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CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

Title: Utility of PET/MR in Surgical Planning for Breast Cancer Treated with Neoadjuvant Chemotherapy

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LCCC 1716: Utility of PET/MR in Surgical Planning for Breast Cancer Treated with Neoadjuvant Chemotherapy

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: David S. Lalush, PhD

PI Signature: David S. Lalush

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

The purpose of the study is to assess the utility of combined, simultaneous positron emission tomography (PET) and magnetic resonance imaging (MRI), collectively called PET-MR, in assessing response to neoadjuvant chemotherapy and surgical treatment decisions for operable breast cancers. Adult patients with operable breast cancer that are being treated at UNC with neoadjuvant chemotherapy followed by potentially curative surgical resection will be identified through the Multidisciplinary Breast Tumor Board. Patients who are being treated with neoadjuvant chemotherapy followed by surgical resection and for whom pre- and post-treatment MR imaging is part of planned treatment will undergo additional pre-treatment and post-treatment PET/MR. The response to treatment will be assessed at post-treatment by evaluating change in tumor size from MRI, change in response to dynamic contrast enhanced (DCE) MRI, and 18F-fluorodeoxyglucose (18F-FDG) avidity from PET. Patients will then undergo surgery. Their pathology will be reviewed for treatment effect as assessed by residual cancer burden (RCB) score. Patients will be followed and assessed for recurrence.

This study is designed to provide preliminary information on the progression of tumor size, DCE-MRI response, and FDG avidity during and after treatment in 25 patients diagnosed with operable breast cancer. The primary objective is to evaluate the capabilities of MRI/PET in prediction of RCB score as compared to standard-of-care MRI alone. A secondary objective will be to quantify the progression of PET- and MRI-based quantitative metrics at pre-, and post-treatment time points, and correlate these quantitative measures with RCB score.

Information from this study may be used to estimate effect size for power calculation and sample size considerations for possible future studies in the use of combined PET-MR to be used in determination of which patients are candidates for breast-conserving surgery versus mastectomy. Existing studies point to the possibility of this combined imaging information enabling more patients to be candidates for breast-conserving surgery with no impact to recurrence rate.

1.2 Background

Simultaneous PET/MR imaging [1]–[7] offers exciting opportunities to visualize and quantify soft-tissue tumors [2]. MRI offers superb soft-tissue contrast for anatomical information as well as a flexible suite of other techniques providing functional and physiological information. PET offers sensitive molecular imaging via radioactive tracers, and is widely used for assessment of tumor glucose metabolism. Together, the two modalities provide complementary, synergistic information. Because of MRI's superior soft-tissue contrast, it is considered a much better anatomical guide for PET quantitative analyses for tumors in soft tissue regions as compared to standard-of-care PET-CT. Simultaneous PET-MR also provides inherently-aligned PET and MR, efficient simultaneous acquisition, and the opportunity for new approaches to PET quantitative analysis guided by detailed MR images.

The primary treatment for non-metastatic breast cancer is excision, but neoadjuvant chemotherapy has been shown to convert significant numbers of patients from mastectomy candidates to breast-conserving surgeries without impacting rates of local recurrence [8]. It also frequently reduces tumor size and therefore enhances cosmetic outcomes in lumpectomies [8]. Neoadjuvant chemotherapy has been shown to result in high correlation between pathologic complete response and long-term outcomes [8].

