Accepted Manuscript

Title: PET/MRI of the Breast

Authors: Donna M. Plecha, Peter Faulhaber

PII: S0720-048X(17)30185-7
DOI: http://dx.doi.org/doi:10.1016/j.ejrad.2017.05.006
Reference: EURR 7819

To appear in: *European Journal of Radiology*

Received date: 21-3-2017
Revised date: 3-5-2017
Accepted date: 3-5-2017

Please cite this article as: Plecha Donna M, Faulhaber Peter.PET/MRI of the Breast.*European Journal of Radiology* http://dx.doi.org/10.1016/j.ejrad.2017.05.006

Title: PET/MRI of the Breast

Donna M. Plecha, M.D. (Corresponding Author)
University Hospitals Cleveland Medical Center
Department of Radiology
Mather Pavilion, B402
11100 Euclid Ave
Cleveland, OH 11406
Phone: 216-844-5330
Fax: 216-844-7178
Donna.Plecha@UHhospitals.org

Peter Faulhaber, M.D.
University Hospitals Cleveland Medical Center
11100 Euclid Ave
Department of Radiology
Cleveland, OH 44106

Highlights:
The feasibility of breast PET/MRI has been proven in recent literature, however the clinical usefulness has yet to be established. Review of the literature reveals the technical considerations and future potential of functional and multiparametric PET/MRI imaging of the breast.

Abstract:
The future clinical use of the combination of positron emission tomography (PET) with 2-Fluoro[F-18]-2-Deoxy-D-Glucose (FDG)and MRI is still unclear. If a patient requires a PET and breast DCE-MRI for staging purposes, both scans can be done in the same visit. In the breast, DCE-MRI is better at lesion detection (sensitivity), margin evaluation, and has a higher specificity than CT. The potential for multiparametric qualitative and quantitative imaging is also an advantage of PET/MRI which provides opportunity to improve tumor characterization and may ultimately lead to outcome prediction. This review discusses technical and clinical aspects of this emerging technology in breast cancer patients.

Introduction:

For years hybrid positron emission tomography (PET) with 2-Fluoro[F-18]-2-Deoxy-D-Glucose (FDG) and CT has offered combined anatomic and functional molecular information leading to increased specificity in oncological imaging of breast cancer patients. PET/CT with FDG is used for initial (staging) and subsequent therapy evaluation (restaging and response to therapy). It is not indicated for initial diagnosis of breast cancer or staging of the axilla due to relatively low sensitivity. For breast cancer diagnosis with FDG PET there was a variation in methods, some studies were performed with the patients in the supine position and other studies were performed with the patients prone. The prone position is the most sensitive but there remain limitations in sensitivity secondary to resolution (partial volume effects) and tumor FDG avidity[1]. There have been attempts to improve the sensitivity of FDG PET with newer instruments such as positron emission mammography (PEM) which have had some success by improving resolution[2]. Newer PET/CT instruments have not improved the sensitivity of diagnosing breast cancer with FDG. The CT portion of the exam is relatively insensitive to characterize breast cancer anatomically.

In recent years newer hybrid PET/MRI technology has emerged which combines the capabilities of dynamic contrast enhanced MRI (DCE-MRI) and PET, in an attempt to utilize the superb soft tissue characterization of MRI and the metabolic characterization of PET. Breast PET/MRI offers many potential advantages over PET/CT. Radiation dose is less with PET/MRI compared with PET/CT. Since the patient is in the exact same position for the PET and MRI scanning, there is

better alignment of lesions and anatomy. If a patient requires a PET and breast DCE-MRI for staging purposes, both scans can be done in the same visit. In the breast, DCE-MRI is better at lesion detection (sensitivity), margin evaluation, and has a higher specificity than CT. The potential for multiparametric qualitative and quantitative imaging with technologies such as perfusion imaging, diffusion weighted imaging (DWI), and MR spectroscopy (MRS), is an advantage of PET/MRI which provides opportunity to improve tumor characterization and may ultimately lead to outcome prediction.

