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Review Article

Failure to Launch: Lessons Learned from a PET-MRI Pilot Grant Study in Patients with Triple Negative and Her2/Neu Enriched Breast Cancer

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Abstract

Lessons learned from launching a pilot clinical radiology study include the importance of multi-disciplinary engagement and adequate support from research staff.

Keywords: PET-MRI; pilot grant study; lessons learned; triple negative breast cancer; teamwork

Introduction

Advancing imaging technology through translational research techniques is a major hallmark of the field of Radiology and ranks amongst the highest of medical innovations [1]. However, radiologists continue to face many challenges and barriers in developing these advancements through research studies. These barriers must be recognized and addressed in order to successfully conduct a clinical radiology research study.

Early studies of MRI imaging drew criticism for methodologic deficiencies, in part due to lack of dedicated training in research methodology for many radiologists. [2] Beyond lack of dedicated research training, additional barriers to research in radiology include the need for protected research time resulting in time away from the radiologists' clinical schedule, paying for scanner time, and "cultural" barriers including difficulty in attracting research-oriented individuals into the primarily clinical field of radiology. [1] Within the current structure of radiology residency (5 years) and fellowship (1 year), it is often difficult for trainees to develop solid collaborative relationships between radiologists and other clinicians within a subspecialty. [1] Critical elements necessary for a successful research program noted by Krestin (2007) include access to funding, a team of motivated key project personnel, and a long-term view of the end goal. [3]

Here we present the challenges and lessons learned at our institution during the implementation of an approved pilot grant study, "Assessment of pathologic complete response using simultaneous dynamic contrast-enhanced breast MRI (DCE-MRI) and FDG-PET in the triple negative and HER2-enriched breast cancer population."

Pilot Grant Study Protocol:

Study Aims and Hypothesis:

The initial pilot grant proposal for this prospective study was submitted in 2017. The study aimed to evaluate the predictive values of pathologic complete response (pCR) utilizing 18F-FDG PET-MRI focused on the triple negative and HER2-enriched patient population. This is a subset of tumors in which the prediction of pathologic complete response is crucial to patient care. At the time of pilot grant application, optimal accuracy and predictive values had not been shown with the standard of care post-neoadjuvant chemotherapy (NAC) MRI. We hypothesized that adding the metabolic information from PET would increase the accuracy and specificity in predicting pCR in the triple negative and HER2-enriched subset population. The study received funding approval in 2017.

Study Recruitment and Enrollment:

This pilot study planned to enroll a total of 25 patients. Eligibility criteria included female patients aged 18-89 with biopsy proven Stage II-III triple negative or HER2 positive breast cancer who were planning to undergo neoadjuvant chemotherapy per recommendation of a breast oncologist. Exclusion criteria included patients with the same age range and mixed hormone receptor profile, evidence or concern of metastatic disease, previous ipsilateral breast cancer, lumpectomy, or mastectomy, any previous therapy for current diagnosis including surgery, radiation, and systemic therapy, and any contraindication to MRI, male patients, adults unable to be consented, pregnant women, and prisoners.

The initial study protocol stated that study participants would be referred by clinicians in surgery or oncology. Our initial plan (applying only to first visits before the start of the NAC treatment) was for patients with biopsy proven triple negative or Her2/neu enriched breast cancer to be referred to the medical oncologist by the breast surgeon. Patients that needed to be evaluated for extent of disease and that meet criteria for NAC would have a whole-body PET/CT and a breast MRI ordered by the oncologist. Prospective participants would be approached in the clinic by the clinical coordinator following the medical oncology consultation. Patients consenting to participate in our study would be scheduled to have both body PET/CT and Breast MRI scans on the same day in scanners that are in adjacent rooms. In addition to full diagnostic breast MRI sequences, these patients would undergo 10-15 minutes of extra scan time to acquire breast PET/MRI images for research purposes. An alternate recruitment scenario (applying to the first visit) was for patients with biopsy proven triple negative or HER 2-enriched breast cancer to be referred to the medical oncologist by the breast surgeon. Those that meet criteria for NAC would be approached in clinic by the clinical coordinator following the medical oncology consultation. A pre and post NAC research breast PET/MRI would be

ordered by the oncologist or surgeon. Scheduling of the PET/MRI would be facilitated by the clinical coordinator.

