CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER: CASE 8212

STUDY TITLE: Evaluation of PET-MRI in initial staging of high grade rectal cancer patients and in the follow up of colorectal cancer patients.

PRINCIPAL INVESTIGATORS:

Raj Paspulati MD
Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106
(216) 844-1542

CO-PI:

Smitha Krishnamurthi MD
Department of
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106
(216) 844-1006

Conor Delaney MD PhD
Department of Surgery
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106
(216) 844-7874

CO- INVESTIGATORS:

Sasan Partovi MD
Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve University

Nghi Nguyen, MD, PhD
Department of Radiology
University Hospitals Case Medical Center

Andrew Sher, MD
Department of Radiology
University Hospitals Case Medical Center

Claudia Martinez-Rios, MD
Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve University

Case Western Reserve University
STATISTICIAN: Ronald D. Novak, Ph.D., M.P.H., M.P.A.

Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve Radiology
11100 Euclid Avenue
Cleveland, OH 44106
(216) 844-7519

SPONSOR: Philips Healthcare

CLINICAL FACILITY: University Hospitals Case Medical Center

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Case Cancer IRB: Pending

STUDY COORDINATOR: Clinical Trials Unit
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106-5065

TABLE OF CONTENTS

Contents

1.0 BACKGROUND AND RATIONALE

Colorectal cancer is the 2nd leading cause of cancer related deaths in the US(1). Colon cancer accounts for 71% and rectal cancer for the remaining 29%(2). Treatment for both entities is primarily surgical with a 90% survival at 5 years when diagnosed in a localized stage, 70% for regional and 10% for metastatic disease(3). Imaging plays a crucial role in the diagnostic workup of these diseases. Both, CT and MR, have their roles in diagnosis and initial staging of both colon (CT colonography) and rectal cancer (Pelvic MR). Furthermore they also contribute substantially in follow up and restaging, along with PET-CT.

Determining T and N staging of rectal cancer is mainly done with MR given its superior tissue resolution over CT and PET-CT(4, 5). In particular for T staging similar accuracy was reported when comparing endoscopic ultrasound and MRI in cases of histologically proven rectal cancer (4). While T2 weighted sequences give a detailed anatomy and reach of the lesion as well as morphologic data regarding lymph nodes of the area, DWI sequences helps evaluate the cellular composition of both the tumor and lymph nodes showing as hyperintense lesions those with a high cellular component. On the other hand, PET-CT is used mainly in aggressive, or high grade, rectal cancer and locally advanced stages because of its high sensitivity depicting metastatic disease which might either change the therapeutic approach or suspend unnecessary interventions(6, 7). The diagnostic accuracy of PET/CT for M staging is higher than that of CT alone.

Follow up in successfully treated patients, both in colon and rectal cancer, contributes to increased survival rates, as it has been proven that patients undergoing liver imaging during follow up have a 25% lower mortality rate(8). While CT is the image modality of choice, because of availability and price, MR is more sensitive for detecting and classifying liver lesions(9) while PET-CT is more sensitive in detecting extrahepatic disease(10).

Given the obvious advantages, described above, of both MR and PET-CT in staging, follow up and restaging of these diseases, it is our objective to test the performance of PET-MRI in these diseases since it is our belief that this hybrid imaging modality will prove superior to current single imaging modality options, namely MRI, CT and PET-CT.

2.0 OBJECTIVES

Our objective is to test the diagnostic performance of PET-MRI in two different settings. The first setting is the staging of preoperative high-grade rectal cancer patients, defined by T3 stage or higher or N1 stage or higher or presence of metastasis, that are referred to PET-CT and MRI. In this population Pathology will be the gold standard when available for local staging and PET/CT for M staging. When Pathology is not available, both MRI and PET/CT results will be used to determine T and N stage.

The second setting is the follow up of colorectal cancer patients that are referred to PET-CT with or without a diagnostic MRI request by their physicians. In this second group the gold standard for recurrence will be obtained from analyzing CEA levels and PET/CT and MRI results. Pathology results will be used as well whenever available.

A secondary objective is to test different attenuation correction MR sequences and novel diagnostic MR sequences.

3.0 PATIENT/SAMPLE SELECTION

Every patient that is scheduled to get a PET-CT at UH Case Medical Center either for preoperative high-grade rectal cancer or for colorectal cancer follow-up will be invited to join this pilot study. Initially, 10 patients per group will be invited to participate. We expect to recruit this number of patients in a two year period at the most.

