**Note: Sample uses older template format

3T MRI for pre-hepatectomy detection of colorectal cancer metastases to liver

Study Chair (PI)
Claude B. Sirlin, MD
Associate Professor
Dept. of Radiology
Chief, Body MRI
Director, Liver Imaging Group
University of California, San Diego
MR3T Research Lab
408 Dickinson Street
San Diego, CA 92103-8226

***Co-investigators**, and contact info.*
Mark Bydder, PhD
Michael Middleton, MD, PhD
Gavin Hamilton, PhD
Marquis Hart, MD
Michael Peterson, MD, PhD

Statistician
Anthony Gamst, PhD

Original Date: *Insert date of final and approved protocol (blank during this workshop)*
Version Date: *Version 6, January 10, 2008*
Activation Date: *On activated protocols only (blank during this workshop)*

Table of Contents

3T MRI for pre-hepatectomy detection of colorectal cancer metastases to liver

PROTOCOL OVERVIEW

This is prospective pilot study on subjects with colorectal cancer (CRC) metastases to the liver. Subjects will undergo a research MRI of the liver prior to curative hepatectomy. Each focal lesion (benign or malignant) identified at imaging will be characterized with respect to 21 imaging features such as size, shape, margination, heterogeneity, kinetic enhancement pattern, and overall confidence for malignancy. Features will include binary, categorical, ordinal, and continuous variables. Sixteen features will be standard and five (T2*, ADC, shear modulus, late venous phase signal intensity, and hepatocellular phase signal intensity) will be experimental. The MR sequences used to obtain the three quantitative experimental lesion features (T2*, ADC, shear modulus) will be acquired twice for each subject.

After surgery, the hepatectomy specimen will be imaged *ex vivo* at 3T and then sliced into 5-mm sections. Using the *ex-vivo* images as the link, all focal lesions (benign or malignant) detected on the pre-hepatectomy research MR exam or in the resected pathology specimen will be co-localized. Lesions will be sampled and submitted for histology. A board-certified surgical pathologist will review the slides and determine the final histological diagnosis for each lesion (malignant or benign).

SPECIFIC AIMS/OBJECTIVES

The **primary aim** is to estimate for each MRI feature the per-lesion sensitivity, specificity, and area under the ROC curve for the diagnosis of CRC metastases, using the dichotomous histological diagnosis (malignant or benign) as the reference standard.

The **secondary aims** are to (1) estimate and compare the per-lesion area under the ROC curve of a multivariate model that uses experimental as well as standard MRI features versus that of a model that uses only standard MRI features for the diagnosis of CRC metastases and (2) estimate the intraclass correlation coefficient of repeated quantitative measurements (T2*, ADC, and shear modulus) on each lesion.

ELIGIBILITY

Consecutive subjects with colorectal cancer (CRC) metastases to the liver willing and able to undergo a research MRI of the liver within 10 days prior to hepatectomy.

REQUIRED SAMPLE SIZE

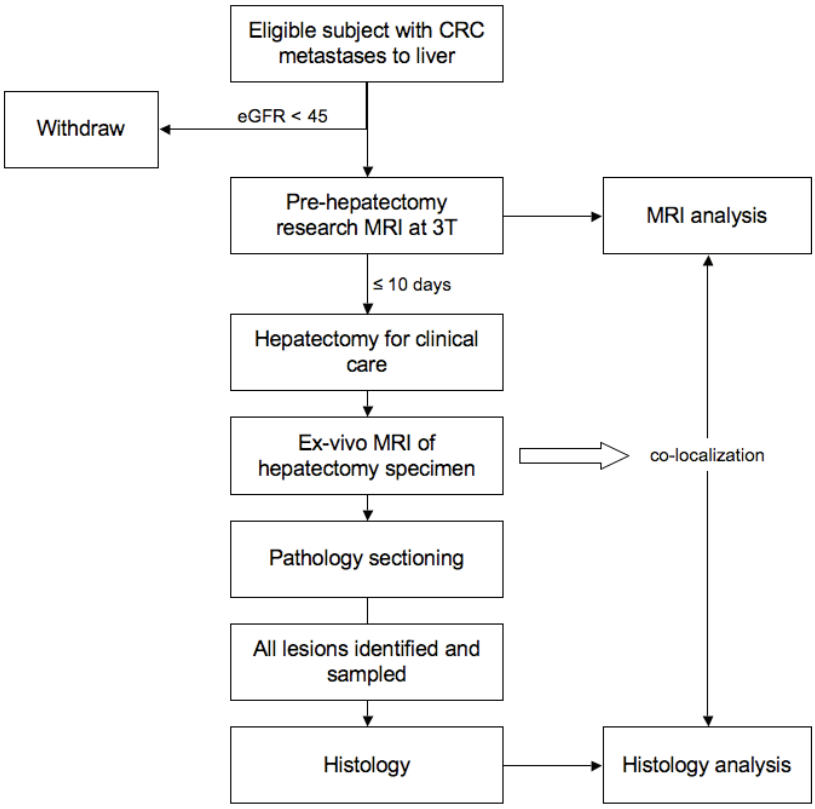
30 subjects will be enrolled in this pilot study.