The decision of whether to pursue mastectomy or breast-conserving surgery is based on several sources of information, including biopsy and imaging. MRI is part of the standard of care for some of these cases. Assessment of the effect of neoadjuvant treatment by measuring morphological and perfusion changes from pre-treatment to post-treatment offers an important, but incomplete picture of the status of the tumor prior to surgery. PET imaging is generally not part of the standard-of-care regimen, but 18F-FDG-PET has been shown in several studies to be correlated with risk of recurrence [9]–[11] as well as with treatment response in neoadjuvant chemotherapy [12], [13]. Additional information on the response to neoadjuvant therapy and metabolic status of the tumor prior to surgery offers a better-informed decision environment for risk-assessment. It may ultimately reduce the need for multiple operations to remove residual tumor and could potentially lead to a level of imaging accuracy where surgery could be omitted in those with a complete imaging response. One of the key barriers to the use of PET in breast imaging is the difficulty of aligning a conventional PET-CT image with a separately-acquired MRI image, given that each imaging modality will use different positioning systems and the breast is highly deformable. An integrated PET-MR system inherently solves this problem, since the PET and MRI images can be acquired simultaneously with perfect registration between the two. Also, with the excellent soft-tissue contrast of MRI, the system has the potential for greater anatomical detail to guide interpretation of FDG activity. UNC has one of the few PET-MR scanners in the country, making it one of few centers in the US capable of conducting this study.

1.3 Purpose and Rationale

This is a prospective study of the use of combined PET-MR [1-7] for assessment of response to neoadjuvant chemotherapy in operable breast cancer. There are no prior studies evaluating combined, simultaneous PET-MR for this purpose, although there are studies evaluating each modality individually. These studies suggest our guiding hypothesis: that simultaneous PET and MRI, acquired at pre- and post-treatment time points, will offer image metrics that are predictive of response to neoadjuvant chemotherapy. If so, in the future, application of PET-MRI may result in conversion of more patients to breast-conserving surgery (as opposed to full mastectomy) without impacting re-excision rates and long-term outcomes.

We propose that the change between PET/MR studies from pre- to post-therapy will accurately predict response to neoadjuvant chemotherapy. We will enroll patients with breast cancer deemed by the Multidisciplinary Breast Tumor Board to require neoadjuvant chemotherapy due to need for tumor downstaging in the breast to facilitate breast conservation or to otherwise optimize cancer

care. Patients enrolled will be limited to those who will have pre- and post-treatment clinical MRI as part of their planned treatment. These clinical scans will be performed on hospital MRI scanners as normally done. Patients in our study will receive additional PET/MRI scans at each time point on the Biograph mMR combined PET-MRI scanner at the Biomedical Research Imaging Center. The PET-MRI scans will be evaluated retrospectively and will not be used in the determination of treatment.

These patients will receive pre-treatment imaging and then proceed through their course of neoadjuvant chemotherapy followed by post-treatment imaging. Next, patients will receive curative intent surgery and be followed in the usual fashion and assessed for local and/or distant recurrent disease. The pathology results will be consulted to obtain the Residual Cancer Burden (RCB) score.

Quantitative measures from PET and MRI will be computed: the change in PET tumor-mean standardized uptake value (SUV), change in tumor size as assessed by MRI, and quantitative measures from DCE-MRI from pre- to post-treatment. The image-based quantitative measures will be correlated with the pathology outcomes to evaluate predictability of the image measures for treatment response. Patients will be followed with the intent of further correlating image measures with clinical outcomes.

2.0 STUDY OBJECTIVES/AIMS AND ENDPOINTS

2.1 Primary objectives

2.1.1 To compare MRI-PET with standard-of-care MRI in early prediction of response to neoadjuvant chemotherapy at pre-treatment and post-treatment time points;

2.2 Secondary objectives

2.2.1 To estimate the correlation between changes from pre-treatment to post-treatment in the Metabolic Tumor Volume metric from PET acquired on the PET-MRI scanner and the Residual Cancer Burden score from the pathology report;

2.2.2 To evaluate metrics combining multiple features from simultaneous positron emission tomography (PET maximum SUV, metabolic tumor volume, total lesion glycolysis) and magnetic resonance imaging (MRI tumor size, DCE quantitative measures) in early prediction of response to neoadjuvant chemotherapy at pre-treatment and post-treatment time points.