Inclusion Criteria:

- Either having a T3 (The cancer has grown through the muscularis propia and into the outermost layers of the colon or rectum but not through them) or higher, node positivity or metastatic lesion in the context of rectal cancer or being studied for colorectal cancer follow up, independent of the renal function
- PET-CT should be requested by a referring physician. In the case of having an MR requested as well, it will be reported from the MRI images generated in the PET-MRI
- Stable physical medical conditions to undergo a MRI

- Informed consent must be given and signed prior to study enrollment
- Patient should be over 21 years old

Exclusion Criteria

- Refuse to give and/or sign the informed consent
- Subjects who do not meet the above mentioned inclusion criteria
- Subjects who have a pacemaker
- Subjects who have a metallic prostheses either in the pelvis or in the abdomen that will interfere with the MR imaging of that anatomical area
- Subjects who suffer from claustrophobia
- Pregnant women
- Cognitive impairment that affects the subjects ability to give consent

4.0 REGISTRATION PROCEDURES

The potential participant will be informed of the ongoing protocol during the visit to his referring physician where he will also be provided the consent form. He/She will then be formally invited to participate in this research study at the time of the appointment for the diagnostic PET-CT examination. A member of the research team will provide all information and answer questions related to the planned study. This study member will also screen the potential candidate for the inclusion and exclusion criteria. The candidate subject will only qualify for the participation in the study if meeting all inclusion/exclusion criteria as listed in Sections 3.2 and 3.3. The patient will then first be screened for MRI safety using the standard MRI informed consent form as typically used for all diagnostic MRI as a standard of care at UHCMC.

If the candidate subject is confirmed to meet the inclusion/exclusion criteria and to qualify for safety features for a diagnostic MRI scan and is interested in participating, the Informed Consent form will be given to the patient. The patient will have the opportunity to discuss the Informed Consent Form with family or friends from the time he/she is consented to the time of the examination.

The study team member will then obtain the permission from the patient to participate. The member of the research team will go over the informed consent form with the candidate subject.

5.0 RESEARCH PLAN

5.1 Study procedures and data analysis plan

Patients who enroll in this study will receive their clinically requested diagnostic PET-CT and a PET-MRI. When a diagnostic MRI is additionally requested, a report will be generated from the MRI images obtained in the PET-MRI. Both exams will be performed at the Seidman Cancer Center as part of their normal diagnostic care and will meet all of the institutionally imposed criteria for these studies. For research purposes, additional MR sequences that are completely harmless to the patient, but haven't yet been FDA approved for the clinical arena, will be performed. If any additional relevant information is discovered because of these latter sequences proper communication of these findings to the referring physician will be done.

Using the same F18-FDG injection PET-MRI will be performed, before or after the clinically requested PET-CT. If an MRI has also been requested, the report will be generated from the MRI images performed in the same scanner as the PET-MRI. After completion of the first scan, be it the PET-MRI or the PET-CT, the patient will immediately undergo the other examination. No additional F18-FDG injection will be required. MR contrast agents may be injected if it's requested by the referring physician and there are no contraindications. As a preparation for the MRI examination, all subjects except those with prior rectal surgery will receive a small amount of rectal gel to allow enhanced lesion detection. Intramuscular glucagon (1 mg) will be administered to all subjects to help relax the bowels during the MRI examination, unless there are contraindications to it which include history of glucagon hypersensitivity or pheochromocytoma. If the MRI is clinically ordered, the rectal gel and glucagon administrations are standard of care. However, they are research if the MRI is not ordered by the referring physician.

The patient will be inside the PET-MRI scanner for approximately 60-90 minutes whether or not an MRI is performed.

All the imaging data obtained from the patient will be stored in the Radiology Department research PACS after a unique code that links the patient to its identifiers is assigned by a CREC-trained certified co-investigator. All the clinically requested exams will be archived in the Department of Radiology clinical PACS system. Similarly, the PI's and Co-PI's reports that are generated from the clinical images obtained will be permanently archived in Radiology's IDX medical record system. If after reviewing the research data, a finding not previously seen in the clinical images, becomes apparent appropriate steps will be taken to inform the patients referring physician.

5.2 Risks

The risks associated with the PET/MRI scan are the same risks as those posed by individual PET and MRI scans. A known risk related to MRI examinations is that the MRI magnet could attract certain kinds of metal that may cause injury to the patient. In order to avoid that, patients will be screened for any hazardous metal object that they may have or is implanted inside their body which includes heart pacemakers, intracranial aneurysm clips, heart valve prostheses and other implanted devices that are not compatible with MRI. Although there is no risk from ionizing radiation with MRI, subjects will be exposed to strong magnetic fields and radiofrequency pulses common to clinically used MRI systems, neither of which are associated with any known detrimental health effects.

Some of the experimental MR sequences that will be performed are not yet approved by the FDA for clinical use or have been partially approved for a certain type of surface coil in our scanner. These are already being used in a research setting and during clinical workup of patients outside the USA(11) without evidence of any adverse events.

