both SUV and MR slope

had a higher recurrence rate (78%) than those that did not (13%) (79). Additional studies have

shown that both PET and MRI metrics change in response to chemotherapy in pathologic

responders (62, 80), and that changes in SUV_{max} may be more accurate than changes in tumor

size, but none of these metrics predicts with 100% accuracy.

Highlighting the potential for advanced integrated PET/MR, advanced MR techniques including

Sodium ([23]Na) MR and 1H-MRSI have also been investigated together with PET. Jacobs et al

investigated changes in sodium concentrations with [23]Na MR in 6 patients before and after

initial rounds of treatment and compared with ^{18}F-FDG PET/CT and DCE MRI (81). Tissue

sodium concentrations increased in all partial responders and decreased in the single non-

responder, whereas MRI tumor volumes and SUV_{max} decreased in both partial responders and

in non-responders. Cho et al. (82) compared 1H-MRSI with PET. The authors found mean %

reductions for total choline, SUV_{max}, SUV_{peak}, and TLG were greater in the pCR group than in non-pCR group, however, no cut-off values could separate responders from non-responders.

DISTANT METASTASES

In patients with breast cancer who require whole-body imaging prior to definitive treatment or for follow-up after therapy, PET/MRI is a versatile imaging tool that can provide whole-body staging during a single exam; suggested imaging sequences are listed in Table 1. (Figure 3). Although who requires whole body PET-based imaging is not standardized, a study of untreated breast cancer patients by Groheux et al showed that PET/CT detects unsuspected metastatic disease in 2.3% of clinical stage IIA patients, who are predominantly patients with tumors between 2cm and 5cm and, less commonly, patients with tumors less than 2cm but with axillary nodal disease, and that this percentage increases steadily up to 47.1% of clinical stage IIIC patients, who are patients with any tumor size who have involvement of an internal mammary node, a supra-clavicular node, or at least 10 axillary nodes (83) . In addition, PET/CT is used to assess for metastatic disease in treated breast cancer patients who present with new symptoms or with rising tumor markers. In terms of PET-based imaging, multiple studies have demonstrated improved sensitivity of whole-body PET/MRI over whole-body PET/CT in the context of breast cancer and other cancers (Table 2), including for detection of liver and bone metastases – the two most common sites of distant breast cancer spread (84). In a study of 242 breast cancer metastases in 51 patients, PET/MRI demonstrated significantly improved detection of 40 liver metastases compared with PET/CT ($p < 0.001$), and significantly improved

detection of 107 bone metastases compared with PET/CT (p = 0.012); brain metastases were also identified by PET/MRI in 5 patients (44). Similar findings of improved detection of osseous breast cancer metastases with PET/MRI versus PET/CT were described in a series of 65 bone metastases in 17 patients with recurrent breast cancer by Sawicki et al. (85). In a study by Catalano et al., PET/MRI identified significantly more breast cancer metastases to bone compared with PET/CT (141 vs 90, p < 0.001) in 25 patients (86). Catalano et al. also reported significantly improved whole-body staging in 51 patients with invasive breast cancer using PET/MRI versus PET/CT (50/51 vs 38/51 correct, p < 0.01) (87).

Regarding pulmonary metastases, in the same study of 242 breast cancer metastases mentioned above, PET/CT showed a trend towards improved detection of 23 lung metastases compared with PET/MRI (p = 0.065) (44). However, the clinical importance of lung lesions missed by PET/MRI is unclear. In a study of 208 patients with various primary malignancies (including 15 with breast cancer), 97% of lung nodules $\leq$ 1 cm not identified on PET/MRI were stable or resolved on follow-up; in a single patient, three such lung nodules not seen by PET/MRI did progress (88).

Finally, especially when looking for recurrences, it should be noted that while PET/MRI is sensitive for lesions throughout the body dedicated breast MRI or prone breast PET/MRI is superior to supine whole-body PET/MRI, for breast lesions, likely due to tissue collapse in the supine position. In a study by Kong et al., only 4/10 (40%) sub-centimeter breast cancers were seen on whole-body PET/MRI (49). In a study by Sasaki et al., primary breast cancers were seen in all 94 patients on dedicated prone breast/MRI, while whole-body PET-MRI did not identify primary breast cancers in 7/94 (7%) patients (89). Therefore, in patients with elevated tumor

markers and negative whole body imaging, consideration may be given to dedicated breast imaging. A comparison of PET/MRI with MRI and PET/CT for clinical tasks is provided in Table 3.