STUDY DESIGN

Prospective, pilot study.

PRIMARY ENDPOINTS

The per-lesion sensitivity and specificity (binary and dichotomized categorical features) and the area under the ROC curve (ordinal and continuous features) for the diagnosis of CRC metastases.


Eligible subject with CRC metastases to liver
eGFR < 45
Withdraw
Pre-hepatectomy research MRI at 3T
MRI analysis
≤ 10 days
Hepatectomy for clinical care
Ex-vivo MRI of hepatectomy specimen
co-localization
Pathology sectioning
All lesions identified and sampled
Histology
Histology analysis

1.0 ABSTRACT

Colorectal cancer (CRC) is the second leading cause of death from cancer in the United States. It affects more than 1,000,000 Americans; over 50% of patients develop liver metastases. The best curative solution for patients with liver metastases is complete excision of tumor burden via hepatectomy. In current practice, preoperative imaging is performed to identify metastases and plan the resection. Multidetector computed tomography (CT) and 1.5T magnetic resonance imaging (MRI) are the most commonly used techniques for this purpose but have less than 25% sensitivity for metastases smaller than 1 cm. Failure to detect sub-centimeter metastases is clinically relevant; in up to one third of hepatectomy patients, missed metastases contribute to incomplete resection and lead to hepatic recurrence within six months of surgery. To reduce the frequency of missed metastases, more sensitive imaging techniques are needed. 3T MRI is an appealing option to address this need. It provides greater soft tissue contrast than CT and greater signal-to-noise ratio and contrast agent sensitivity than 1.5T MRI. Thus, it can generate high-resolution, high-contrast images that may improve the ability to detect small lesions.

In this prospective pilot study, consecutive eligible subjects with CRC metastases to the liver will undergo a research 3T MRI of the liver within 10 days prior to curative hepatectomy done for clinical care. One radiologist will review the MR images and, for each focal lesion identified at imaging on each subject, assess 21 (16 standard and 5 experimental) imaging features such as size, shape, margination, heterogeneity, kinetic enhancement pattern, and overall confidence for malignancy. Features will include binary, categorical, ordinal, and continuous variables. The MR sequences used to obtain three quantitative lesion features (T2*, ADC, shear modulus) will be acquired twice for each subject.

The **primary aim** of this pilot study will be to estimate the per-lesion sensitivity and specificity for binary and dichotomized categorical MRI features and the area under the ROC curve for ordinal and continuous features MRI features for the diagnosis of CRC metastases, using the dichotomized histological diagnosis (CRC metastasis versus other) as the reference standard. Per-lesion co-localization of pre-operative imaging and pathology will be achieved by performing high-resolution *ex-vivo* MR imaging of the hepatectomy specimen prior to pathology sectioning

The **secondary aims** will be to:

1) estimate and compare the per-lesion area under the ROC curve of a multivariate model that uses experimental as well as standard MRI features versus that of a model that uses only standard MRI features for the diagnosis of CRC metastases.

2) estimate the intraclass correlation coefficient of repeated per-lesion quantitative measurements (T2*, ADC, and shear modulus).

This pilot study will be used to plan a future clinical trial. The future trial will further assess the multivariate models and evaluate if 3T MRI is more sensitive and specific than 1.5T MRI and multidetector CT for diagnosing CRC metastases to the liver.

2.0 BACKGROUND AND SIGNIFICANCE

Background:

Colorectal cancer (CRC) is the second leading cause of death from cancer in the United States, and accounts for more than 10% of all cancer-related deaths. In 2007, there will be an estimated 153,000 new cases of CRC and 52,000 deaths from CRC in the United States[1], and over 1,000,000 new cases of CRC worldwide[2]. A total of 1,002,000 Americans had CRC in 2000, and the associated health care costs were $7.5 billion; the number of Americans with CRC is expected to increase to 1,522,000 by 2020 and the estimated health-care costs to increase to $11.4 billion[3].

