LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

LCCC XXXX: Utility of PET/MR in Assessing Response to Neoadjuvant Radiation Therapy in the Treatment of High Grade Sarcomas

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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: 

Date: 07/05/2016

Version Date: 6/20/2016

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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 radiation therapy in the treatment of high grade sarcomas. Adult patients with potentially curable high grade sarcomas that are being treated at UNC with neoadjuvant radiation therapy followed by potentially curative surgical resection will be recruited through the Department of Surgery. Patients who are being treated for potentially curable high grade sarcomas with neoadjuvant radiation therapy followed by surgical resection will undergo pre-treatment, mid-treatment, and post-treatment PET/MR and the response to treatment will be assessed at mid-treatment and post-treatment time points by evaluating change in tumor size from MRI and 18F-fluorodeoxyglucose (18F-FDG) avidity from PET. Patients will then undergo curative intent resection. Their pathology will be reviewed for treatment effect as assessed by percent necrosis, size, and resection margins. Patients will be followed and assessed for recurrence.

This study is designed to provide preliminary information on the progression of tumor size and FDG avidity during and after treatment in 30 patients diagnosed with potentially curable high-grade sarcomas. The primary objective is to evaluate the capabilities of PET and MRI, individually and combined, in early prediction of patients who will and will not respond to neoadjuvant radiation therapy. A secondary objective will be to quantify the progression of PET- and MRI-based metrics at pre-, mid-, and post-treatment time points.

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 predict, at a mid-treatment time point, which sarcoma patients will respond to, and therefore continue with, neoadjuvant radiation therapy, and which patients will not respond and should be spared additional time and radiation dose before proceeding to surgery.

1.2 Background

The only curative treatment for non-metastatic sarcomas is complete surgical resection. Nonetheless, most patients who undergo curative intent surgery will have positive gross or microscopic margins. Of those who are treated with complete resections, a large proportion will recur locally. Radiation has been shown to improve the rate of complete resection, and improve local control rates. Neoadjuvant radiation has even been shown to improve 3 year overall survival in high grade extremity sarcomas. The utility of radiation in the treatment of sarcomas has been shown in multiple studies. Still, utilization of adjuvant and neoadjuvant radiation in the United States remains low. This is partially related to the large discrepancy within subtypes of sarcomas and varied response to radiation among different grades of sarcoma within the same subtype. The underutilization of neoadjuvant radiation

is also partly in due to some controversy about which patients should undergo neoadjuvant radiation as opposed to adjuvant radiation versus no radiation at all.

PET/CT and MRI are two modalities that are utilized in the diagnosis, treatment, and follow up of extremity soft tissue and retroperitoneal sarcomas. PET activity has been shown to correspond with treatment response in many tumor types. MR has a specific advantage in imaging of soft tissues which is especially important in extremity and retroperitoneal sarcomas. An integrated PET/MR system has the potential benefit of reducing patient time, and expenditures, as well as avoiding the ionizing radiation associated with CT. Further the integrated system has the potential for greater anatomical detail in the context of FDG activity. The University of North Carolina leads in the utilization of neoadjuvant radiation for sarcoma and has one of the few combined PET-MR imaging systems in the US.

There exists a need to identify those patients with high grade sarcomas who will benefit from neoadjuvant radiation therapy. This will enable us to focus our resources on delivering effective radiation therapy to those patients who will benefit from them and minimize the associated risks and consequences of radiation in those patients who will not benefit from them and allow those patients to move quickly to curative intent surgery.

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 radiation therapy in high-grade sarcomas. There are no prior studies evaluating combined, simultaneous PET-MR for this purpose, although studies indicate that PET, at a mid-treatment time point, is predictive of response to neoadjuvant chemotherapy in sarcomas [8] and that PET and MRI, acquired separately, are correlated with response to neoadjuvant chemotherapy at a post-treatment time point [9]. These studies suggest our guiding hypothesis: that simultaneous PET and MRI, acquired at a mid-treatment time point, provide image-based quantitative measures that are associated with and predict response to neoadjuvant radiation therapy in high-grade sarcomas. If so, in the future, application of PET-MRI at mid-treatment may be used to determine the course of treatment for patients at this stage, whether to continue neoadjuvant therapy, or to spare time, expense, and radiation dose for nonresponders.