CLINICAL RELEVANCE

PET/MR is a promising flexible imaging tool that may be of use in dedicated breast exams and in whole body exams. When used with multiple MRI parameters, breast PET/MRI has shown promise in reducing unnecessary biopsies that would be recommended based on ther current standard DCE-MRI (50). However, the radiation dose and imaging, processing, and reading times associated with such an exam make it unlikely this type of breast imaging will become part of our clinical routine. Instead, breast PET/MR may be more important before and during neo-adjuvant therapy, where multiple layers of imaging parameters may eventually be converted into radiomic data that may lend increased precision to breast cancer treatments; and in local staging, where the improved evaluation of the axilla potentially afforded by PET/MRI may eventually preclude the need axillary lymph node tissue sampling (6, 66). For breast cancer patients in need of whole body staging or post-treatment surveillance, PET/MR outperforms PET/CT at a much lower radiation dose (44). Here, the inclusion of DWI in PET/MRI protocols adds sensitivity to whole-body exams, to which PET adds specificity.

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Tables

<u>Table 1. Whole-body PET/MRI in patients with breast cancer: Suggested MRI sequences by imaging station</u>

<u>Station</u>	<u>T1-weighted sequences</u>	<u>T2-weighted sequences</u>	<u>Notes</u>
All	Coronal 3D gradient-echo	Coronal high-speed turbo-spin echo T2	For DIXON-based μ-map
Bone/Pelvis	Radial non-contrast 3D gradient-echo, or T1 Dixon	Axial high-speed turbo-spin echo or Axial 3 b-value DWI	Non-contrast T1 for fat-containing lesions
Liver/Abdomen	Radial 3D fat-suppressed gradient-echo, with or without contrast*	Axial high-speed turbo-spin echo, Axial 3 b-value DWI, Axial fat-saturated T2	Fat-saturated T2 for fat-containing lesions
Lung/Thorax	Radial 3D fat-suppressed gradient-echo with or without contrast		

Brain/Head	Post-contrast magnetization	T2 post-contrast FLAIR
Pre-contrast for	prepared rapid gradient-echo, or	
hemorrhage[†]	pre-contrast 3D gradient-echo[†]	
FLAIR for leptomeningeal		disease

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* Contrast injection at the liver station facilitates non-contrast evaluation of the pelvic bones, contrast-enhanced assessment of the liver, and delayed post-contrast visualization of the brain.

[†] Pre-contrast evaluation of the brain is only possible if contrast was not injected at the liver station.

Table 2. Whole-body PET/MRI versus PET/CT for the detection of organ-specific metastases

Study*	Primary Cancer	Metastatic Site*				
		Liver	Bone	Lung	Pleura	Lymph nodes
Beiderwellen[93]	Various		n=48; 48, 45			
Drzezga[22]	Various	n=11; 9, 11	n=14; 14, 14	n=15; 15, 15		n=27; 27, 27
Eiber[94]	Various		n=90; 86, 86			
Heusch[23]	Various					n=13; 13, 11
Huellner[24]	Various			n=17; 17, 17		n=74; 74, 74
Jeong[95]	Various	n=1; 1, 1	n=11; 11, 11			
Melsaether[44†]	Breast	n=40; 36, 29	n=107; 103.5, 98	n=23; 18.5, 22.5	n=16; 16, 16	n=60; 57, 54
Pace[19]	Breast		n=11; 11, 11	n=3; 3, 3		n=35; 35, 35
Schäfer[96]	Pediatric	n=5; 5, 5	n=4; 4, 4			n=28; 28, 28

* For each study, the number of metastases to a particular organ is indicated (if evaluated), followed after the semicolon by the number of metastases identified by PET/MRI and PET/CT, respectively.

† This study by Melsaether et al. included two PET/MRI readers and two PET/CT readers. The number of lesions identified by PET/MRI and PET/CT in this table indicates the average of the two readers for each modality.