About 50-60% of patients with CRC eventually develop liver metastases. Thus, it is estimated that over 500,000 Americans currently have CRC metastases to the liver. Chemotherapy may slow the growth of liver metastases and may even cause their temporary regression but it cannot eliminate metastases. The best curative option for these patients is surgical resection, which provides a 5-year survival rate of up to 58%[4-7]. However, in about 60% of patients who undergo resection, the tumor will recur[8], and in 30-40% the tumor recurrence will be isolated to the liver[9,10]. Most hepatic recurrences are diagnosed within six months of surgery[8,10,11] and probably represent liver metastases that were already present but undetected at the time of hepatectomy[12]. Recurrences may be treated with repeat resection[10,11,13-15] with a median disease free 5-year survival from 16-48%[16], but only 30-39% of affected patients are candidates for such surgery[10,13]. Because of the problems associated with recurrent disease, one recent study reported that 87% of patients who undergo primary hepatic resection receive no substantial survival benefit from surgery[10].

To prevent hepatic recurrences and improve surgical outcomes, it is necessary preoperatively to diagnose the number, size, and location of all macroscopic liver metastases. In this way, the surgeon can plan the resection and successfully excise the metastases or determine that surgery is futile[12]. According to current evidence-based guidelines, the diagnostic modality of choice for identification of potentially resectable lesions is either computed tomography (CT) or gadolinium-enhanced MR imaging[17]. Nevertheless, the diagnostic performance of each modality is disappointingly low. In a recent meta-analysis[18], MR had a higher per-lesion sensitivity than CT overall (78% vs. 64%), but both modalities had poor sensitivity for metastases smaller than 1 cm (12% and 23%). Failure to detect sub-centimeter metastases is clinically relevant because these lesions eventually will grow, manifest as recurrent disease, and cause morbidity and mortality.

Because preoperative diagnosis of sub-centimeter metastases is poor, many authors advocate intra-operative ultrasound as the final diagnostic procedure[19-21], and studies have shown that intra-operative ultrasound can identify resectable metastases missed at preoperative imaging in about 20% of patients[19]. However, intra-operative ultrasound also may miss lesions[22,23], particularly in patients with fatty liver related to obesity or neo-adjuvant chemotherapy prior to hepatectomy[24]. Moreover, false positive findings may occur and lead to excessively aggressive resection[19]. Equally important, intra-

operative ultrasound is performed during surgery and thus cannot be used preoperatively to select patients most likely to benefit from attempted resection[23].

Our **long-term goal** is to improve the clinical outcomes of pre-hepatectomy patients with CRC metastases to the liver by developing non-invasive imaging techniques that accurately detect resectable CRC metastases.

3T MRI is a promising modality for achieving this goal. It provides superior soft tissue contrast compared to CT as well as greater signal-to-noise ratio and contrast agent sensitivity compared to 1.5T MRI. Thus, it can generate high-resolution, high-contrast images to detect small as well as large metastases. Because benign lesions of the liver are common, it will be necessary to accurately characterize lesions as malignant or non-malignant and develop interpretation algorithms with high positive predictive value for metastases. In the last ten years, radiologists have emphasized the use of dynamic imaging using extracellular contrast agents for lesion detection and characterization. The increasing use of neo-adjuvant chemotherapy for CRC with anti-angiogenesisis agents prior to surgery, however, may confound interpretations based only on vascularity assessment. Several experimental MR sequences, such as diffusion-weighted imaging, MR elastography, and hepatocellular phase imaging after administration of a hepatobiliary agent, assess tissue properties other than vascularity and show promise for lesion characterization. Some of these experimental sequences (e.g., diffusion-weighted imaging) intrinsically have low signal-to-noise ratio and are likely to benefit from application at higher field strength. Accordingly, we have developed a 3T MRI protocol for diagnosis of CRC metastases to the liver. The protocol includes experimental in addition to standard sequences.

Our **long-term hypothesis** is that, in pre-hepatectomy patients with CRC metastases to the liver, 3T MRI performed with experimental sequences will diagnose CRC metastases to the liver with higher sensitivity and specificity than current techniques.

Significance:

This pilot study will be used to plan a future clinical trial. The future trial will evaluate if 3T MRI is more accurate than 1.5T MRI and multidetector CT. The successful completion of the aim of the future trial will lead to (a) more appropriate selection of CRC patients for curative hepatectomy, (b) improved preoperative planning, (c) more complete excision of intrahepatic tumor burden, and (d) reduced frequency of hepatic recurrence. These benefits will translate into improved quality of life and prolonged survival for CRC patients selected for resection. This will also reduce the morbidity, mortality, and health care costs associated with unnecessary laparotomies in the 87% of patients who currently do not have a survival benefit from surgery[10]. Because there are over 500,000 Americans with CRC metastases to the liver, the number of patients who may benefit from more accurate pre-hepatectomy imaging is large. Moreover, the knowledge gained from this proposal may lead to more accurate imaging diagnosis and clinical outcomes of patients with other types of liver lesions, such as metastases from non-CRC malignancies as well as primary hepatic malignancies.

