Title:	A Pilot Study of PET/MR for Rectal Cancer Treatment Monitoring and Surveillance
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A Pilot Study of PET/MR for Rectal Cancer Treatment Monitoring and Surveillance

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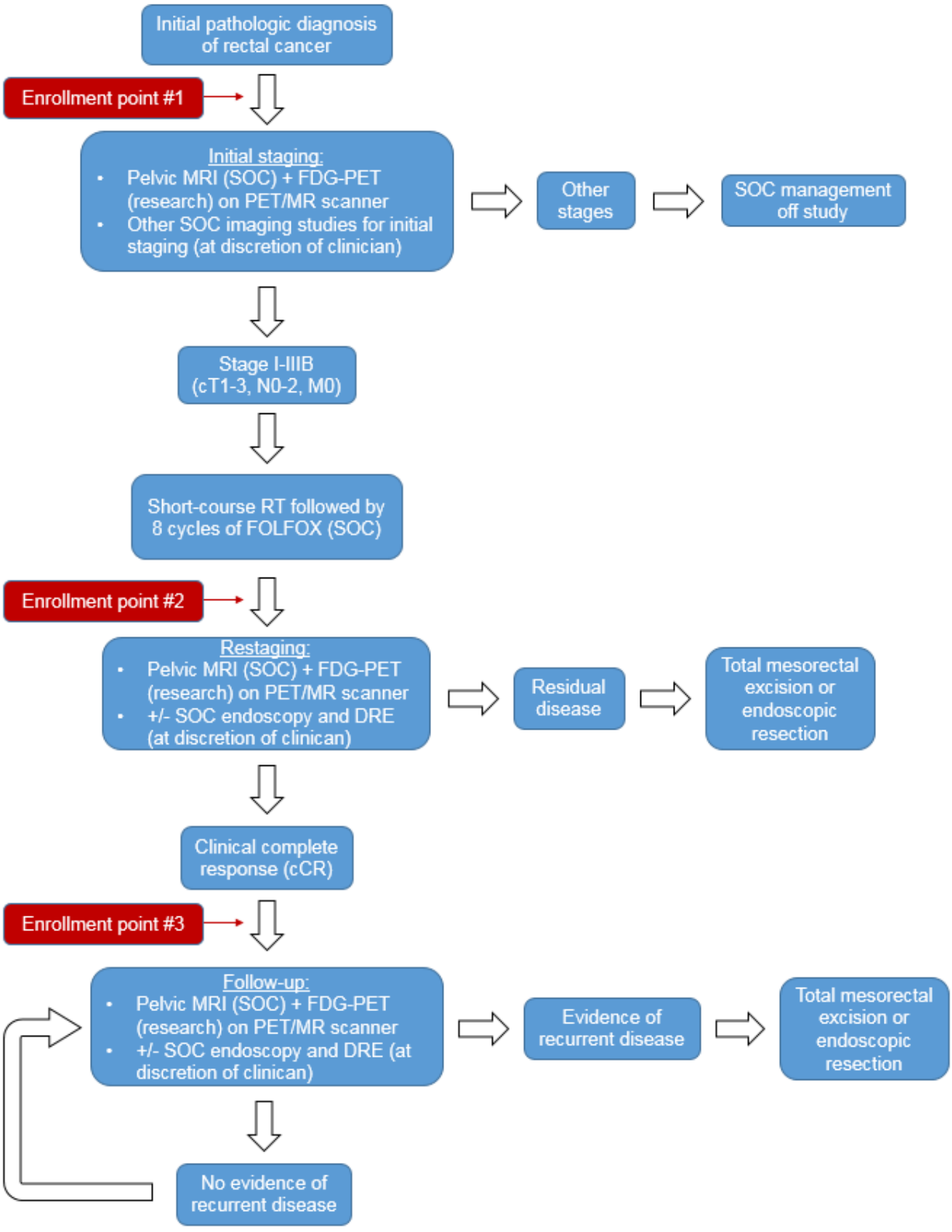
1. SCHEMA