We propose that a PET/MR study at the midpoint of radiation treatment will accurately predict which patients will respond to neoadjuvant radiation therapy. We will enroll patients with high-grade sarcomas as identified by preoperative biopsy that will be treated with neoadjuvant radiation into the study. The standard of care for these patients is to receive MRI scans at pre-treatment and post-treatment time points. Patients in our study will receive their standard pre- and post-treatment imaging in the form of PET/MR, with PET conducted simultaneously with MRI, and within the context of the study they will also receive one additional PET/MR at the end of the second week of therapy. These patients will then receive curative intent surgery and be followed

in the usual fashion and assessed for local and/or distant recurrent disease. The pathology will be assessed for completeness of resection and percent of necrosis. On the basis of pathology, patients will be classified as responsive or non-responsive to therapy. Quantitative measures from PET and MRI will be computed: the change in PET tumor-mean standardized uptake value (SUV) and tumor size as assessed by MRI, from pre- to post-treatment, and from pre- to mid-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 Determine whether there is a significant difference between response groups in PET mean SUV fractional change (baseline to mid-treatment).

2.2 Secondary objectives

2.2.1 Determine whether there is a significant difference between response groups in MRI tumor size fractional change (baseline to mid-treatment).

2.2.2 Determine whether there is a significant difference between response groups in PET mean SUV fractional change (baseline to post-treatment).

2.2.3 Determine whether there is a significant difference between response groups in MRI tumor size fractional change (baseline to post-treatment).

2.2.4 Assess the correlation in PET mean SUV change and MRI tumor size change from baseline to mid-treatment, in addition to baseline to post-treatment.

2.3 Exploratory Objectives

2.3.1 To assess the utility of combined, simultaneous positron emission tomography (PET mean SUV) and magnetic resonance imaging (MRI tumor size), in early prediction of response to neoadjuvant radiation therapy in the treatment of high-grade sarcomas at mid-treatment and post-treatment.

2.3.2 Examine the utility of using maximal SUV in place of mean SUV in prediction of response

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 a biopsy-proven high-grade retroperitoneal or soft tissue extremity sarcoma confirmed by independent evaluation of a UNC sarcoma specialized pathologist.

3.1.4 Must have surgically curable disease as evaluated by initial imaging by our UNC surgeons.

3.1.5 Must be in acceptable health to undergo radiation therapy and curative intent surgery as assessed by UNC surgeons and radiation oncologist.

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

3.1.7 Must receive their neoadjuvant radiation therapy and curative intent surgery at UNC Hospitals – Chapel Hill location.

3.1.8 Women of childbearing potential must have a negative serum or urine pregnancy test performed within 7 days prior to first 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 Creatinine > 1.4 mg/dL **OR** GFR < 30mL/min