For some types of MRI scans, when clinically indicated and requested by the physician, MR contrast agents may be used to enhance the MR images. These contrast agents to be used are approved by the FDA, are commercially available, and are used within label indications. With these contrast agents there is a risk of an allergic or fibrotic reaction which

occurs more often with x-ray contrast than with MRI contrast agents. Every effort will be made to minimize the risk of such reactions in this study by not exposing subjects who have a history of kidney disease (GFR >30mg/min), which is the cohort who most frequently exhibits fibrotic reactions, to these contrast agents. Generally, an intravenous injection of 10-20 ml will be used provided that the subject has no known reaction to contrast agents used in previous MRI scans. As with all such injections, bleeding, bruising, dizziness, fainting or infection may occur. Also, the injection may be painful but the discomfort should be brief and efforts will be made to minimize the pain. These risks, however, are part of the patient's clinical care and not a consequence of the research.

The MRI scanner makes a loud buzzing sound during the exam that could affect a patient's hearing. In order to protect patient from this sound, they will be provided earplugs during the exam. There might also be some claustrophobia-related discomfort involved with being required to lie still in a small space. If this occurs, patients can signal the technologist attending the MRI/PET who will terminate imaging immediately. The subject will be removed from the MRI machine and regarded as being withdrawn from the study. In effect, the screening process for the MRI portion of PET/MRI imaging will be the same as that done with clinical MRI. The risks associated with a PET scan include radiation exposure from the radioactive tracer. However, additional injection of a radiopharmaceutical is not required for the proposed study since patients will have been injected for their clinical PET scan. Thus, participation in this study does not expose subjects to additional ionizing radiation.

Finally, there is the potential risk of breach of confidentiality. To diminish this risk, we will assign each patient a unique study code that will link data to patient identifiers and the key will be stored separately. Deidentification will take place while transferring the images to the research PACS and will be performed by a CREC-trained certified co-investigator. The key connecting deidentified data to the patient will be generated at that same moment by the same co-investigator and stored in a laptop with an encrypted hard drive for three years after completion of the study, after which it will be destroyed. Only the PI and the co-investigator in charge of deidentifying patient data will have access to that computer that will be kept by the PI in his office.

5.3 Benefits

While there is no direct benefit anticipated for patients in this study, the study may lead to advantages for them because of the improved resolution of imaging being offered by MRI which would not otherwise, in some cases, be performed. The study also spares patients two separate visits for a pelvic MRI, and abdominal CT, when an MRI would otherwise have been ordered.

There may be a benefit for further patient populations in that the investigators create knowledge about the performance of the PET-MRI as a one stop exam for these diseases.

5.4 Alternatives to Participation

This study does not involve a change to the standard clinical care of the participant, except for additional imaging time. There will be no consequences to individuals who withdraw or step down from the study. The subject will not undergo the PET-MRI imaging sequences if he/she refuses to take part in the study. Only the clinically indicated diagnostic PET-CT and, if requested, MRI will be performed. If a subject withdraws during the procedure of the study, the investigators will use the data as acquired up to the point of withdrawal.

5.5 Data and Safety Monitoring

Data and safety monitoring of subjects enrolled in the study will be performed by the principal investigator (PI) and co-investigators. All of the patients will be informed about the minimal risks related to their diagnostic PET-MRI study.

6.0 STUDY PARAMETERS

The study parameter is the PET-MRI data. The results of the analysis of this data (MRI findings, SUV, etc.) will be reported using special spreadsheets designed for this

purpose and will be introduced into an electronic database (REDCAP) using the code given to the patient as the only PHI.

7.0 CORRELATIVE STUDIES (if applicable)

This study is not designed as a correlative study.

8.0 STATISTICAL CONSIDERATIONS

The sample size was determined by the number of patients Philips Healthcare® has agreed to fund and is acceptable for a pilot study. Continuous variables will be expressed as mean ± standard deviation. Comparisons between continuous variables will be performed by using the Student *t* test. Comparisons between qualitative variables will be performed by using the χ^2 test with the Yates' correction or McNemar's test as appropriate.

Sensitivity, specificity, positive and negative predictive values, and accuracy for PET-CT and PET-MRI with their 95% confidence interval will be calculated by using the standard formulas according to the criterion standard. Concordance between PET-CT and PET-MRI techniques will be assessed by using the McNemar test that evaluates whether the discrepancies between both techniques are higher than those observed by chance alone.

All calculations and statistical parameters will be calculated using Systat, Ver. 13.05 (Systat Software, Chicago, IL) or MedCalc Software, Ver. 12.3 (MedCalc Software bvba, Brussels, Belgium).

9.0 RECORDS/DATA TO BE KEPT

As with all patient images obtained in the Department of Radiology, the PET-MRI and PET-CT images that are obtained in this study will be archived in the Department of Radiology's research PACS system. The clinical MRI and PET-CT images will be archived in the Department of Radiology clinical PACS system. Similarly, the PI's and Co-PI's reports that are generated from the clinical images obtained will be permanently archived in

Radiology's IDX medical record system. Copies of the results tabulated as described in Section 5 and 6 will be kept for a period of 3 years after publication or after approval of marketing the PET/MRI.

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