Technical Considerations

Putting PET and MRI together in one room or one inside the other has limitations since each device interferes with the other. PET detectors in or near an MRI would degrade the magnetic field homogeneity and cause artifacts. Meanwhile, the MRI magnetic field distorts the photomultiplier signal in the PET. In addition, the gradient coils in the MRI can cause eddy currents in the PET electrons. Historically, there are three solutions to this problem. One solution, is a sequential system with the MRI and PET/CT in separate rooms with a shuttle table between them. The table facilitates accurate registration but this is not considered a true “fused” PET/MRI[3]. A second sequential solution is the PET and MRI in the same room separated by 3 meters with some additional shielding to the PET. Note there is no longer a CT as in the first solution[4]. In both sequential devices, the PET is time of flight (TF). The third solution is considered simultaneous imaging with the PET detectors inside the MRI. There are two simultaneous devices, one with non-time of flight PET and the other with time of flight[5, 6].

These scanners rely on PET detectors and electronics that are MRI compatible such as avalanche photodiode detectors or silicone photomultiplier tubes.

In addition to the problem of having compatible electronics in hybrid PET/MRI devices, another problem is correcting the PET images for attenuation. The standard for PET is to correct for soft tissue absorption of annihilation photons (511 keV) within the body. This is done by creating a transmission scan from the CT of the X-ray absorption accounting for the difference in photon energy between X-rays and 511 keV photons[7]. However, MRI is unable to measure attenuation since there is no direct relation between MR signals and photon absorption. Different models of attenuation are used to create attenuation maps from MR images. This is typically done by segmentation of tissue into classes such as, lung, fat, and soft tissue[8]. There is currently no correction for bone on commercially available scanners. However, methods are being tested to include bone[9]. There are SUV differences between PET/CT and PET/MRI some of which reflect lack of correction for bone. There is generally good agreement in lesion detection between the two hybrid machines. SUV values are often lower with PET/MRI compared to PET/CT and there is additional variation between types of instruments, sequential (same room) versus simultaneous.

One study of multiple myeloma with a simultaneous PET/MRI demonstrated similar lesion detection with FDG between PET/CT and PET(non TF)/MRI but generally lower SUV's with the latter[10]. A study at our institution on normal tissues with FDG comparing PET/CT to sequential PET/MRI demonstrated lower SUV values in mediastinal blood pool with PET/MRI, for

example[11]. This decrease likely reflects the time delay between the PET/CT and the PET/MRI. Other tissues such as bone marrow showed a higher SUV with PET/MRI. Tissues with relatively low metabolic activity such as lung and fat showed no difference between the two modalities. In general, then, there are SUV differences when using the different hybrid devices but image quality and lesion detection appears to be similar.

Targeted breast only PET/MRI imaging

DCE-MRI is commonly used to evaluate the breast for extent of disease in recently diagnosed breast cancer patients. The high special resolution and assessment of vascular permeability and neoangiogenesis leads to high sensitivity of DCE-MRI of the breast. However the high sensitivity can come at a cost of low specificity[12]. Combining the functional information of DCE-MRI with that of glucose metabolism of PET may improve specificity of breast DCE-MRI. By fusing PET images of the breast with DCE-MRI Moy and colleagues demonstrated an increase in PPV from 77% to 98% and an increase in specificity from 53% to 97%[13]. Expanding the functional information even further with multi-parameter breast DCE-MRI combined with PET may lead to a more targeted, and specific exam for patients. A multi-parameter breast MRI study by Pinker et al. combined 4 parameters; DCE-MRI, DWI, spectroscopy, and fused images from prone PET/CT with DCE-MRI, to show improved differentiation of benign and malignant breast lesions. Pinker's study used ^{18}FDG -PET/CT images performed on patients on a different day, no longer than 7 days from the DCE-MRI. Pinker and colleagues discovered all four parameters resulted in the highest accuracy for breast cancer diagnosis[14]. Figures 1 and 2 are examples of patients who underwent ^{18}FDG -PET/MRI with DWI. Both cases demonstrate diffusion restriction on DWI with

b=600, contrast enhancement with DCE-MRI and ^{18}FDG avidity in the index lesions. Both Fig 1 and Fig 3 demonstrate that even small satellite lesions can be seen with DCE-MRI and ^{18}FDG PET, potentially increasing specificity for smaller lesions in the breast seen on DCE-MRI.