3.2.5 Body Mass Index (BMI) > 35

3.2.6 Active vaginal bleeding requiring packing and emergent radiation therapy

3.2.7 Pregnancy or lactating female

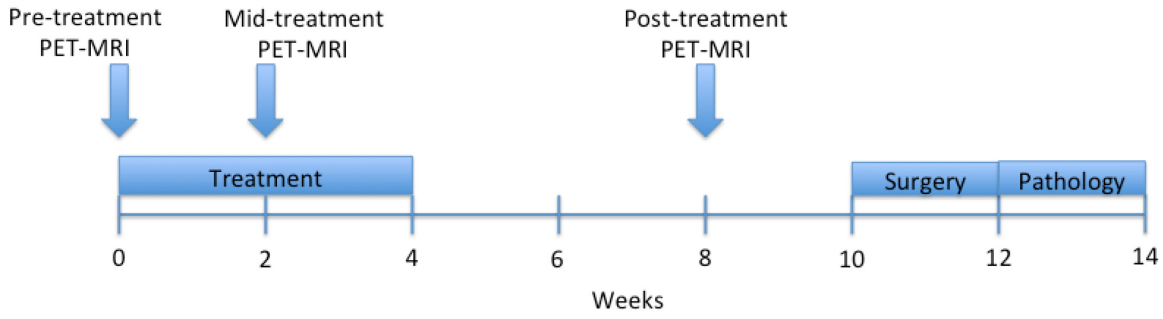
3.2.8 History of a prior malignancy within past 5 years are excluded unless they have been disease free for 3 or more years

3.2.9 Substance abuse, medical, psychological, or social conditions that may interfere with the patient's participation in the study

3.2.10 Evidence of distant disease on physical exam or initial imaging
3.2.11 Medical conditions precluding radiation therapy or curative intent surgery
3.2.12 Previous radiation exposure precluding radiation therapy
3.2.13 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 clinics of the surgical oncologists, orthopedic oncologists, radiation oncologists, and sarcoma multi-disciplinary conference at UNC. Once identified the patients will be recruited and addressed at the clinics of the surgical oncologists, orthopedic oncologists, and/or radiation 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. Enrollment and informed consent will be facilitated by a 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 FDG-PET-MRI scan, they will be required to have a blood draw at UNC Hospitals for creatinine before their FDG-PET-MRI scan visit.

4.4 FDG-PET-MRI

All patients will undergo a gadolinium enhanced MRI with simultaneous acquisition of [^{18}F] Fludeoxyglucose Positron Emission Tomography (FDG F18-PET) at the three 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 three 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 as compensation for their time.

4.5 Duration of Study Intervention

The study intervention is complete once the patient receives their last (8 weeks 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	Treatment	Mid-	Treatment	Post-	Surgery	Pathology	Long-

	0 weeks	+0 to +2 weeks	treatment +2 weeks	+2 to +4 weeks	treatment +8 weeks	+8 to +10 weeks	+10 to +12 weeks	term follow-up[2] >+12 weeks
Screening								
Informed Consent								
Pregnancy test[1]								
PET-MRI								
Radiation Therapy								
Surgery								
Pathology								

[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, by using a cloth over their eyes or a fan providing cool air to the subject. 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 he/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 1.32 rem for each scan for a total of 3.96 rem for the full set of three 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 13.2 years from natural background radiation for participants completing three 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 79 % 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, and patients with creatinine clearance < 30 ml/min will be excluded from this study.

As part of the MRl 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, live; 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.

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, in assessing response to neoadjuvant radiation therapy in the treatment of high grade sarcomas. The overall design is to image patients with PET-MR at three time points, pre-treatment, mid-treatment, and post-treatment, and correlate quantitative measures from imaging with results of pathology to determine if the mid-treatment PET-MR scan provides information that predicts response to radiation therapy. The primary endpoint is to quantify the association between

pathology determination of response/nonresponse and image metrics from PET at midtreatment. Exploratory aims will address the development of a prediction model for response mid-treatment change in PET and MR, and will evaluate the use of combined PET and MR metrics for prediction compared to each metric alone.

Patients will be identified at the Multidisciplinary Sarcoma Board at UNC. Patients will be high-grade sarcoma patients that are to be treated with neoadjuvant radiation therapy followed by curative intent surgery. 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 by either the PI, the sarcoma nurse navigator, the radiation oncologist, the surgeon, or a member of their team 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 such as tumor subtype, grade, Ki-67 score, size, invasion into adjacent organs, etc. 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 and proceed to neoadjuvant radiation therapy per the direction of the radiation oncologist. At the end of the second week of radiation therapy the patient will undergo a mid-treatment PET/MR. The patient will the complete their radiation therapy. Four weeks after radiation therapy the patient will undergo a post-treatment PET/MR, and proceed for curative intent surgery at 6-8 weeks post radiation 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 12 mCi 18-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 sequences, and the Dixon PET-MR attenuation-correction sequence.