2.3 Exploratory Objectives

2.3.1 None

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subject must meet all of the inclusion criteria to participate in this study:

3.1.1 Age ≥ 18 years of age (no upper age limit)

3.1.2 Signed, IRB-approved written informed consent

3.1.3 Must have clinical T1-3, N0-3, M0 disease. All phenotypes are acceptable..

3.1.4 Must have surgically curable disease as evaluated by the UNC Multidisciplinary Tumor Board.

3.1.5 Must have pre- and post-treatment MRI imaging as part of the treatment plan.

3.1.6 Must be able to meet size restrictions for the PET-MR scanner: chest depth and abdominal depth less than 27 cm (approximately the smallest 55% of women will meet this), as measured on imaging or with physical template.

3.1.7 Must be in acceptable health to undergo chemotherapy and curative intent surgery as assessed by Multidisciplinary Tumor Board.

3.1.8 Must be able to understand and comply with study procedures for the entire length of the study.

3.1.9 Must receive their chemotherapy and curative intent surgery at UNC Hospitals.

3.1.10 If patient has a history of prior malignancy, including melanoma, patient must be cancer-free for three or more years. Non-melanoma skin cancers will be included even if not cancer-free for three years.

3.1.11 Women of childbearing potential must have a negative serum or urine pregnancy test performed within 7 days prior to each PET/MRI

3.2 Exclusion Criteria

Any subject meeting any of the following exclusion criteria at baseline will be ineligible for study participation:

3.2.1 Inability to tolerate MRI (e.g., inability to lie flat for >1 hour)

3.2.2 Presence of pacemaker, intracranial aneurysm clip, bladder stimulator, cochlear implant or metal near eyes or near pelvis that would create excessive imaging artifact

3.2.3 Poorly controlled diabetes mellitus

3.2.4 Chronic severe renal insufficiency or renal dysfunction due to hepato-renal syndrome

3.2.5 Body Mass Index (BMI) > 35

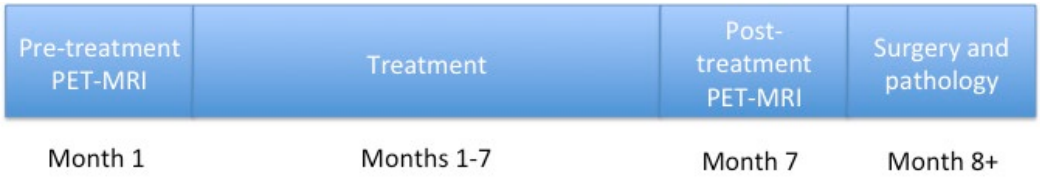
3.2.6 Patient receiving neoadjuvant endocrine therapy (due to low likelihood of complete response)

3.2.7 Pregnancy or lactating female

3.2.8 Substance abuse, medical, psychological, or social conditions that may interfere with the patient's participation in the study
3.2.9 Evidence of distant disease on physical exam or initial imaging
3.2.10 Medical conditions precluding chemotherapy or curative intent surgery
3.2.11 Incarcerated or otherwise institutionalized at time of enrollment

4.0 STUDY PLAN

4.1 Schema



4.2 Patient Identification and Consent

Patients will be identified at the Multidisciplinary Breast Tumor Board at UNC. Once identified, the patients will be recruited and addressed at the clinics of the surgical oncologists, and/or medical oncologists at UNC. The recruitment will take place in the privacy of the UNC clinics in private rooms and guided by the subject's treating physicians. Body measurements may be taken with a physical template to verify that patient will meet size restrictions for PET-MR scanner. The study coordinator will verify that the planned treatment is still consistent with inclusion criteria. Enrollment and informed consent will be facilitated by the study coordinator. Patients will then proceed to treatment as determined by the multidisciplinary tumor board.

4.3 Blood Draw for Creatinine

If subjects do not have a serum creatinine value within 30 days prior to a scheduled DCE-MRI scan, they will be required to have a blood draw at UNC Hospitals for creatinine before their DCE-MRI scan visit. This is the normal procedure for performing DCE-MRI on the clinical scans, and so these blood values can also be used for DCE-MRI performed on the PET-MRI scans.