Preoperative staging in patients recently diagnosed with breast cancer aids the multidisciplinary team in making treatment choices. A recent study by Botsikas and colleagues evaluated PET/MRI in preoperative breast cancer staging. The study included 101 breast lesions and 198 lymph node groups in 58 patients who underwent PET/MRI. They compared PET/MRI to MRI alone. The sensitivity for primary cancers was superior with DCE-MRI (100%) compared with quantitative PET/MRI (77%). The sensitivity for lymph nodes was also superior with DCE-MRI (88%) compared to PET/MRI (79%). However specificity for DCE-MRI (67%) was inferior to PET/MRI (100%) for primary cancers. There was no statistical significance for specificity for lymph nodes between the DCE-MRI and PET/MRI[15].

Recent advances are pushing the edge of the envelope even further. Schmitz and colleagues used a simultaneous PET/MRI system to obtain DWI DCE-MRI/PET images and correlated them to whole-slide histology in 5 estrogen receptor and progesterone receptor positive patients with biopsy proven invasive carcinoma. By using this approach they were able to show how molecular, structural (microscopic, anatomic), and functional information could be simultaneously obtained noninvasively to identify precancerous and malignant subtypes within heterogeneous tumors. In the future, multiparametric molecular and functional imaging may be able to provide comprehensive tumor profiling[16]. Image analysis in multiparameter imaging may be able to

increase the clinically relevant information gleaned from current imaging studies as outlined in a review of Radiomics by Gillies and colleagues[17].

Whole body (Torso) PET/MRI imaging

What is the best use of PET/MRI with FDG? This is still an open question in oncology. One role in breast cancer could be in cases where a patient would ordinarily have both a breast DCE-MRI and ^{18}FDG -PET/CT for initial evaluation. PET/MRI could potentially serve as the substitute for two separate scans. Breast cancer evaluation is an interesting possibility since many patients undergo an MRI of the breast after initial diagnosis and then get a PET/CT for initial therapy evaluation (staging). At present, there is no data to indicate PET/MRI could replace PET/CT as the standard of care for initial and subsequent therapy evaluation. However, in patients undergoing a DCE-MRI of the breast for staging the primary breast cancer and in whom distant metastases are suspected, a patient could undergo PET/CT first as standard of care followed by breast DCE-MRI with PET of the breasts on a PET/MRI machine. Alternatively, one could perform PET/MRI of the torso followed by PET/DCE-MRI of the breast at the same setting.

For example, at our institution, we performed PET/CT for initial therapy evaluation on a group of patients followed by PET/MRI on a sequential machine as a pilot study. Patients fasted for at least 4 hours and received an intravenous injection of 333 – 555 MBq (9-15 mCi) FDG. Patients then underwent clinical FDG PET/CT of the torso in supine position at approximately one hour followed by PET/MRI in prone position with a breast coil. For the PET portion the patient first underwent a free breathing 3D T1 weighted spoiled gradient echo (GE) sequence for mapping of attenuation followed by PET. PET was performed over two bed positions at 5 min per bed

position. The MRI portion included pre-contrast axial T1 weighted 3D GE, short tau inversion recovery (STIR) axial, and T1 weighted 3D GE fat saturated pulse sequences. Contrast was then administered and 5 axial T1 weighed 3D GE sequences were acquired each lasting 1.5 seconds each. Diffusion weighted images were performed with a 2D echo-planar imaging sequence. The PET images of the breast were reconstructed at both 4 and 2mm voxels. This protocol with PET/CT first could also be adapted to a simultaneous PET/MRI machine.

Alternatively, for patients with newly diagnosed breast cancer that require whole body PET and breast DCE-MRI for staging purposes, whole body PET/MRI without a CT, would offer patients a one stop imaging alternative which may provide more information at a reduced radiation dose compared to conventional PET/CT. When comparing whole body PET/CT to PET/MRI, Pace et al. demonstrated equivalent detection of the primary lesion as well as nodal, bone and pulmonary metastatic disease in 36 patients with breast cancer[18]. In another study by Taneja et al. 36 patients underwent whole body unenhanced PET/MRI followed by DCE-MRI of the breast and then an enhanced whole body PET/MRI. This took a total of just over an hour. Their protocol included simultaneous PET and MRI of the torso with a DIXON sequence both for attenuation correction and lesion localization. Additional MRI sequences of the brain were acquired. Torso imaging was followed by DCE-MRI imaging of the breasts in prone position with simultaneous PET acquisition. Due to limitations for evaluation of lung nodules a subsequent diagnostic CT of the chest was performed. Their study found a sensitivity of 100% for combined PET/MRI for the primary lesion for example. Most of their patients had single primary lesions. Metastatic disease detected was similar at the patient level for PET and MRI alone. However significantly more