The PET/MRs at each time point will be evaluated 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), 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 UNC surgeons will record the resectability of the tumor, and the gross appearance of the resection (R0-grossly negative, R2-grossly positive), as well as any evidence of metastatic disease, presence or absence of invasion to surrounding organs, or multifocal disease. The PET/MRs will be evaluated by UNC radiologists 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 sarcoma as to the degree of necrosis (none, <10%, 10-50%, 51-90%, >90%, 100%), status of margins (R0-negative margins, R1-microscopically negative margins, R2 – grossly positive margins), the presence and absence and number of affected lymph node involvement if applicable, and presence or absence of invasion to adjacent organs. Again, all data will be stored on a secured, password protected server.

7.2 Sample Size and Accrual

The study will enroll 30 eligible patients that are being treated at UNC Hospitals. To test for a difference in change scores between response groups at a given time point (for example, mid-treatment change from pre-treatment) we will utilize the non-parametric Wilcoxon Rank Sum test. An advantage of using this nonparametric method is that the effect size is expressed in probabilistic terms, since the difference scores have been transformed into ranks, the statistical comparisons take place in this space, and the magnitude and variability of the difference scores are not needed. This means the power and sample size for each time point's difference scores will be the same.

Let $X = x_1, x_2, \ldots x_n$ represent a sample of size n difference scores for responders and $Y = y_1, y_2, \ldots Yn$ represent a sample of size n difference scores non-responders. Now let $p = P(X>Y)$, or the probability that a difference score in the responder group greater than the difference score in the non-responder group. Please note that we could just as easily frame the probability $p = P(Y>X)$. Intuitively, one can see that a p=0.5 would mean that either X>Y and Y > X would be equally likely. This p would be the measure of the nonparametric or distribution-free effect size. The Wilcoxon signed-rank method tests the null hypothesis that the distributions of the two samples are equal , which corresponds to a p=0.5.

Assuming 30 patients complete the study, we will have approximately 90% power assuming p = 0.82, with a Type I error rate of 0.05 and utilizing the Wilcoxon Rank Sum test [1] to test for a difference in PET mean SUV from pre-treatment to mid-treatment. For correlating the fractional change in PET mean SUV with change in MRI tumor volume between time points, with n = 30 subjects, we will have approximately 82.5% 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.

[1] Noether, G. E. (1987). Sample size determination for some common nonparametric tests. *Journal of the American Statistical Association*, *82*(398), 645-647.

7.3 Data Analysis Plans

Quantitative imaging measures (mean SUV, maximum SUV, MRI-based tumor

volume) will be compounded for all patients. Difference scores including the fractional change from pre-treatment to mid-treatment (early response) and the fractional change from pre-treatment to post-treatment (late response) will be computed for all quantities. Subjects will be classified into responders and non-responders on the basis of degree of necrosis (>90% necrosis = good response; <90% necrosis = poor response). Median, range, mean, and variance of each image measure will be computed for each response group. Differences in all quantitative measures between the response groups will be assessed with the non-parametric Wilcoxon Rank Sum test, and correlations between quantitative measures will be determined using the non-parametric Spearman's rank correlation coefficient and Pearson product-moment correlation coefficient. To develop a predictive model for early response, we will train a logistic regression classifier on the binary response data utilizing various PET SUV and MRI-based imaging measures (in terms of change from pre-treatment to mid-treatment) as covariates. All subsets selection with BIC will be used to determine the best combination of PET and MRI imaging measures to predict binary response, and empirical measures of predictive performance such as leave-one-out cross validation and Receiver-Operating-Characteristic (ROC) curves ,(evaluated as to the area under the ROC curve) will be computed.

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 "SARC_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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