4.4 FDG-PET-MRI

All patients will undergo a MRI scan with simultaneous acquisition of [^{18}F] Fludeoxyglucose Positron Emission Tomography (FDG F18- PET) at the two time points noted. 18F-FDG is a positron-emitting radiopharmaceutical used for diagnostic purposes. It is a glucose analog that concentrates in cells relying upon glucose as an energy source or in cells whose reliance on glucose increases under pathophysiological conditions. Diabetic patients may need stabilization of blood glucose levels on the day before and on the day of administration of FDG F18.

Injection of gadolinium contrast agent will be performed in the usual manner and images simultaneously obtained with MRI. Patients will have fasted for at least 6 hours before intravenous injection of FDG. To minimize radiation-absorbed dose to the bladder, patients should drink at least an 8 ounce glass of water prior to drug administration. Whenever possible, patients should take the following precautions for 12 hours after injection: used toilets should be flushed several times after each use, and hands should be washed thoroughly. If blood, urine or feces soil clothing, the clothing should be washed separately.

Each patient will be imaged at two time points as noted. For each visit, patients will be scheduled for PET-MRI imaging at Marsico Hall and will receive imaging-day instructions from the study coordinator. The study coordinator will meet the patient at the imaging facility and escort them to the imaging suite. Women of childbearing potential will undergo repeat urine pregnancy test within 7 days prior to each PET/MRI.

Patients will be paid $50 each upon completion of the second PET-MRI as compensation for their time.

4.5 Duration of Study Intervention

The study intervention is complete once the patient receives their last (post-treatment) PET-MRI scan. The patient may be withdrawn from the study prior to this point if any of the following apply:

- Inter-current illness prevents completion of imaging studies
- Unacceptable adverse event(s) prevents completion of imaging studies
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for completion of study in the judgment of the investigator.

4.6 Duration of Follow Up

Patients will be followed up via review of their medical records through disease recurrence or survival for up to 5 years.

4.7 Removal of Patients from Protocol

Patients may be removed if they experience unanticipated claustrophobia causing intolerance to the MR. If patients require lorazepam in order to tolerate the MR, they will be withdrawn from study participation.

4.8 Abstraction of Medical Records

De-identified records will be reviewed and data extracted for clinical outcomes. Treatment response will be documented based on pathology results, as well as any information on recurrence and survival. Information collected may help to establish preliminary data for future studies.

5.0 TIME AND EVENTS TABLE

5.1 Time and Events Table

	Baseline 0 weeks	Treatment +0 to +6 months	Post-treatment +6 months	Surgery +7 months	Pathology +7 to +8 months	Long-term follow-up[2] >+8 months
Screening	■					
Informed Consent	■					
Pregnancy test[1]	■		■			
Clinical MRI	■		■			
PET-MRI	■		■			
Chemotherapy		■				
Surgery				■		
Pathology					■	
Monitoring						■

[1]If clinically applicable women of childbearing potential will undergo urine or serum pregnancy test within 7 days prior to baseline scans; urine pregnancy test within 7 days prior to each subsequent PET/MRI.
[2]Long-term follow-up will be restricted to abstraction of medical records for any data on recurrence and/or survival for up to three years post treatment.

6.0 EXPECTED RISKS/UNANTICIPATED PROBLEMS

6.1 Assessment of Safety

In general, any patient enrolled on this protocol will be evaluable for adverse events.

6.2 Expected Risks

6.2.1 Risks of PET/MRI

Emotional Distress

Emotional distress is possible during MRI. Technologists will ask subjects, before injection, if they are claustrophobic. Also, technologists will do their best to help comfort any subject who is claustrophobic but chooses to continue. Technologists will hand subjects a squeeze ball alarm and instruct them to use it in case of any discomfort. The technologist will also inform the subject that she is free to stop at any time, for any reason.