Initial pathologic diagnosis of rectal cancer
Enrollment point #1
Initial staging:
• Pelvic MRI (SOC) + FDG-PET (research) on PET/MR scanner
• Other SOC imaging studies for initial staging (at discretion of clinician)
Other stages
SOC management off study
Stage I-IIIB (cT1-3, N0-2, M0)
Short-course RT followed by 8 cycles of FOLFOX (SOC)
Enrollment point #2
Restaging:
• Pelvic MRI (SOC) + FDG-PET (research) on PET/MR scanner
• +/- SOC endoscopy and DRE (at discretion of clinican)
Residual disease
Total mesorectal excision or endoscopic resection
Clinical complete response (cCR)
Enrollment point #3
Follow-up:
• Pelvic MRI (SOC) + FDG-PET (research) on PET/MR scanner
• +/- SOC endoscopy and DRE (at discretion of clinican)
Evidence of recurrent disease
Total mesorectal excision or endoscopic resection
No evidence of recurrent disease

2. OVERVIEW

Non-operative management (NOM) is an increasing utilized treatment strategy in the United States for select patients with non-metastatic rectal cancer. NOM involves initial treatment with radiation therapy and chemotherapy, followed by close surveillance if there is no evidence of residual disease on pelvic MRI, lower endoscopy, or digital rectal examination (DRE). It is unknown whether positron emission tomography (PET) utilizing the glucose analogue ^{18}F-fluorodeoxyglucose (FDG) provides any useful imaging information beyond standard-of-care pelvic MRI in detecting residual or recurrent disease during the post-treatment restaging and surveillance periods. The goal of pilot study is to assess the feasibility of FDG-PET/MRI for monitoring rectal cancer disease status in the setting of rectal cancer NOM. Data from this study will be used to guide the design of future clinical trials involving FDG-PET/MRI for rectal cancer NOM.

3. BACKGROUND AND SIGNIFICANCE

3.1. Rectal cancer treatment

With the exception of a small group of favorable-risk stage I tumors, the standard therapy of stage I-III rectal cancer includes a total mesorectal excision (TME). TME in the form of an abdominoperineal resection (APR) results in a permanent stoma, which may significantly impact a patient's self-image and quality of life. TME in the form of a low anterior resection (LAR) obviates the need for an ostomy but often adversely affects bowel function. Consequently, there is considerable interest in NOM, the mainstay of which is chemoradiation, as a primary treatment strategy for rectal cancer patients, with several studies reporting excellent post-treatment complete clinical response (cCR) rates and low rates of local recurrence at 1 year post-treatment [1–4]. Furthermore, short-course radiation therapy (i.e., 25 Gy given in 5 fractions) has shown promise as a more convenient option with similar clinical outcomes, when compared with conventional treatment regimens (e.g., 50.4 Gy in 30 fractions) [5–7].

To this point, an interim analysis of a recent phase I study at Washington University found that NOM consisting of short-course radiation therapy followed by adjuvant chemotherapy resulted in a cCR rate (based on pelvic MRI, DRE, and lower endoscopy) of 89% (8 of 9 patients) after completion of therapy, with a persistent cCR rate of 88% (7 of 8 patients) at a median follow-up of 10.9 months. Consequently, NOM consisting of short-course radiation therapy plus adjuvant FOLFOX chemotherapy is now the standard of care for stage I-III rectal cancer at Washington University. After completion of chemoradiation, patients undergo frequent follow-up, with rectal assessments (pelvic MRI, DRE, and lower endoscopy) every 3 months for the first year and every 4 months for the second year. At the time of detected recurrence, patients then undergo TME or endoscopic resection, as clinically appropriate. Based on this treatment paradigm, it is critical to optimize the sensitivity of follow-up imaging for residual or recurrent disease so as to ensure that NOM failures are detected as early as possible, when surgery is still feasible and potentially curative.