Study Procedures:

Enrolled participants would undergo a simultaneous PET/MRI examination, following the same protocol for both visits, before neoadjuvant and after neoadjuvant chemotherapy. The patient would follow the department protocol for both the PET and the MRI portions of the exam, including filling questionnaires as well as having blood glucose and renal function testing prior to scanning. Patients with a clinical whole-body PET/CT order would follow the same preparations, but would complete their PET/CT scan first and then walk to the PET/MRI scanner in the adjacent room to have the breast PET/MRI performed.

A subspecialty trained breast radiologist would interpret the MRI portion of the examination, blinded to the PET examination. A subspecialty trained nuclear medicine radiologist would interpret the PET portion of the examination, blinded to the MRI examination. After the individual blinded reads, a joint read for the PET/MRI would be created by both the breast trained radiologist and the nuclear medicine trained radiologist. After neoadjuvant chemotherapy, another PET/MRI would be ordered by the oncologist, following the same protocol. Tumor characteristics would be recorded, including changes in tumor size, morphology, kinetic curve information, and the standard uptake value (PET). A detailed evaluation of the lumpectomy specimen or mastectomy specimen would be performed by pathology. Pathologic complete response would be defined as the complete absence of in situ or invasive disease in the final surgical specimen. Those patients who achieve complete pathological response would be recorded with evaluation of associated imaging characteristics on PET/MRI. The accuracy, positive predictive value and negative predictive values of PET/MRI in predicting pCR would be calculated to evaluate for support of the hypothesis. Statistical significance would be assessed by logistic regression analysis.

Study Timeline:

Our intended recruitment plan was to recruit 25 local study subjects in the 8 months following the opening of the study. Each enrolled study subject would complete two PET/MRI scans (lasting approximately 2 hours each) during a six-month period. One PET/MRI would be completed before chemotherapy treatment and the second following chemotherapy treatment. Subject enrollment and data collection was anticipated to be complete in 2 years. The estimated date for the investigators to complete the study was April 1, 2020.

Challenges and Lessons Learned:

Challenge 1: Low patient enrollment.

In 2017, our study initially met with difficulty with patient enrollment. Although the pilot grant had been designed with multidepartment support, including Breast Surgery and Breast Oncology, patient enrollment was very low. Due to the COVID-19 pandemic in 2020, the relocation of two of the original collaborating oncologists and dedicated research coordinator as well as a lack of dedicated research time for the remaining researchers, study initiation was postponed to 2022.

In early 2022, additional radiologists joined the team with the hope of completing the study. We aimed to combat the initial low enrollment experiences in 2017 by coordinating with the clinicians at a higher level of engagement, and invited input from Breast Oncology and Breast Surgery at research meetings. Unfortunately, though there was interest from the clinical teams to participate in project planning, and it was difficult to connect with clinical colleagues for various reasons to coordinate recruitment of patients who met the inclusion criteria. These reasons again included lack of a dedicated research coordinator for radiology and lack of dedicated research time. This lack of engagement and input from the multi-disciplinary clinical team was a significant obstacle to patient enrollment. Breast oncologists and surgeons are the main drivers of ordering standard of care imaging studies for patients who have been recently diagnosed with breast cancer and identifying which patients are candidates for NAC. We attempted to overcome the obstacle of clinician engagement and reluctance to assume an active role in the study by conducting short meetings with Breast oncology to determine the utilized clinical criteria for ordering staging PET CT and breast MRI imaging, rather than staging CT chest, abdomen, and pelvis examinations. However, the burden of management continued to fall on the ordering oncologist.

Lesson Learned: Multidisciplinary partnership is imperative.

Challenges	Lesson Learned
Low patient enrollment	Multidisciplinary partnership is imperative.
Coordination between clinical services	Effective leadership and adequate support from research staff are key.
Low multidisciplinary engagement	"Coming together is a beginning. Keeping together is progress. Working together is success." - Henry Ford.

Table 1:

Caption: Challenges and lessons learned from launching a pilot clinical radiology study are listed in Table 1.