Radiation

Radiation: The PET/MRI scans will expose study participants to controlled amounts of limited radiation. The total dose of radiation from these tests is not anticipated to cause any adverse effects of any significance over that which they may experience over their standard of care diagnostic imaging and subsequent therapies. Patients enrolled in this pilot study will receive an estimated dose of radiation as specified by the Radiation Safety Committee. The amount of risk to this estimated dose will be equated to the annual radiation exposure limit for radiation workers in the informed consent. This radiation exposure involves a small risk and is necessary to obtain the information desired.

This research study involves exposure to radiation from radiotracer used for PET/MR scan. The radiation dose subjects will receive in this study is 1.1 rem for each scan for a total of 2.2 rem for the full set of two scans. For comparison, a person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources. The radiation dose that subjects will receive in this study is equivalent to the radiation exposure that everyone receives in 7.3 years from natural background radiation for participants completing two scans. For comparison, the people who work with radiation (radiation workers) are allowed to receive a radiation dose of 5 rem per year. The amount of radiation exposure received in this study is equal to 44 % of the annual radiation exposure limit for radiation workers. This radiation exposure involves only a small risk and is necessary to obtain the research information desired. The radiation exposure described here is what subjects will get from this research study only. It does not include any exposure subjects may have received or will receive from other tests outside of this study that are a part of their medical care.

FDG

Information about FDG F18 was obtained from the Prescribing Information (August 5 2004); http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ . According to this document , reviews of the oncology literature did not reveal reported adverse reactions when using 18F-FDG as a diagnostic in conjunction with PET. In a subset (n=42) of a safety database of epilepsy patients (n=374), 4 patients had transient hypotension, 6 had hypo- or hyperglycemia and 3 had transient increases in alkaline phosphatase.

Gadolinium

An extremely rare disease called Nephrogenic Systemic Fibrosis (NSF) is associated with the use of gadolinium contrast agents in patients with chronic

severe renal insufficiency or renal dysfunction due to hepato-renal syndrome or in the peri-operative liver transplantation period. Exclusion criteria for this study are in compliance with the Food and Drug Administration's advisory statements.

As part of the MRI procedure subjects may receive a dye called gadolinium. Gadolinium makes it easier to see details on the MRI pictures. If subjects have any problems with their kidneys, they may be at risk for a condition called Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy. NSF has been reported to occur between 2 days and 18 months following injection of gadolinium. There is no known treatment for NSF. Some people have even died from this. Signs and symptoms of NSF may include: burning, swelling, hardening or tightening of the skin, blood vessels and internal organs (heart, lungs, liver; yellow spots on the white part of the eyes; joint swelling and stiffness; pain in the hip bones or ribs; muscle weakness.

Subjects' study doctor will check how well their kidneys work before they are given gadolinium. Depending on how well their kidneys work, they may be given a reduced dose or they may not be able to take gadolinium at all. NSF has not been reported in people with normal kidneys.

<u>Experimental MRI Breast Coil</u>
The PET-MRI scan will use a non-FDA approved experimental breast coil for MRI imaging. While the manufacturer offers a FDA-approved coil for this device, it is quite expensive and beyond the means of this pilot study. Future funding resulting from this pilot study will hopefully include the FDA-approved coil. The experimental coil is intended only to assist in this pilot research project. It is not intended for clinical use and therefore will not require FDA approval. Further, a coil passing manufacturer-recommended safety testing (described below) represents a non-significant risk to the patient and therefore does not require an Investigational Device Exemption.

This coil is intended to position the patient comparable to the coil used for clinical MRIs and to provide image quality comparable to the clinical MRIs. The coil is a passive detection device, so it does not carry significant electrical current and is not considered an electrical hazard. The primary risk is of surface heating. Prior to patient imaging, extensive thermal studies will be conducted to verify that the coil will remain in a safe temperature range for the MRI sequences to be applied in this study.

The PET-MRI system manufacturer provides a detailed procedure for safety testing of new coils. *The experimental breast coil will be tested with this procedure and must pass all tests before use with subjects in the study.* Failure of any test will require adjustment and/or redesign and retesting of the complete procedure. This procedure requires (1) no electrical parts exposed to possible patient contact; (2) no sharp edges; (3) fuses or passive circuits for coils > 10 cm diameter; (4) measurement and calibration of specific absorption rate (SAR) monitoring to ensure accurate estimation of energy applied to tissue during coil use; (5) change

in surface temperature due to gradient eddy currents must be less than 4 ºC; (6) change in surface temperature due to transmit signal must be less than 4 ºC.