3.2. PET/MRI

Since its introduction, positron emission tomography (PET) / computed tomography (CT) has revolutionized oncologic imaging [8]. Utilizing the tracer 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG), a glucose analogue, PET/CT readily identifies hypermetabolic lesions and localizes them to specific anatomic locations. Consequently, FDG-PET/CT has become the standard of care for the initial staging and subsequent treatment response assessment for numerous solid neoplasms throughout the body, including the chest and abdomen [9,10]. However, due to certain intrinsic limitations of CT, PET/CT is often supplemented by magnetic resonance imaging (MRI), which provides excellent soft tissue contrast, in order to assess local tumor extent. Moreover, some tumor types are not significantly hypermetabolic relative to their surrounding normal tissues in which they arise, thereby reducing the utility of PET imaging with FDG. Hybrid PET/MRI scanners, which acquire PET data and MRI data simultaneously, have the potential to streamline oncologic imaging protocols by providing the functional and anatomic information necessary for accurate whole-body tumor staging in a single examination.

PET/MRI offers potential advantages over PET/CT or MRI alone for the locoregional staging of rectal cancer (see subsequent section for discussion of metastatic staging). Although highly accurate for determining the extramural depth of tumor spread and detecting involvement of the mesorectal fascia (i.e., T-staging) [11,12], MRI generally relies on size criteria alone for the determination of nodal involvement. For example, one study found that using a short-axis diameter of > 5 mm to define nodes as suspicious results in an overall accuracy of only 34% [13]. In contradistinction, FDG-PET/CT has been shown to have an overall accuracy of 79% for nodal staging (N-staging) [14]. Thus, PET/MRI may have the ability to combine the excellent T-staging accuracy of MRI with the relatively higher N-staging accuracy of PET/CT. This advantage could be particularly valuable to patients with lymph node metastases that would otherwise be outside of the standard surgical/radiation field. Currently, due to limited evidence, PET does not generally play a role in T-staging. However, FDG-PET may provide useful adjunctive information in determining local tumor extent and assessing treatment response [15–17].

Despite the high accuracy of pelvic MRI for the initial staging, its ability to predict the presence and extent of tumor following pre-operative neoadjuvant chemoradiation is less certain. For example, in a consecutive cohort of 48 patients treated with chemoradiation for locally advanced rectal cancer, van den Broek et al. found that pelvic MRI correctly predicted the T-stage in only 47-68% of cases and the N-stage in only 68-70% of cases, with relatively poor inter-observer agreement [18]. Furthermore, a 5-point MRI-based tumor regression grade (mrTRG) did not reliably predict the histopathologic tumor regression grade in this study, likely related to treatment-induced changes that can either obscure or mimic residual disease. In contrast, Lee et al. demonstrated that a modified 3-point mrTRG has superior accuracy and inter-observer agreement, with the ability to stratify patients with respect to disease-free survival [19]. Similarly, FDG-PET-based assessments of response to neoadjuvant chemoradiation have also been shown to predict disease-free survival in patients with locally advanced rectal

cancer [20]. A meta-analysis by Maffione et al. found a post-treatment response index of 63% and a post-treatment SUV_{max} of 4.4 to be optimal for predicting a major pathologic response [21]. Thus, it is conceivable that the simultaneous assessments of PET and MRI metrics of treatment response afforded by FDG-PET/MRI could be complementary or synergistic in identifying residual disease or detecting recurrent disease in rectal cancer patients managed with NOM.

4. STUDY OBJECTIVES

4.1. Primary objective

To determine the feasibility of PET/MRI for rectal cancer treatment response assessment and post-treatment surveillance for patients receiving chemoradiation as part of an NOM strategy.

4.2. Secondary objective

To estimate the added value of PET/MRI relative to MRI only for detecting residual or recurrent rectal cancer following chemoradiation in patients on an NOM protocol.

5. ELIGIBILITY CRITERIA

5.1. Inclusion criteria

1. At least 18 years of age
2. Biopsy-proven rectal adenocarcinoma, with clinically suspected or previously known stage I-III (cT1-4, N0-2, M0) disease
3. Anticipated or prior chemoradiation as part of an NOM treatment strategy
4. Ability to understand and willingness to sign an IRB-approved written informed consent document

5.2. Exclusion criteria

1. Prior surgical resection of rectal cancer (endoscopic or TME)
2. Contraindication to MRI (see appendix for screening sheet)
3. Comorbidities that would limit patient's ability to cooperate with a PET/MRI examination (e.g. dementia, inability to follow commands, claustrophobia, tremors, requirement for oxygen by nasal cannula, etc…).
4. Implanted devices or materials that may interfere with MRI imaging or create significant artifact
5. Pregnancy
6. Contraindication to gadolinium contrast or FDG
7. End-stage renal disease

5.3. Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for the study.

6. REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken in order to register patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

6.1. Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

6.2. Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

6.3. Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

7. STUDY PROCEDURES

Study subjects will be recruited from the population of adult patients referred to Washington University's Radiation Oncology program for an initial biopsy-proven diagnosis of rectal cancer (Enrollment point #1) or previously treated with chemoradiation by Washington University's Radiation Oncology program as part of a NOM strategy for rectal cancer (Enrollment points #2 and #3). Individuals treated with equivalent regimens at other institutions are not eligible. Note that Enrollment point #3 can include patients that have already undergone one or more standard-of-care surveillance imaging sessions. Furthermore, for subjects entering at Enrollment points #2 and #3, there is no requirement that a subject have undergone an FDG-PET examination previously to be eligible.

Patients who meet the inclusion criteria will be recruited to undergo FDG-PET/MRI in lieu of the standard pelvic MRI at ***up to 6 time-points*** at which it would normally be performed in their care for the period of time extending 30-36 months from the time of enrollment (depending on enrollment point) . In the surveillance period, when patients typically undergo pelvic MRI every 3 months, the FDG-PET/MRI will be done in lieu of the standard pelvic MRI on an approximately every-other-scan basis. In other words, the FDG-PET/MRI will occur roughly once every 6 months. Target enrollment is 10 patients by the end of year 1 of recruitment and 20 patients by the end of year 2 of recruitment (unless early stopping rule is

satisfied). For subjects entering study at each of the three time points, imaging will consist of the following, assuming no indication for surgery or exclusion criterion is identified:

1. Enrollment point #1 (6 imaging sessions)
   a. Initial staging FDG-PET/MRI
   b. Restaging FDG-PET/MRI
   c. Surveillance FDG-PET/MRI #1
   d. Surveillance FDG-PET/MRI #2
   e. Surveillance FDG-PET/MRI #3
   f. Surveillance FDG-PET/MRI #4
2. Enrollment point #2 (6 imaging sessions)
   a. Restaging FDG-PET/MRI
   b. Surveillance FDG-PET/MRI #1
   c. Surveillance FDG-PET/MRI #2
   d. Surveillance FDG-PET/MRI #3
   e. Surveillance FDG-PET/MRI #4
   f. Surveillance FDG-PET/MRI #5
3. Enrollment point #3 (6 imaging sessions)
   a. Surveillance FDG-PET/MRI #1
   b. Surveillance FDG-PET/MRI #2
   c. Surveillance FDG-PET/MRI #3
   d. Surveillance FDG-PET/MRI #4
   e. Surveillance FDG-PET/MRI #5
   f. Surveillance FDG-PET/MRI #6

Subjects will be prepared for PET imaging according to our standard clinical protocol, accessible here: http://gamma.wustl.edu/web-procedure-manual/12-pet/. Subjects will fast for at least 4 hours. All subjects will complete an MRI screening evaluation form. Subjects will have intravenous (IV) access established prior to entering MRI zone 3 or the scanning room. Prior to the administration of FDG, a negative point-of-care urine pregnancy test will be required for all women of child-bearing potential. All subjects must have a blood glucose ≤ 200 mg/dL at the time of FDG administration. Subjects with blood glucose > 200 mg/dL can be managed per our standard protocol (website listed above) to achieve a satisfactorily low blood glucose, at the discretion of the study PI. Subjects not satisfying these criteria will be excluded and replaced. These patients will still receive standard-of-care MRIs at the time of the scheduled FDG-PET/MRI, though FDG will not be injected and PET will not be performed.