3.0 SPECIFIC AIMS/OBJECTIVES

We will perform 3T MRI in pre-hepatectomy patients with CRC metastases to the liver and, for each focal lesion identified at imaging on each subject, assess 21 imaging features such as size, shape, margination, heterogeneity, kinetic enhancement pattern, and radiologist's overall confidence for malignancy. Features will include binary, categorical, ordinal, and continuous variables. Sixteen features will be standard and five (T2*, ADC, shear modulus, late venous phase signal intensity, and hepatocellular phase signal intensity) will be experimental. The MR sequences used to obtain the three quantitative experimental lesion features (T2*, ADC, shear modulus) will be acquired twice for each subject. In addition to the per-lesion MR features, two-per patient imaging features (abdominal AP diameter at the level of the portal vein bifurcation and the presence of ascites) will be assessed. Three demographic features (subject age, gender, ethnicity) will be available for the multivariate analyses.

Primary aim:

The primary aim is to estimate for each MRI feature the per-lesion sensitivity and specificity (binary and dichotomized categorical features) or the area under the ROC curve (ordinal and continuous features) for the diagnosis of CRC metastases, using the dichotomized histological diagnosis (CRC metastasis versus other) as the reference standard. Per-lesion co-localization of pre-operative imaging and pathology will be achieved by performing high-resolution *ex-vivo* MR imaging of the hepatectomy specimen prior to pathology sectioning

Primary endpoint:

The per-lesion sensitivity and specificity for binary and dichotomized categorical features and the area under the ROC curve for ordinal and continuous features for the diagnosis of CRC metastases.

Secondary aims:

The secondary aims will be to:

1) estimate and compare the per-lesion area under the ROC curve of a multivariate model that uses experimental as well as standard MRI features versus that of a model that uses only standard MRI features for the diagnosis of CRC metastases.

2) estimate the intraclass correlation coefficient of repeated quantitative measurements (T2*, ADC, and shear modulus) on each lesion.

Secondary endpoints:

1) The areas under the ROC curves of multivariate models.

2) Intraclass correlation coefficient between repeated quantitative measurements.

4.0 STUDY OVERVIEW

In this prospective pilot study, consecutive eligible subjects with CRC metastases to the liver will undergo a research MRI of the liver within 10 days prior to curative hepatectomy done for clinical care. One radiologist will review the MR images and, for each focal lesion (benign or malignant) identified at imaging on each subject, assess 21 imaging features such as size, shape, margination, heterogeneity, kinetic enhancement pattern, and overall confidence for malignancy. Features will include binary, categorical, ordinal, and continuous variables. Sixteen features will be standard and five (T2*, ADC, shear modulus, late venous phase signal intensity, and hepatocellular phase signal intensity) will be experimental. The MR sequences used to obtain the three quantitative experimental lesion features (T2*, ADC, shear modulus) will be acquired twice for each subject. After surgery, the hepatectomy specimen will be imaged *ex vivo* at 3T and then sliced into 5-mm sections. Using the *ex-vivo* images as the link, all focal lesions (benign or malignant) detected on the pre-hepatectomy research MR exam or in the resected pathology specimen will be co-localized and submitted for histology. Thus, every lesion detected at pre-hepatectomy imaging will be co-localized on the pathology specimen and every lesion detected on the pathology specimen will be co-localized on the pre-hepatectomy MR images. A board-certified surgical pathologist will review the slides and determine the final histological diagnosis for each lesion. The dichotomized per-lesion histology diagnosis (malignant versus benign) will serve as the per-lesion reference standard. Subjects are expected to have between one and ten CRC metastases in the hepatectomy specimen (average of three) and zero to five benign lesions (average of one). Subjects are not expected to have any malignancies other than CRC metastases.

Number of participants:	30
Recruitment time frame:	18 months
Number of sites:	1
Type of study:	clinical, single-arm, pilot study

5.0 PARTICIPANT SELECTION

Patients of all races and ethnic backgrounds at least 18 years old will be considered eligible for this study. Consecutive subjects will be recruited from those patients scheduled to undergo hepatectomy for clinical care by the study surgeon. Each subject entered into the study will have a diagnosis of at least one resectable CRC metastasis of the liver.