The experimental breast coil will also be tested on five normal volunteers under a separate protocol before use with cancer patients. These tests are intended to verify that the coil offers suitable image quality for purposes of this study. If the custom breast coil fails to provide adequate image quality in the separate normal-volunteers protocol, we will proceed on this study using the built-in FDA-approved scanner volume coil for MRI detection. In that event, the experimental coil housing will be used merely as a positioning aid and not as a detection device.

6.3 Unanticipated Problems

6.3.1 Definition

As defined by UNC's IRB, unanticipated problems involving risks to study subjects refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

6.3.2 Reporting

Any unanticipated problem that occurs during the conduct of this study and that meets **at least** the first two criteria listed in 6.3.1 must be reported to the UNC IRB using the IRB's web-based reporting system.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Design/Study Endpoints

The purpose of the study is to assess the utility of combined, simultaneous positron emission tomography (PET) and magnetic resonance imaging (MRI), collectively called PET-MR, assessing response to neoadjuvant chemotherapy in breast cancer. The overall design is to image patients with PET-MR at two time points, pre-treatment and post-treatment, and to compare results from PET-MR with those from standard-of-care MRI in the prediction of residual tumor volume. Also, secondary objectives correlate both individual and combined quantitative measures from imaging with results of pathology to determine if the PET-MR scan provides information that predicts response to chemotherapy. The primary endpoint is to compare PET-MR with standard-of-care MRI as predictors of Residual Cancer Burden (RCB) score. The secondary endpoints will address the effectiveness of the

PET metric Metabolic Tumor Volume (MTV) as a predictor of RCB and the development of a prediction model for response from combined quantitative PET-MRI measures.

Patients will be identified at the Multidisciplinary Breast Tumor Board at UNC. Patients will be breast cancer patients that are to be treated with neoadjuvant chemotherapy followed by curative intent surgery, and for whom pre- and post-treatment MRI scanning is to be part of the treatment plan. Once patient identification occurs, the patient will be assessed for the study via the inclusion and exclusion criteria mentioned above. The patient will then be approached a study coordinator and the study protocol explained and all risks outlined. If the patient provides informed consent the patient will be enrolled. Demographic data such as patient age, gender, comorbidities, and previous treatments, etc. will be collected. Tumor characteristics will be collected. All data collected will be kept on a password protected, secured server, and all physical documentation will be stored in a locked cabinet. All data will be collected by the PI and co-investigators.

Patients will then be scheduled for a pre-treatment PET-MR around the same time as clinical MRI and proceed to neoadjuvant chemotherapy per the direction of the oncologist. After therapy the patient will undergo a post-treatment PET-MR around the same time as their clinical MRI, and proceed for curative intent surgery if they are still surgical candidates.

For all PET scans, patients will be instructed to fast, and blood glucose levels will be measured prior to imaging. Patients will be injected with 10 mCi 18F-FDG, and then imaged starting 60 minutes post-injection for ten minutes each at one or two bed positions focused on the primary tumor site. MRI sequences to be run will include conventional anatomic T1- and T2-weighted sequences, high-resolution T1 pre- and post-contrast DCE sequences, and the Dixon PET-MR attenuation-correction sequence.

The PET-MRs at each time point will be evaluated retrospectively by UNC radiologists as to the size of the lesion, the FDG activity as measured by tumor-maximum and tumor-mean standard uptake values (SUVs), additional PET metrics (metabolic tumor volume (MTV) and total lesion glycolysis (TLG)), the presence or absence of invasion to adjacent organs, and the presence or absence of metastatic or multifocal disease. PET images will be evaluated with aligned anatomical MRI for guidance as well as determination of the tumor margins for computation of tumor-mean SUV.