PET imaging will be performed with a PET/MR (Siemens Biograph mMR) scanner, located on the 10th floor West Pavilion of Barnes-Jewish Hospital in the Center for Clinical Imaging Research (CCIR). The MR system is a 3.0T whole-body MRI system with features similar to the Siemens Verio MR scanner. The PET component features include a detector assembly of 64 Lutetium Oxyorthosilicate (LSO) crystals that form one block. Research PET/MR will be acquired using a single dose FDG PET tracer injection. All patients will undergo a simultaneous list mode PET and MR acquisition beginning 55-65 minutes after administration of FDG according to a standard weight-based scale. Patients will be encouraged to void around 30 min post-injection, approximately 30 min before the start of PET/MR imaging.

The total imaging period is expect to be 30-45 min for each session. This imaging period will be limited to a maximum of 60 min to prevent subject discomfort.

7.1. MRI protocol

The MRI portion of the PET/MRI examination will match the protocol currently utilized as standard-of-care at our institution, and will include the following:

1. Two-point Dixon VIBE and HUGE for PET attenuation correction
2. High-resolution T2-weighted TSE in the oblique transaxial, oblique coronal, and sagittal planes (oblique planes are defined according to orientation of tumor)
3. Large field-of-view transaxial and coronal HASTE images
4. Transaxial diffusion-weighted images (DWI)
5. Full field-of-view T1-weighted high-resolution transaxial (pre-contrast)
6. Pre-contrast and dynamic post-contrast VIBEs

The MR acquisition will begin at the same time as the PET acquisition, which is described in detail below.

7.2. PET protocol

For the first PET/MRI examination, the PET portion will begin at 55-65 minutes after administration of FDG according to the weight-based scale currently used for standard-of-care PET examinations. All patients will undergo a single bed position list-mode PET acquisition centered craniocaudally on the tumor. The acquisition will occur continuously throughout the MRI outlined above for an interval of at least 30 min. A total of 10 static PET image sets will be reconstructed from sequential 3 min frames (i.e., 0-3 min, 3-6 min, 6-9 min, etc.).

These 10 image sets will be assessed by the Principal Investigator for tumor motion throughout the 30 min PET acquisition. If the rectal cancer is deemed to be adequately stationary on review of the images from the first scan, the FDG will be reduced to one-fifth of the initial administered activity for the following scans, with a compensatory increase in the frame length to 15 min for reconstruction of static PET images. This modification will result in substantial dose reductions for subsequent imaging sessions but should not compromise image quality.

7.3. Clinical record

We will collect information from the patient's medical record such as standard of care images and other clinical records for up to 5 years following the last imaging examination performed on protocol. The purpose of this follow-up period is to correlate imaging findings with patient outcomes, as many patients will likely not undergo surgery for residual or recurrent disease during the 24-36 month study period.

7.4. Image storage and interpretation

All MR images will become part of a subject's permanent medical record and receive a full dictation by a qualified radiologist, as per standard-of-care procedures. The PET images will also become part of the subject's permanent medical record (i.e., sent to clinical PACS, EPIC, ClinDesk). A full clinical dictation for the PET will also be generated by an individual with expertise in both MRI and Nuclear Medicine to accompany the images in the medical record. See 10.2 for more details on the image interpretation.

8. ADVERSE EVENT REPORTING

The primary physician on the study team, Dr. Fraum (also the Principal Investigator), will review, evaluate, and manage accumulated safety data from the entire study on an ongoing basis. For the purposes of this imaging study, the research team will collect safety data for the radiotracer FDG for a period of 24 hours (>10 half-lives) after each administration. Adverse event (AE) monitoring will occur at the time of the informed consent is signed and will continue until the end of study participation.

Once the primary study physician, or the Principal Investigator or member of the research team becomes aware of a serious adverse event (SAE), the SAE will be reported to the IRB, Washington University Human Research Protection Office according to current reportable events policy. Adverse events for purposed of this imaging study are defined as any untoward medical occurrence in a subject who received the intravenous injection or FDG as part of our PET/MRI examination. The event does not necessary have to be causally related to FDG to qualify as an adverse event.