Table 3. Imaging evaluation of extent of disease in breast cancer: A review of the literature comparing imaging modalities

Author PET Station	T-stage/ Tumor size	Multifocality	Axillary Nodes	Internal Mammary Nodes	Distant Metastases
Grueneisen[8] Whole body PET/CT Breast PET/MRI	PET/MRI > PET/CT‡ PET/MRI = MRI MRI > PET/CT‡	PET/MRI > PET/CT* PET/MRI = MRI* MRI > PET/CT*	PET/MRI = PET/CT* PET/CT > PET/MRI† PET/MRI > MRI* PET/MRI > MRI† PET/CT > MRI* PET/CT > MRI†		
Goorts[66] Breast PET/MRI and MRI	PET/MRI = MRI	PET/MRI = MRI*		PET/MRI > MRI*	
Jung[48] Breast MRI, Whole body PET/CT		MRI > PET/CT*‡ PET/CT > MRI†‡	MRI > PET/CT* MRI > PET/CT†		
Ergul[9] Breast MRI, Whole body PET/CT		MRI > PET/CT* PET/CT > MRI†	PET/CT > MRI* PET/CT > MRI†		
Taneja[43] Breast PET/MRI		MRI > PET*‡ PET > MRI†	MRI > PET*‡ MRI = PET†		MRI > PET*‡
van Nijnatten[67] Whole body (PET/CT) Axilla (PET/MRI)			PET/MRI > US PET/MRI > MRI PET/MRI > PET/CT		
Jochelson[69] Whole body				MRI > PET/CT*	
Melsaether[44] Whole body					PET/MRI > PET/CT*‡
Sawicki[85] Whole body					PET/MRI > PET/CT*
Catalano[86, 87] Whole body					PET/MRI > PET/CT*‡ PET/MRI > PET/CT†‡
Heusner[91]					PET/CT > DWI*

| Whole body | PET/CT > DWI[†‡] |

* Sensitivity and [†] Specificity indicated where applicable.

[‡] Denotes statistical significance. Note that statistical significance was not demonstrated in several of these studies with small sample sizes.

Absolute comparisons between modalities are reported in this table for reference and do not imply statistical significance unless indicated.

Figure 1. A 38 year old female diagnosed with triple negative invasive ductal carcinoma of the left breast. At the time of the examination, there was no evidence of metastatic disease. (a) The top row is the PET, the middle row is the DCE-MRI, and the bottom row is the fused PET/MRI images. The index lesion is well characterized on these images as a FDG-avid heterogeneously enhancing lesion in the left breast abutting the skin surface. (b) A diffusion weighted image demonstrates increased signal intensity within the mass. (c) The corresponding ADC map demonstrates decreased signal intensity within the mass consistent with diffusion restriction.

Figure 2. A 37 year old female with left breast invasive ductal carcinoma and no evidence of distant metastatic disease. The patient proceeded to complete a course of neo-adjuvant chemotherapy. PET/MRI was performed at time of diagnosis and then following completion of chemotherapy. (a) Pre-neoadjuvant PET/MRI. The top row is the PET, the middle row is the DCE-MRI, and the bottom row is the fused PET/MRI images. The index lesion is well characterized on these images as a FDG-avid heterogeneously enhancing lesion in the left breast. (b) A diffusion weighted image demonstrates increased signal intensity within the mass. (c) The corresponding ADC map demonstrates decreased signal intensity within the mass consistent with diffusion restriction. (d) Post-neoadjuvant PET/MRI. The top row is the PET, the middle row is the DCE-MRI, and the bottom row is the fused PET/MRI images. Following chemotherapy, there is mild increased signal around the biopsy clip on MRI (white arrow), but no FDG activity on PET and no abnormal signal on DWI or the ADC map (e and f), consistent with the complete pathological response confirmed at excision.

Figure 3a. A 62 year old female with a left breast invasive ductal carcinoma with positive left axillary lymph nodes. Whole-body PET/MR detected distant metastatic disease in this patient which was not previously diagnosed. (a) The top row is the PET, the middle row is the DCE-MRI, and the bottom row is the fused PET/MRI images. The index lesion is well characterized on these images as a FDG-avid avidly enhancing mass in the left breast. An unexpected rib metastasis is seen enhacing on DCE MRI and is FDG avid on PET (arrow).

Figure 3b. Whole body PET/MR a. T1-weighted contrast enhanced MRI and b. fused PET/MRI demonstrate an enlarged FDG avid axillary lymph node and an FDG avid mediastinal lymph node. The mediastinal lymph node is best seen on PET. In the pelvis, an iliac metastasis is better seen on (d) fused PET/MRI than c) T1-weighted MRI alone.