metastatic lesions were see seen on MRI than on PET alone. At the breast level the detection of the primary tumor was the same comparing MRI and PET alone. However DCE-MRI detected 14 more breast lesions, 4 of which were false positives. PET/MRI changed management in one third of patients compared to the clinical staging before imaging[19]. The potential for improved detection of metastatic disease, while reducing radiation exposure and evaluating for breast extent of disease at one sitting is appealing especially in young patients with locally advanced disease.

PET/MRI has been shown to have superior diagnostic accuracy compared to PET/CT when detecting bone and liver metastases, which are the most common sites of metastatic disease in breast cancer patients. Combining DWI and DCE-MRI has been shown to increase diagnostic accuracy and confidence compared to PET/CT in patients with liver metastases[20]. In a study by Melsaether and colleagues PET/MRI with DWI imaging yielded better sensitivity for liver and bone metastases, in breast cancer patients, compared with PET/CT at about half the radiation dose[21].

For breast cancer patients being evaluated with whole-body imaging for staging of recurrence, PET/MRI was shown to be superior compared to PET/CT, MRI and CT in a study by Sawicki et al.[22]. In their study PET/MRI detected 100% of the metastatic lesions compared to the other imaging modalities. The results imply PET/MRI should be considered a valuable alternative, with less radiation, in whole-body imaging of recurrent breast cancer.

Quantitative multiparameter PET/MRI

For years quantitative PET has included measuring standard uptake values (SUV) and metabolic tumor volume (MTV). Quantitative perfusion characteristics during DCE-MRI, include measuring volume transfer constant between blood plasma and the interstitial environment (K^{trans}) and the transfer constant from the interstitial environment to the blood plasma (k_{ep}) as well as initial slope of the enhancement curve (MRslope). DWI is a short MRI technique that reveals the microscopic cellular environment evaluating diffusion restriction, using the apparent diffusion coefficient (ADC) as a quantitative measurement. Tumors have lower ADC values compared to normal breast tissue in most instances because of increased diffusion restriction. MRI spectroscopy (MRS) uses total choline (tCho) as a quantitative measurement which is usually elevated in tumors compared to normal breast tissue[23].

The development of metastatic disease is closely linked to tumor microenvironment[24]. Quantitative measurements during imaging of a breast tumor microenvironment and tumor characteristics may lead to accurate prediction of tumor aggressiveness or metastatic potential. Aggressiveness of breast cancer using PET/MRI was evaluated by Margolis et al. in 12 patients that underwent simultaneous breast DCE-MRI and PET and whole body PET/MRI in terms of metastatic burden and Ki67 status. Results revealed patients with systemic metastases had a significantly lower k_{ep} compared to those with local disease. Metastatic burden correlated positively with K^{trans} and SUV and negatively with k_{ep}. Ki67 tumors had a significantly higher K^{trans} compared to Ki67 negative tumors. A negative correlation was found between metabolic tumor volume and transfer constant[25]. Using quantitative parameters of PET/MRI may aid in

assessment of tumor aggressiveness and metastatic potential which may assist in treatment planning and monitoring response to chemotherapy in breast cancer patients. Further investigation evaluating the clinical usefulness of combining different parameters of PET and DCE-MRI is needed.

Quantitative multiparameter PET/MRI may be helpful in predicting or monitoring response to chemotherapy in breast cancer. Neoadjuvant chemotherapy (NAC) has become standard of care in the treatment of patients with locally advanced breast cancer. Successful NAC gives patients the option of less invasive breast conserving surgery rather than mastectomy. During NAC treating physicians can monitor response to therapy, allowing time for treatment plan changes if there is no disease improvement. Studies have also shown that patients that achieve a pathological complete response (pCR) have overall superior disease-free survival and overall survival[26]. Therefore achieving pCR is an important objective for patients being treated for breast cancer.