5.1 Inclusion Criteria

Potential subjects will be enrolled if they meet the following criteria:

5.1.1. Scheduled for surgical resection of CRC metastases to the liver.

5.1.2. Willing and able to undergo a 3T MR examination for research purposes 10 days or less prior to surgery.

5.1.3. Willing to have surgical resection specimen scanned for research purposes.

5.1.4. eGFR is known from a serum sample drawn 35 days or less prior to hepatectomy or patient is willing to have serum sample drawn.

5.1.5. Age ≥ 18 years old at time of screening.

5.1.6. Women of childbearing potential: willing to take urine pregnancy on day of MRI

5.2 Exclusion Criteria

Potential subjects will be excluded if any of the following conditions are met:

5.2.1. Contra-indications to MR imaging such as pacemaker, non-MRI compatible aneurysm clip, other non-MRI compatible mechanical and/or electrical device, or severe claustrophobia. Subjects with milder forms of claustrophobia that can be successfully allayed with oral anxiolytic therapy will be allowed. The study surgeon will prescribe the anxiolytic for such subjects.

5.2.2. Inability to undergo MRI due to severely compromised pulmonary, cardiovascular, or mental status.

5.2.3. Contra-indications to Gd-based contrast media such as history of prior allergic reaction to Gd-based contrast media.

5.2.4. Lack of intravenous access

5.2.5. eGFR < 45

5.2.6. on dialysis

5.2.7. Known or suspected nephrogenic systemic fibrosis

5.2.8. Nursing mother

5.2.9. Pregnant

5.2.10. Any other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study

5.3 Recruitment Procedures

The study surgeon performs 40 hepatectomies for CRC metastases per year. For clinical care, he sees patients at preoperative clinic four weeks prior to the scheduled hepatectomy. A study research coordinator will attend the surgeon's preoperative clinic. The surgeon will inform potentially eligible subjects about the research study. If the subject agrees, the research coordinator will meet briefly with the subject (considered the pre-registration visit, see below), give the subject an informational flyer, and schedule a registration visit (see below).

The study surgeon has collaborated with our research group closely for three years. Historically, over 75% of the patients he has recruited for our research studies have been successfully enrolled. Therefore, conservatively, we anticipate that at least 50% of his patients will be willing to and able to be enrolled in our study.

6. 0 STUDY PROCEDURES

6.1 Institutional and Investigator Requirements

All scans will be performed at the MR3T Research Laboratory at the University of California, San Diego. The laboratory has a General Electric (Milwaukee, WI) Twin Speed 3T scanner (system 14X) with 40 mT/m gradient strength. The system includes an 8-element torso phased array coil with parallel imaging capabilities for scanning human subjects and a cardiac coil that is suitable for scanning tissue specimens *ex vivo*. The scanner is dedicated for clinical research and will be available for scanning research subjects and *ex-vivo* specimens from 8 am to 8pm seven days a week. Hours of operation will be expanded to accommodate research subjects if necessary. Two certified MR technologists are full-time employees at the MR3T Research Laboratory and will perform all pre-hepatectomy MR scans on research subjects. Additionally, there are two post-doctoral fellows and one research assistant in the MR3T Research Laboratory who will perform the imaging on the hepatectomy specimens *ex vivo*.

6.2 IRB Approval and Informed Consent

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference of Harmonisation guidelines), and applicable government regulations. This protocol and any amendments, including the informed consent form will be submitted to the Institutional Review Board (IRB) for a formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before implementation of the study. All study participants in this study will be provided with an IRB approved informed consent form describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix for a copy of the sample informed consent form). This consent form will be submitted along with the protocol for review and approval by the local IRB. The study participant will be consented with the IRB approved informed consent form before the participant is subjected to any study procedures. The approved informed consent form will be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent. The individual obtaining the consent will emphasize that participation is completely voluntary, that the subject may withdraw at any time, that there may be no direct benefits to subjects, and that there are risks involved in participation.

6.3. Accrual Goals and Monitoring

The goal is to enroll 30 subjects over 18 months (5 subjects every 3 months). Each enrolled subject will be entered into a database. The database will track each subject's progress through the research protocol. The Principal Investigator (PI), research coordinator, and study surgeon will actively monitor subject accrual and discuss and problem solve administrative and logistical issues related to recruitment and enrollment. If accrual falls behind projected enrollment, they will discuss possible solutions such as collaboration with another liver surgeon, expansion to another site, or extension of the recruitment time frame.