The PET/MRs will be evaluated by UNC breast radiologists and nuclear medicine specialists as to the size of the lesion, the FDG activity as measured by SUVmax and SUVmean, the presence or absence of invasion to adjacent organs, and the presence or absence of metastatic or multifocal disease. The pathological specimens will be evaluated by a UNC pathologist specialized in breast cancer as to (1) the size of the primary tumor, (2) the proportion of invasive carcinoma within the primary tumor

bed, (3) the number of axillary lymph nodes involved, and (4) the size of the largest metastasis in an axillary lymph node. These four quantities will be used to compute the RCB score[1]. Again, all data will be stored on a secured, password protected server.

[1]http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

To address the primary endpoint, image metrics from the MRI component of PET-MRI and clinical MRI will be evaluated. The principal metric to be examined is the change in tumor size from pre- to post-treatment. The change in tumor size will be correlated with RCB scores reported by the pathologist.

For the secondary endpoints, quantitative imaging measures (mean SUV, maximum SUV, MTV, TLG, MRI-based tumor volume, MRI DCE imaging parameters) will be compounded for all patients. The fractional change from pre-treatment to post-treatment will be computed for all quantities.

7.2 Sample Size and Accrual

The study will enroll 33 eligible patients that are being treated at UNC Hospitals; of these, 25 are expected to complete the study based on completion rates from previous PET-MR pilot studies at UNC.

7.3 Data Analysis Plans

For the primary endpoint, each subject's change in tumor size will be correlated with the primary outcome (RCB score) and correlation estimated using the Pearson product-moment correlation coefficient. Confidence intervals on the correlation coefficient will be estimated using the Fisher transformation.

For secondary endpoint 2.2.1, the change from pre- to post-treatment in metabolic tumor volume (MTV) from PET imaging will be correlated with RCB score using the Pearson product-moment correlation coefficient. Confidence intervals on the correlation coefficient will be estimated using the Fisher transformation.

For secondary endpoint 2.2.2, each subject's set of quantitative measures will be compiled and an optimal linear regression between the image metrics and the outcome measure (RCB score) will be derived. Prediction performance will be evaluated using a leave-one-out cross-validation strategy.

For correlating individual metrics with RCB scores, with n = 25 subjects, we will have approximately 73% power to detect a Pearson correlation of at least 0.5, assuming a two-sided Type I error rate of 0.05 and utilizing the correlation test.

7.4 Data Management

Image datasets will be stored on a secure server in the Biomedical Research Imaging Center with patient identifiers removed. De-identified copies of these may be stored temporarily on password-protected computers or portable hard drives for use in data analysis. Quantitative data extracted from the images and results of data analysis will be maintained on a secure server. All data will be archived on a password-protected computer in the office of the PI and backed up with a RAID system. Datasets will be maintained for at least five years from the close of the study.

8.0 STUDY MANAGEMENT

8.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing a IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

8.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB-approved consent form

8.3 Registration Procedures

Once patients have consented to be a subject in this trial, they will be assigned an encoded false patient name/number, such as "BR_001". This identifier will be used

throughout the study in the data analysis. The study coordinator will have the key to relate the patient's true name to the study identifier, and will coordinate the acquisition and de-identification of relevant clinical patient data so that study personnel not directly involved in patient care will not have access to any personally identifiable information. The study coordinator will secure all information related to patient identifiers on a restricted-access, password-protected computer.

All patients must be registered with a study coordinator at the University of North Carolina Biomedical Research Imaging Center before enrollment in the study. The Study Coordinator will verify that the patient meets all criteria to participate in the study before registration.

8.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.4.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC IRB approval.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

8.4.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

8.4.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.

- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation in OnCore® (or other appropriate database set up for the study), and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Unanticipated Problems:
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB (see section 6.3.1) must be reported by the Study Coordinator using the IRB's web-based reporting system.

8.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

8.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept

on file until five years after the completion and final study report of this investigational study.

8.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

9.0 REFERENCES

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