The decrease in metabolic activity of breast cancer responding to chemotherapy has been demonstrated with a decrease of ^{18}F-FDG uptake on PET imaging[27-29]. DCE- MRI has also been shown to demonstrate response to chemotherapy with decrease in size of the cancer as well as changes in ADC and tCho levels[19, 26, 30]. Combining these two modalities leads to the use of multi-parametric imaging in monitoring and predicting response to NAC.

Studies have independently shown that decreasing SUV_{max} , increasing ADC values and decreasing tCho levels after the first dose of chemotherapy have been associated with pCR[27-34]. It would seem logical that combining different parameters may increase predictability of pCR or ultimately outcome such as recurrence free survival.

Lim et al. evaluated if changes in quantitative parameters during PET/MRI could predict recurrence free survival after one dose of NAC. Out of 54 patients, 13(24%) had recurrence during follow up. Their results revealed that a greater decrease in SUV_{max} and MR slope, and a greater increase in ADC were associated with recurrence free survival. The combination of PET and DCE-MRI quantitative data also performed better than the individual modalities alone in predicting disease-free survival[35].

Conclusion

PET/MRI of the breast can be performed as a single exam, whole body or breast alone, for initial evaluation or as a follow up to PET/CT to stage recently diagnosed breast cancer patients. There is some variability in types of PET/MRI instruments, sequential versus simultaneous and non-TF versus TF-PET as part of the device. The trend appears to be moving towards simultaneous devices. Further research is needed to determine the best approach now that feasibility has been demonstrated. Many studies have explored the clinical utility of PET/MRI in breast cancer patients. Combining the functional information of multiparametric quantitative and qualitative PET/MRI may increase the clinical impact on patient care. Future studies with breast cancer specific radiotracers may expand the usefulness of PET and breast PET/MRI imaging in breast cancer patients.

Conflict of Interest

Dr. Plecha and Dr. Faulhaber do not have any conflict of interest to report that would pertain to this review article titled: “PET/MRI of the breast”.

1. Avril, N., et al., *Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations.* J Clin Oncol, 2000. **18**(20): p. 3495-502.
2. MacDonald, L., et al., *Clinical imaging characteristics of the positron emission mammography camera: PEM Flex Solo II.* J Nucl Med, 2009. **50**(10): p. 1666-75.
3. Veit-Haibach, P., et al., *PET-MR imaging using a tri-modality PET/CT-MR system with a dedicated shuttle in clinical routine.* MAGMA, 2013. **26**(1): p. 25-35.
4. Zaidi, H., et al., *Design and performance evaluation of a whole-body Ingenuity TF PET-MRI system.* Phys Med Biol, 2011. **56**(10): p. 3091-106.
5. Delso, G., et al., *Performance measurements of the Siemens mMR integrated whole-body PET/MR scanner.* J Nucl Med, 2011. **52**(12): p. 1914-22.
6. Zeimpekis, K.G., et al., *Clinical Evaluation of PET Image Quality as a Function of Acquisition Time in a New TOF-PET/MRI Compared to TOF-PET/CT--Initial Results.* Mol Imaging Biol, 2015. **17**(5): p. 735-44.
7. Kinahan, P.E., et al., *Attenuation correction for a combined 3D PET/CT scanner.* Med Phys, 1998. **25**(10): p. 2046-53.
8. Martinez-Moller, A., et al., *Tissue classification as a potential approach for attenuation correction in whole-body PET/MRI: evaluation with PET/CT data.* J Nucl Med, 2009. **50**(4): p. 520-6.
9. Delso, G., et al., *Preliminary study of the detectability of coronary plaque with PET.* Phys Med Biol, 2011. **56**(7): p. 2145-60.
10. Sachpekidis, C., et al., *Comparison of (18)F-FDG PET/CT and PET/MRI in patients with multiple myeloma.* Am J Nucl Med Mol Imaging, 2015. **5**(5): p. 469-78.
11. Kershah, S., et al., *Comparison of standardized uptake values in normal structures between PET/CT and PET/MRI in an oncology patient population.* Mol Imaging Biol, 2013. **15**(6): p. 776-85.
12. Peters, N.H., et al., *Meta-analysis of MR imaging in the diagnosis of breast lesions.* Radiology, 2008. **246**(1): p. 116-24.
13. Moy, L., et al., *Role of fusion of prone FDG-PET and magnetic resonance imaging of the breasts in the evaluation of breast cancer.* Breast J, 2010. **16**(4): p. 369-76.
14. Pinker, K., et al., *Improved differentiation of benign and malignant breast tumors with multiparametric 18fluorodeoxyglucose positron emission tomography magnetic resonance imaging: a feasibility study.* Clin Cancer Res, 2014. **20**(13): p. 3540-9.
15. Botsikas, D., et al., *Clinical utility of 18F-FDG-PET/MR for preoperative breast cancer staging.* Eur Radiol, 2016. **26**(7): p. 2297-307.