An adverse event can be any unfavorable or unintended sign, symptom or disease temporally associated with the injection of FDG whether or not it is considered related to the radiotracer or PET/MRI. Serious adverse events must be serious unexpected, and reasonably related to the research. Events that do not meet the requirements for SAE reporting will be reviewed by the primary study physician and the Principal Investigator and documentation of the fact that even does not meet SAE reporting requirements will be maintained in the subject's chart. Subjects will be monitored for adverse events from the time of consent through follow-up or to the end of study participation. Subjects who experience an adverse event will be instructed to inform a member of the research team as soon as possible. The Principal Investigator or designee will contact the participant to begin adverse event evaluation and complete the appropriate reporting forms. The study coordinator will review the subject's medical records for clinical history as made available.

The primary study physician and the Principal Investigator will determine the intensity of the adverse events.

8.1. Definitions

8.1.1. Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Attribution (Relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website at: http://www.hhs.gov/ohrp/policy/advevntguid.html.

8.1.2. Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

8.1.3. Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

8.1.4. Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

8.1.5. Unanticipated Problems

- 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;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved 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) than was previously known or recognized.

8.1.6. Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subject research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

8.1.7. Serious Noncompliance

Definition: noncompliance that materially increases risks, and results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

8.1.8. Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation. Pre-approval of all protocol exceptions must be obtained prior to the event.

8.2. Reporting to the Human Research Protection Office (HRPO)

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

8.3. Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

8.4. Time Frame for Reporting Required Events

As noted above, minimal adverse events are associated with FDG-PET/MRI. If we are made aware of an AE/SAE, then we will report this to the HRPO in the timeline noted in section 8.2.

9. DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in month 1, month 2, and subsequent months
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The primary study physician and study principal investigator and Research Patient Coordinator will monitor any potential issues on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

10. IMAGE AND DATA ANALYSIS

10.1. Primary objective

The primary objective is to determine technical feasibility of PET/MRI for rectal cancer treatment response assessment and post-treatment surveillance for patients receiving chemoradiation as part of a NOM strategy. Technical feasibility (**the primary endpoint**) will be defined as completion of the PET/MRI rectal cancer protocol with acceptable image quality in ≥70% of scans. This proportion is based on a predicted success rate, informed by prior experience with PET/MRI studies. For patients imaged at multiple time points after enrollment (see **7**), all available PET/MRIs will be included in the feasibility analysis. Patients able to remain on the scanner for the full duration of the planned data acquisition without any serious adverse events (see **8.1.2**) will be considered to have *completed* the PET/MRI rectal cancer protocol. Image quality will be assessed by the Principal Investigator on review at a dedicated workstation with specialized PET/MR software. A standardized Likert-based scoring scheme will be

utilized to capture subjective assessments of image contrast (1 = worst; 5 = best), image resolution (1 = worst; 5 = best), and image artifact 'freeness' (1 = worst; 5 = best). Image sets scoring ≥ 3 in all three categories will be considered of *acceptable quality*.

The first imaging session for the first two subjects enrolled will occur with the Principal Investigator present in the scanner control room to direct the tweaking of acquisition parameters and imaging planes in real time. If the Principal Investigator is satisfied with the quality of the reconstructed PET and MR images from these first two cases, as viewed on a dedicated workstation with specialized PET/MR software, the imaging protocol will be considered optimized, and the relevant acquisition parameters will be 'locked' as the default for subsequent imaging sessions for these two patients and for all other enrolled subjects. The Principal Investigator will review each of the remaining cases after it is finished (i.e., not in real time but soon after completion) to simulate conditions under which PET/MRI examinations are typically performed (i.e., technologist operating scanner without radiologist present), making an assessment of image quality at that time according to a predetermined qualitative scale.

10.2. Secondary objective

The secondary objective is to estimate the added value of PET/MRI relative to MRI only for detecting residual or recurrent rectal cancer following chemoradiation in patients on a NOM protocol. The MRI component of the PET/MRI will be performed as a standard-of-care examination, with the formal study interpretation flowing to the subject's medical record and replacing the interpretation that would normally be provided by the clinical reading room. These interpretations will include descriptions of local tumor extension (T-stage) and locoregional lymph node involvement (N-stage). Any potential sites of metastatic disease (M-stage) will also be described, though assessment will be limited to the pelvis. For post-treatment imaging studies, an mrTRG will also be provided according to a standardized scale.