6.4. Study Calendar / Schedule

Study procedure	Visit 1 Pre-registration	Visit 2 Registration	Visit 3 Phone call *within 1 week prior to MRI*	Visit 4 MRI *2-10 days prior to hepatectomy*	Visit 5 Admission to hospital for hepatectomy	Hepatectomy and specimen imaging
Determine eligibility	X	Confirm eligibility				
Review MRI safety	X			X		
Give info. flyer	X					
Obtain consent		X		Confirm consent		
Register subject		X				
Collect demo. data		X				
Serum sample		*				
Review instructions		X	X	X		
Subject reminder			X			
Pregnancy test				*		
Weigh subject				X		
Insert IV catheter				X		
Research MRI				X		
Acute AE monitoring				X		
Compensate subject				X		
Delayed AE monitoring					X	
Standard of care therapy					X	X
Ex-vivo MRI						X

* = select subjects

6.5. Pre-registration / Determination of Eligibility (Visit 1)

The study surgeon will perform the initial determination of eligibility when he sees his patients at preoperative clinic. He will inform potentially eligible subjects about the study and ask them if they would be willing to meet with the study coordinator. The study coordinator will attend the surgeon's preoperative clinic and, during the clinic, meet briefly with willing subjects. This brief meeting will represent Visit 1, the pre-registration visit. At this pre-registration visit, the coordinator will outline the research protocol to the subject; give the subject an informational flyer, an MRI screening safety questionnaire,

and a consent form; ask for the subject's verbal permission to confirm eligibility by reviewing relevant medical records under the supervision of the surgeon; record the subject's preferred contact information; and schedule the subject for a registration visit.

6.6. Registration Visit (Visit 2)

At the registration visit, the coordinator will explain the protocol in greater detail and answer the potential subject's questions. The MRI screening questionnaire and consent form will be reviewed. With the subject's verbal permission, eligibility criteria will be rechecked. If the eligibility criteria are met, the subject will be asked to sign informed consent and the subject will be registered in the trial. The research coordinator will record demographic data (gender, date of birth, self-reported ethnicity, and self-reported racial group) as well as clinical and laboratory data related to the eligibility criteria (diagnosis of CRC metastases to liver, absence of history of nephrogenic systemic fibrosis, and eGFR). If an eGFR obtained for clinical care is not available within 35 days of the scheduled hepatectomy, then a serum eGFR laboratory test will be ordered. The serum sample will be obtained by a certified phlebotomist or other qualified medical professional as a study procedure. The coordinator will schedule the research MRI examination and review with the subject pre-MRI instructions.

6.7. Reminder Phone Call (Visit 3)

Within one week prior to the MRI, the coordinator will call the patient to remind him or her about the MRI appointment. The coordinator will briefly review the MRI instructions and answer any questions.

6.8. Research MRI (Visit 4)

The research MRI will be done 2-10 days prior to the scheduled hepatectomy. The research coordinator and technologist will meet the subject upon arrival at the MR3T facility and confirm consent, re-review MR safety screening questionnaire, obtain a urine pregnancy test (if the subject is a woman of child bearing potential), and weigh the subject (to determine the appropriate contrast agent dose). The MRI examination will be performed (see Section 6.11). The PI or study investigator will monitor each MR examination and observe the subjects for adverse events until the subjects leave the MR facility. Adverse events will be recorded on a an adverse event form (Section 8.0). Immediately prior to discharge from the MR facility, subjects will be given compensation as detailed in the consent form.

6.9. Pre-operative Admission/Post-MRI Visit (Visit 5)

The study surgeon will admit the subject to the hospital prior to hepatectomy. At the time of pre-operative admission, the surgeon will ask the subject about any delayed adverse events that occurred after the research MRI. This will represent Visit 5 for this trial. The surgeon or his representative or the will record the adverse event information on a data entry sheet.

6.10. Criteria for Removal from Study

Registered subjects will be withdrawn from the study if any of the following conditions are met:

6.10.1. Research MRI is not performed
6.10.2. Intravenous access cannot be established.
6.10.3. eGFR < 45 on blood sample drawn after registration
6.10.4. Subject has a positive urine pregnancy test after registration.
6.10.5. Hepatectomy is not performed.
6.10.6. Subjects withdraws his/her consent.
6.10.7. Exclusion criteria are discovered after registration but prior to MRI

6.11. Imaging Acquisition, Archival, and Interpretation

6.11.1. Overview

Two MR examinations will be performed: a pre-hepatectomy MR examination on subjects (Section 6.11.2) and an *ex-vivo* MR examination on the resected specimen (Section 6.11.4). Both MR examinations will be performed on the same 3T research scanner. The only identifying information entered into the scanner will be the subject's study ID and date of birth. The study radiologist will analyze the pre-hepatectomy MRI only. The PI and other study investigators will use the combined information from the pre-hepatectomy MRI, *ex-vivo* MRI, and pathology specimen to define the surgical margin on the pre-hepatectomy images and to generate a lesion reference standard table (Section 6.13).