16. Schmitz, J., et al., *Decoding Intratumoral Heterogeneity of Breast Cancer by Multiparametric In Vivo Imaging: A Translational Study.* Cancer Res, 2016. **76**(18): p. 5512-22.
17. Gillies, R.J., P.E. Kinahan, and H. Hricak, *Radiomics: Images Are More than Pictures, They Are Data.* Radiology, 2016. **278**(2): p. 563-77.
18. Pace, L., et al., *Comparison of whole-body PET/CT and PET/MRI in breast cancer patients: lesion detection and quantitation of 18F-deoxyglucose uptake in lesions and in normal organ tissues.* Eur J Radiol, 2014. **83**(2): p. 289-96.
19. Taneja, S., et al., *Simultaneous whole-body (1)(8)F-FDG PET-MRI in primary staging of breast cancer: a pilot study.* Eur J Radiol, 2014. **83**(12): p. 2231-9.
20. Reiner, C.S., et al., *Protocol requirements and diagnostic value of PET/MR imaging for liver metastasis detection.* Eur J Nucl Med Mol Imaging, 2014. **41**(4): p. 649-58.
21. Melsaether, A.N., et al., *Comparison of Whole-Body (18)F FDG PET/MR Imaging and Whole-Body (18)F FDG PET/CT in Terms of Lesion Detection and Radiation Dose in Patients with Breast Cancer.* Radiology, 2016. **281**(1): p. 193-202.
22. Sawicki, L.M., et al., *Evaluation of (1)(8)F-FDG PET/MRI, (1)(8)F-FDG PET/CT, MRI, and CT in whole-body staging of recurrent breast cancer.* Eur J Radiol, 2016. **85**(2): p. 459-65.
23. Rahbar, H. and S.C. Partridge, *Multiparametric MR Imaging of Breast Cancer.* Magn Reson Imaging Clin N Am, 2016. **24**(1): p. 223-38.
24. Robinson, B.D., et al., *Tumor microenvironment of metastasis in human breast carcinoma: a potential prognostic marker linked to hematogenous dissemination.* Clin Cancer Res, 2009. **15**(7): p. 2433-41.
25. Margolis, N.E., et al., *Assessment of Aggressiveness of Breast Cancer Using Simultaneous 18F-FDG-PET and DCE-MRI: Preliminary Observation.* Clin Nucl Med, 2016. **41**(8): p. e355-61.
26. von Minckwitz, G., et al., *Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes.* J Clin Oncol, 2012. **30**(15): p. 1796-804.
27. Wahl, R.L., et al., *Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation.* J Clin Oncol, 1993. **11**(11): p. 2101-11.
28. Schelling, M., et al., *Positron emission tomography using [(18)F]Fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer.* J Clin Oncol, 2000. **18**(8): p. 1689-95.
29. Smith, I.C., et al., *Positron emission tomography using [(18)F]-fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy.* J Clin Oncol, 2000. **18**(8): p. 1676-88.
30. Tozaki, M., et al., *Predicting pathological response to neoadjuvant chemotherapy in breast cancer with quantitative 1H MR spectroscopy using the external standard method.* J Magn Reson Imaging, 2010. **31**(4): p. 895-902.
31. Minarikova, L., et al., *Investigating the prediction value of multiparametric magnetic resonance imaging at 3 T in response to neoadjuvant chemotherapy in breast cancer.* Eur Radiol, 2016.
32. Meisamy, S., et al., *Neoadjuvant chemotherapy of locally advanced breast cancer: predicting response with in vivo (1)H MR spectroscopy--a pilot study at 4 T.* Radiology, 2004. **233**(2): p. 424-31.

33. Kawamura, M., et al., *Early prediction of response to neoadjuvant chemotherapy for locally advanced breast cancer using MRI.* Nagoya J Med Sci, 2011. **73**(3-4): p. 147-56.
34. Leong, K.M., P. Lau, and S. Ramadan, *Utilisation of MR spectroscopy and diffusion weighted imaging in predicting and monitoring of breast cancer response to chemotherapy.* J Med Imaging Radiat Oncol, 2015. **59**(3): p. 268-77.
35. Lim, I., et al., *The combination of FDG PET and dynamic contrast-enhanced MRI improves the prediction of disease-free survival in patients with advanced breast cancer after the first cycle of neoadjuvant chemotherapy.* Eur J Nucl Med Mol Imaging, 2014. **41**(10): p. 1852-60.

Figures:

Figure 1: A 49 year old female who presented with a palpable mass in the right breast. At the time of presentation she had two adjacent masses in the right breast and abnormal axillary lymph nodes on ultrasound. She was diagnosed with estrogen receptor positive, progesterone receptor positive and HER-2/NEU negative, stage IIB breast cancer. (a) The top row is the DCE-MRI, the middle row is the PET and the bottom row are the fused PET/MRI images. The index mass (white arrows) and satellite lesion (red arrows), in the upper outer quadrant of the right breast, are well delineated on the DCE-MRI and PET images. (b) Diffusion weighted image, with b value=600, demonstrating increased signal intensity within the mass (arrow). (c) ADC map demonstrating decreased signal intensity within the mass signifying restriction (arrow). (d) The top row is the DCE-MRI, the middle row is the PET and the bottom row are the fused PET/MRI images. The level II axillary lymph node (red arrow) is evident on all images posterior to the pectoralis minor muscle.

Figure 2: A 67 year old female who had never had a mammogram, presented with bilateral breast masses. She underwent bilateral breast biopsies and lymph node biopsy. She was diagnosed with estrogen receptor positive, progesterone receptor positive and HER-2/NEU negative stage IIIC locally advanced invasive ductal breast cancer. (a) The top row is the DCE-MRI, the middle row is the PET and the bottom row are the fused PET/MRI images. The index mass (red arrow) involving the right nipple enhances on DCE-MRI and is FDG avid on PET. The large level II necrotic axillary lymph nodes (blue arrow) posterior to the pectoralis minor muscle are well seen on the DCE-MRI, PET and fused PET/MRI images. (b) The contralateral left breast cancer (green circle) is well visualized on the DCE-MRI, PET and fused PET/MRI images. Level II right axillary lymph nodes (red arrow) are also apparent. The more necrotic lymph nodes are not as FDG avid. (c) Diffusion weighted images, with b value=600, demonstrating the right nipple mass (white arrow) with increased signal intensity and the level II axillary lymph nodes with necrosis (red arrow) and increased signal intensity within the left breast mass (blue arrow). (d) ADC map demonstrating decreased signal intensity within the right nipple mass (white circle), level II right axillary lymph nodes (white arrow) consistent with restriction (e) ADC map of left breast mass (white circle) with decreased signal intensity signifying restriction as well as the right level II lymph nodes (white arrow).

Figure 3: 40 year old patient who presented with a palpable right breast mass and underwent an excisional biopsy for diagnosis at an outside institution, diagnosing estrogen receptor positive, progesterone receptor positive and HER-2/NEU negative stage IIIA invasive mammary carcinoma. Her PET/MRI was obtained after her excisional biopsy. (a) The top row is the DCE-MRI, the middle row is the PET and the bottom row are the fused PET/MRI images. There is a post-surgical seroma with FDG avid inferior edge of the seroma (white arrows). There are two anterior lesions enhancing on DCE-MRI and with increased uptake of FDG consistent with additional sites of multicentric disease (red arrows). There is also a small focus of additional disease measuring less than 5mm in the posterior central aspect of the right breast (blue arrows) which enhances on DCE-MRI and has FDG avidity. (b) The same patient has an abnormal level I lymph node seen on both DCE-MRI and PET images.