Then, the same study reader interpreting the MRI (initially blinded to the PET data) will qualitatively and quantitatively (e.g., post-treatment SUV_{max}) assess the reconstructed PET images (with and without MRI fusion). This reader will then render a PET/MRI tumor regression grade (pmrTRG) based on the PET and MRI data, using a standardized scoring system. Changes in the perceived disease status (i.e., mrTRG vs. pmrTRG; **the secondary endpoint**) will be recorded. This study interpretation will also flow to the patient's clinical chart via a separate report. The patient's multidisciplinary care team will consider the pmrTRG in conjunction with results of other available data (e.g., lower endoscopy and DRE) and make a decision whether to categorize the case as cCR.

Subjects deemed to have anything other than cCR will be evaluated for surgical management (TME or endoscopic resection). In contrast, subjects deemed to have a cCR will continue on the NOM surveillance protocol, with repeat PET/MRIs at regular intervals as indicated in the Schema (also see **7**). These subsequent PET/MRIs will be analyzed as outlined in the preceding two paragraphs. Thus, the secondary endpoint will consider all scans that each patient undergoes, rather than just the first scan (as outlined in **10.1** for the primary endpoint). Pathology and clinical follow-up

data will be collected for up to 5 years after enrollment of the patient in the study for correlation with the PET/MRI findings.

11. STATISTICAL CONSIDERATIONS

The primary endpoint is the feasibility of PET/MRI for rectal cancer treatment response assessment and post-treatment surveillance for patients receiving chemoradiation as part of an NOM strategy. We are interested in the feasibility of PET/MRI for this indication to aid in the planning of a larger prospective trial of short-course radiation therapy followed by adjuvant chemotherapy for the NOM of rectal cancer patients, potentially using PET/MRI to assess for residual or recurrent disease following chemoradiation.

The primary endpoint, feasibility, will be analyzed using descriptive statistics, including exact 95% confidence intervals. Similarly, the secondary endpoint, changes in perceived disease status resulting from the addition to FDG-PET to MRI, will also be analyzed with descriptive statistics, including exact 95% confidence intervals.

A sample size of 20 patients, with an anticipated average of 3 scans/patient, will provide approximately 60 scans for feasibility assessment. If we observe a feasibility rate of 83.3% (i.e., 50 of 60 scans completed imaging sessions with adequate image quality), the exact 95% confidence interval for that proportion and sample size would be 72-92%. The lower limit of this confidence interval will effectively indicate that feasibility is ≥70% and that the study has met its primary endpoint.

If a feasibility rate of 90% is observed for the first 20 scans after the optimization phase, the 95% confidence interval for that rate would be 68.3-98.8%. This lower bound will be deemed close enough to 70% to constitute success with respect to achieving the primary endpoint. Thus, enrollment of additional subjects could cease at this point (**early stopping**) at the discretion of the Principal Investigator. Notably, already enrolled subjects would continue receiving additional scans per protocol and will be included in the secondary endpoint analysis.

12. STUDY CALENDAR

Enrollment point	Screening	Initial staging FDG-PET/MRI	Restaging FDG-PET/MRI	Surveillance #1 FDG-PET/MRI	Surveillance #2 FDG-PET/MRI	Surveillance #3 FDG-PET/MRI	Surveillance #4 FDG-PET/MRI	Surveillance #5 FDG-PET/MRI	Surveillance #6 FDG-PET/MRI
#1	X	X	X	X	X	X	X		
#2	X		X	X	X	X	X	X	
#3	X			X	X	X	X	X	X

Important calendar notes:

- Surveillance scans will not be performed only if a subject undergoes surgery for a suspected recurrence at an earlier time point (see study schema).
- There is no time restriction with respect to when these imaging studies must occur. The FDG-PET/MRIs can occur whenever the subject would have otherwise received an MRI as part of his/her standard-of-care imaging at the designated stages of care as outlined above for each enrollment point.
- Enrollment point #3 can include patients that have already undergone one or more standard-of-care surveillance imaging sessions.

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