Often, radiologists are seen in the role of a consultant for the diagnosis and treatment of breast cancer, rather than performing in the role of a primary provider in cancer care. Thus, it is imperative that, in pilot studies which require an enrollment of a certain subset of patients, that there is buy-in and participation in the study from all clinical team members, including oncology and surgery, who have a primary patient-facing role in the diagnosis, treatment, and management of breast cancer. Multi-disciplinary clinical team members often have an advantage over radiology in being able to meet with and discuss treatment plans at length with their patients as well as to provide them with potential avenues for involvement in research studies. Barring active participation in the study, the clinical services in the hospital should be open to collaboration with radiology for pilot studies, as it is this work which allows for innovation and improved patient outcomes.

Challenge 2: Coordination between clinical services.

In late 2022, we chose to redirect our efforts to improve study enrollment by identifying recently biopsy-proven triple negative or Her2/neu-enriched breast cancers in conjunction with our pathology colleagues, who participate in a weekly Breast Cancer Radiology-Pathology conference and identify these cases as part of their clinical workflow. We hoped that by identifying the patients shortly after their biopsy, prior to their first appointment with the Breast Oncology or Breast Surgery departments, that we would be able to contact the departments to discuss if this patient is a candidate for a standard of care PET-CT/Breast MRI prior to NAC and therefore may be eligible for our PET-MRI study. Unfortunately, this workflow also failed to yield additional patients for enrollment due to the difficulty in coordination between the varying clinical services, and the lack of a research manager or support staff who could assist with contacting the clinical team as well as contact the patient for informed consent.

We further anticipated obstacles related to coordination of care beyond patient enrollment, including making the clinical appointment for each patient and booking the research scanner time on the PET-MRI scanner. Scanner time on the research scanner must be reserved and paid for from the research stipend.

Lesson Learned: Effective leadership and adequate support from research staff are key.

The coordination required for a successful radiology pilot study is immense. Initially, there must be coordination between radiology and the clinical team members, who would help to identify patients who meet the inclusion

criteria. There must then be coordination for providing the patient with informed consent, scheduling the patient for their research scans and standard of care imaging, as well as reserving specific scanner time. Organizing tasks for a radiology pilot study do not end with patient enrollment, and it is important to have a research or study coordinator who may be able to act as a point person to help to coordinate all the moving parts (including managing the interdisciplinary teams and ensuring technologist support staff for performing the research scans as well as coordinating the actual patient imaging appointments).

Challenge 3: Low multidisciplinary engagement.

The lack of multidisciplinary engagement in the pilot study formed a significant barrier to the successful launch of the research study. A radiology pilot study, especially one which seeks to illuminate the utility of new imaging techniques, requires a shared goal and vision from not only the radiology department, but also the clinical teams who are the primary providers for the patients. Although each department is working in their own way to provide excellent patient care, the success of a radiology pilot study requires the dismantling of each department's tendency to work in silos, and instead work together as a multidisciplinary team.

Lesson Learned: "Coming together is a beginning. Keeping together is progress. Working together is success." - Henry Ford.

Forming a team of motivated individuals who each have clearly defined roles and strengths, including multidisciplinary and research staff input, would help to mitigate many of the challenges of launching a radiology pilot study. Defining clear roles for each participant in the study (including radiologists, pathologists, surgery or oncology clinicians, research coordinators, technologists, research staff) would help to lessen everyone's strain of balancing a clinical workload with research activities and hopefully to ensure continued success. Even after enrolling the first patient and coordinating their first research study, there remains a significant amount of coordination required to complete a successful study. Teamwork, clear communication, and dedication are required each step of the way, with the team constantly growing and working together to ensure success.

Conclusion:

The combination of lack of multi-disciplinary team engagement, support from research staff in the form of a study coordinator, and multi-disciplinary care coordination resulted in the failure to launch of our pilot study. We closed the study in April 2023, and though we were not successful in completing our primary objective of completing the study and evaluating 18-F FDG PET/MRI in the triple negative and Her2/neu enriched population of breast cancer patients, we did gain valuable insight into the barriers to initiating a radiology pilot study and ideas to implement for the future to assure future success.

Highlights:

- Many barriers can impact successful completion of a clinical radiology research studies.
- Barriers to clinical translational radiology research studies include low patient enrollment, coordination between clinical services, and low multidisciplinary engagement.
- Multi-disciplinary team engagement, effective leadership, care coordination, adequate support from research staff, and a focus on teamwork are critical in the overall success of a clinical radiology research study.

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