6.11.2. Pre-hepatectomy MR imaging acquisition

6.11.2.1 Subject safety.

The PI or a study investigator will monitor the subject for adverse events from subject arrival to departure from the MR facility. Adverse events will be recorded (Section 8.0).

6.11.2.2 Subject preparation.

Subjects will be instructed to fast for a minimum of two hours prior to MRI. A certified technologist or other qualified medical professional will insert an intravenous catheter. The site and gauge of the catheter access will be noted. When intravenous access cannot be obtained, the use of centrally placed intravenous access (port) is acceptable if the subject has such access placed for clinical reasons and if the port is graded for use with a power injector. Subjects will be positioned supine, and a dielectric pad and an 8-element phase array coil will be centered over the abdomen at the level of the liver.

6.11.2.3 Gd-based contrast media.

Gadobenate dimeglumine (MultiHance, Bracco) at a dose of 0.1 mmol/kg (maximum dose of 10 mmol for subjects ≥ 100 kg) will be injected at 2 ml/sec using a power injector followed by a 20 ml saline flush at the same rate.

6.11.2.4 Examination quality.

The PI will monitor the MRI exams for image quality. Artifacted sequences will be repeated. The research coordinator will track the successful acquisition of each sequence on a data entry sheet and record what sequences were repeated.

6.11.2.4. MR protocol.

The following protocol will be programmed into the research scanner ("CRC Protocol"). This protocol will take about 90 minutes: 30 minute from the beginning of the preparatory sequences through the completion of Image Set 8, a 55-minute break between Image Set 8 and Image Set 9 during which the subject can be taken out of the scanner depending on subject preference, and about one minute to acquire Image Set 9.

- Preparatory sequences (will not be analyzed)
  - Localizer
  - Parallel imaging calibration scan
  - Coronal T2w SSFSE: TR 1500, TE 90, matrix 320x192, slice thickness 8 mm, gap 0 mm, bandwidth 100 kHz, parallel imaging off. Options: SCIC, extended dynamic range.
- **Image Set 1.**
  - Axial T2w SSFSE: TR 1500, TE 90, matrix 320x224, slice thickness 5 mm, gap 0 mm, bandwidth 83 kHz, parallel imaging on (acceleration factor = 2). Options: SCIC, extended dynamic range. FOV 30 to 50 cm depending on body habitus. Phase FOV 100%.
- **Image Set 2.**
  - Axial T2w FRFSE: Parameters pending. Same FOV as Image Set 1.
- **Image Set 3.**
  - Axial T1w SPGR: TR 200-300 depending on breathhold capacity and liver size, TE 2.3, flip angle 70, matrix 320x224, slice thickness 5 mm, gap 0 mm, bandwidth 62.5 kHz, parallel imaging on (acceleration factor = 2). Options: SCIC, extended dynamic range. Same FOV as Image Set 1.
- **Image Set 4.**
  - Axial six-echo SPGR: TR 200-300 depending on breathhold capacity and liver size, TE 2.3, 4.6, 6.9, 9.2, 11.5, 13.8, matrix 320x224, slice thickness 5 mm, gap 0 mm, bandwidth 141 (check) kHz, parallel imaging on (acceleration factor = 2). Options: extended dynamic range. We have previously confirmed that the exact TR does not affect the estimated T2* value. Same FOV as Image Set 1.
  - Repeat.
- **Image Set 5.**
  - Axial six-b-value DW EPI: TR 2500-3500 depending on breathhold capacity and liver size, TE 50 msec, b-values of 0, 10, 50, 250, 500, 750 sec/mm^2, matrix 128x160, slice thickness 10 mm, gap 0 mm, bandwidth 62.5 kHz, parallel imaging on (acceleration factor = 2). Options: extended dynamic range, zoom gradient, one prep scan, b-value order reversed. We have previously confirmed that the exact TR does not affect the estimated ADC value. Same FOV as Image Set 1.
  - Repeat.
- **Image Set 6.**
  - Axial MR elastography with wave frequency of 60 Hz. Parameters pending. Same FOV as Image Set 1?
  - Repeat.
- **Image Set 7.**
  - Dynamic 3D T1w LAVA: TR min, TE min, matrix 320x224, FA 15, slice thickness 4 mm, bandwidth 100 kHz, parallel imaging on (acceleration factor = 2). Options: SCIC, extended dynamic range, zip 2, zoom gradient (if FOV ≤ 35 mm). Obtain before and 20,

80, and 180 seconds after injection of 0.1 mmol/kg gadobenate dimeglumine (MultiHance, Bracco) at 2 ml/sec followed by 20 ml saline flush. Same FOV as Image Set 1.

- **Image Set 8.**
  - Late venous phase LAVA: 5 minutes. Same FOV and other parameters as Image Set 7.
- **Image Set 9.**
  - Hepatocellular phase LAVA: 60 minutes. Same FOV and other parameters as Image Set 7.

6.11.3. Pre-hepatectomy MR imaging interpretation

6.11.3.1. Overview.

The study radiologist will have expertise in MRI of the liver. The radiologist will be trained on a test set to become familiar with the imaging criteria. After the training, the radiologist will review and interpret the pre-hepatectomy research exams. The radiologist will know the subject's study ID and date of birth, and will be aware that the subject has a pre-operative diagnosis of CRC metastasis to the liver. The coordinator will explain to the radiologist the segment(s) that were resected at surgery. The radiologist will be blinded to all other information. MR images (test set and research exams) will be reviewed on high-resolution >4 megapixel gray-scale monitors using the hospital PACS system.

6.11.3.2. Training.

The radiologist will be trained on a test set of 3T MR images obtained on non-study subjects. The test set will include examples of CRC metastases and benign lesions (hemangiomas, cysts, focal nodular hyperplasias, and transient hepatic intensity differences). During the training phase, the imaging criteria outlined below will be defined.

6.11.3.3. Interpretation.

The radiologist will review the nine image sets in a different random order in one reading session for each subject. (Reviewing each image set in a different session is not feasible). The random order of review will reduce bias in the performance of one image set relative to another. During the review of each image set, the radiologist will flag each detected nodule, number each new nodule consecutively, and characterize the corresponding nodule feature(s) as outlined in the Table below. If the radiologist identifies nodules on one image set that were missed on a prior image set, the radiologist will re-review the prior image set and retrospectively characterize the corresponding nodule features. The initial interpretations will be used for specific aim 1 and the final interpretations for specific aim 2. After the nine image sets are reviewed, the radiologist will review all the images in conjunction and score ten global lesion features. The radiologist also will score two per-patient features (anterioposterior skin-to-skin diameter of the abdomen [contiguous] and presence of ascites [four-point ordinal: none, mild, moderate, severe]), as these may conceivably affect image quality.

The research coordinator will enter the radiologist's per-lesion and per-patient interpretations into a data entry sheet. Representative screen capture images showing the

location and identifier of each lesion detected by the study radiologist will be exported in JPEG format. Under the radiologist's supervision, the research coordinator will place regions of interest on image sets 4-6 and record the T2*, ADC, shear modulus values for each nodule and for each of the repeated acquisitions. Both repeated measurements will be used in the analysis of intraclass correlation coefficient. Only the first of the repeated measurements will be used in the sensitivity, specificity, and ROC analyses.

Image Set	**Feature**	**Categories**
1 T2w SSFSE	Signal intensity	Homogeneous • Markedly hypo-intense • Hypo-intense • Iso-intense • Hyper-intense • Markedly hyper-intense Heterogeneous
2 T2w FRFSE	Signal intensity	Homogeneous • Markedly hypo-intense • Hypo-intense • Iso-intense • Hyper-intense • Markedly hyper-intense Heterogeneous
3 T1w SPGR	Signal intensity	Homogeneous • Markedly hypo-intense • Hypo-intense • Iso-intense • Hyper-intense • Markedly hyper-intense Heterogeneous
4 Six-echo SPGR	T2*	Continuous
5 DWI	ADC	Continuous
6 MRE	Shear modulus	Continuous
7 Dynamic 3D T1w	Kinetics	Homogeneous • With retention • With fade • With washout Ring • With retention • With fade/washout Heterogeneous Puddles with retention
8 Late venous phase	Signal intensity	• Hypo-intense • Iso-intense • Hyper-intense

9 Hepatocellular phase	Signal intensity	• Hypo-intense • Iso-intense • Hyper-intense
Global	Long axis diameter	Continuous
	Short axis diameter	Continuous
	Shape	• Round/oval • Lobulated • Irregular • Geographic/polygonal • Wedge • Linear
	Margins	• Sharp • Mixed • Indistinct
	Central heterogeneity	• Yes, consistent with scar • Yes, consistent with necrosis • Yes, uncertain if necrosis or scar • No
	Pseudo-capsule	• