PROTOCOL TITLE: Dedicated Breast PET/MRI in evaluation of disease in women with newly diagnosed breast cancer

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BACKGROUND

Despite advances in treatment, the stage at breast cancer diagnosis remains the most important factor in patient survival. Breast MRI is performed routinely as the mainstay in initial staging and evaluation of additional sites of ipsilateral and contralateral disease prior to oncologic/surgical management. Although the sensitivity of breast MRI is high, specificity is moderate and variable (1- 2), resulting in false positives which delay treatment and result in patient anxiety. Positron emission tomography provides functional and metabolic information that may improve specificity of detection. Recent literature suggests that fusing separately acquired Breast MRI and FDG-PET improves differentiation of benign versus malignant breast lesions, reducing the number of unnecessary biopsies (3-6). However, the potential of novel combined FDG PET/MRI performed simultaneously, which would decrease radiation to the patient, motion misregistration, and study acquisition time, has yet to be investigated.

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STUDY DESIGN

Study design:

Patient cohort and clinical question: This is a single institution study will involve women over age 25 with newly diagnosed breast cancer and for whom a breast MR has been ordered as standard of care will be recruited to undergo a hybrid dedicated Breast PET/MRI for evaluation of extent of disease prior to surgical and oncologic management. The study will investigate any incremental added benefit to breast MRI specificity by the addition of concurrent hybrid breast PET. Our hypothesis is that the combination of Breast PET/MRI, will improve specificity and decrease the number of false positive breast biopsies recommended based on breast MRI findings. Imaging modalities: The study will investigate a new technology of a hybrid 3T PET/MRI with a dedicated breast coil, capable of performing a dedicated breast PET/MRI. Patients with newly diagnosed breast cancer will be recruited to undergo a dedicated breast PET/MRI in lieu of standard of care breast MRI alone. The MRI portion of the PET/MRI will be read routinely by a clinical radiologist on service and given a BI-RADS followed by routine standard of care based on the BI-RADS assessment category. The PET portion of the hybrid PET/MRI will be archived to be used for research purposes only. Subjects will be informed of this in the informed consent. For purposes of the research study, all breast PET/MRIs will be anonymized and broken down into two components: a breast MRI component and the entire study with fused PET/MRI. This will be archived and stored on an IDEAL server. Several reading lists, or sessions, will be created from the archived studies containing 10 patients with a mixture of both the sole breast MRI component of the study for some patients as well as the entire reading session will include MRI only portion for patient A, the entire PET/MRI for patient B, MRI only portion for patient C, entire PET/MRI for patient D, etc, while second reading session presented to a reader will include the entire PET/MRI for patient A, MRI only portion for patient B, entire PET/MRI for patient C, MRI only portion for patient D etc). Readers in the study will be dedicated breast imagers, with prior experience in reading PET/CTs who will be blinded to clinical MRI reports as well as any follow up or pathology. After a reader training period of reading 10 breast PET/MRIs readers will be provided with at random a reading list/session of anonymized studies of breast PET/MRIs from the recruited cohort. Readers will be asked to provide a BIRADS as well as a likelihood of malignancy if BIRADS is greater than 2. After an extinguishing period of 6 weeks, they will read a different reading session PET/MRI portion of the study and provide BIRDAS and likelihood of malignancy if BIRADS is greater than 2. The gold standard will be pathology reports from any biopsies initiated by the breast MRI performed on the patients in this cohort. Negative and benign studies will be deemed true negatives after a period of 2 years without interval recurrence or a mastectomy specimen pathology report without additional sites of disease in addition to known index cancer. In addition, initial appropriate IV 18 F-FDG dosage will be evaluated by performing the first 10 breast PET/MRIs with different IV dosages of 18F-FDG as a pilot study. Routine whole-body PET/CT is performed with 0.15-0.19mci/kg (approximately 10mci of total dose for average weight patient), however counts are collected from at least 5 body stations spending approximately 4 minutes per body station. In our protocol, we will only be acquiring 18F-FDG

counts from the breasts, and since these are acquired for the duration of the breast MRI portion which takes 20 minutes, 20 minutes will be spent acquiring 18-F-FDG counts from the breasts, suggesting that a lower dosage of 18-F-FDG may be sufficient. *Please see attachments for continuation pages of study design section.

Primary Objective:

To assess the added benefit of breast FDG PET to the specificity of breast MRI performed on a hybrid dedicated simultaneous breast PET/MRI in patients with newly diagnosed breast cancer

Secondary Objective:

1. To assess the added benefit of FDG PET to MRI versus MRI alone performed on hybrid dedicated breast PET/MRI in various measures of accuracy (sensitivity, PPV, NPV)
2. To determine the optimal 18F-FDG dosage for a dedicated Breast PET/MRI
3. To assess whether decreased IV FDG dosage (than that used for whole body PET) may be used without compromising PET image quality (signal/noise ratio) while imaging the breast only
4. To explore the relationship of hybrid FDG PET/ MRI imaging features in prediction of breast cancer tumor biology (Estrogen/Progesterone and HER2 receptor status) both of the index cancer as well as the additional cancers diagno8s/9e/1d9 b3:a0s0ePdM on biopsy recommendations from the hybrid FDG PET/MRI
5. To explore the relationship of hybrid FDG PET/ MRI imaging features in prediction of breast cancer tumor recurrence (using a surrogate of Ki-67 and oncotyping when available) both of the index cancer as well as the additional cancers diagnosed based on biopsy recommendations from the hybrid FDG PET/MRI
6. To assess the added sensitivity of hybrid FDG PET/MRI in detection of axillary and internal mammary lymph node metastasis compared to MRI alone
7. To assess perceived patient benefit of undergoing a simultaneous FDG PET/MRI which may potentially decreased number of unnecessary biopsies (if our hypothesis that hybrid FDG PET/MRI has improved specificity over MRI alone holds true), decrease delays in surgery

Statistical Considerations:

1) Sample size: The primary endpoint is to evaluate the specificity by adding breast FDG PET to MRI compared with breast MRI alone for the diagnosis on patients with newly diagnosed breast cancer. Based on the results from previous studies, a specificity for PET/MRI of at most 60% will be considered as unacceptably low as it would provide little benefit over MRI alone. Hence, the null hypothesis that the specificity is 60% will be tested against the alternative hypothesis that the specificity is greater than 78%, i.e., an improvement of 30% on the original specificity. Therefore, a sample size of 42 breast biopsy negative subjects is required for rejecting the null hypothesis with 90% power at the one-sided 0.1 significance level. Given a general 20% positive biopsy rate, we will expect 11 biopsy positives resulting in 53 biopsy subjects. Eventually, with a 40% rate biopsy recommendation, we plan to recruit around 147 patients by allowing a 10% drop-off rate.

2) Statistical analysis: Primary endpoint: the specificity for the diagnosis based on entire PET/MRI and MRI alone will be calculated and reported along with the corresponding two-sided 90% confidence intervals, where the confidence intervals will be constructed using the Wilson score method. Furthermore, a paired McNemar's test will be used to compare the specificity based on the two imaging modalities. Secondary endpoints: sensitivity, PPV, NPV for the diagnosis based on entire PET/MRI and MRI alone will be calculated and reported along with the corresponding two-sided 90% confidence intervals constructed by Wilson score method. Subsequent paired McNemar's tests will be used to compare each diagnosis metric based on the two imaging modalities. The results will be summarized in tabular format. Under a grid of different IV FDG dosages, the corresponding signal to noise ratios (SNR) will be obtained for each patient's breast PET imaging. The average SNR over patie8n/9ts/19v3s:0. 0 IPVM FDG dosages will be summarized in plot format to determine the optimal dosage. To further assess the prediction performance of hybrid FDG PET/ MRI imaging features on breast cancer endpoints, we will use a logistic regression and a cox proportional hazard model for tumor biology and tumor recurrence, as endpoints respectively. Clinical variables and confounders will also be adjusted for each model. Finally, the sensitivity in detection of axillary and internal mammary lymph node metastasis between two imaging modalities will be summarized and compared; and the diagnosis statistics including sensitivity, specificity, PPV, NPV will be summarized and compared under perceived patients.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

Women over age of 25 with newly diagnosed breast cancer and for whom a breast MR has been ordered as standard of care

Exclusion Criteria:

Male subjects Women younger than 25. Pregnant subjects Unable or unwilling to undergo MRI. Previous adverse reaction to 18F-FDG Unwilling to undergo biopsy of MRI positive lesions

DATA AND SAFETY MONITORING PLAN

There will be no use of medical monitors. The study protocol involves administration of trace amounts (micrograms) of radioactive drug FDG. No pharmacological effects can be observed at this mass level.

Due to the risk profile of this study, we do not believe an interim analysis is necessary nor has the sample size been calculated to allow for an interim analysis. Secondary to alpha-spending, the sample size would have to be increased if an interim analysis were to take place. This increase in sample size is not justified given the lack of benefit to such an analysis.

The Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) will not be utilized since it’s not required. There are no therapeutic interventions. This study involves administration of trace amounts (micrograms) of radioactive drug FDG. No pharmacological effects can be observed at this mass level. 18F-FDG has been widely used for research and is approved by the FDA for routine clinical diagnostic studies.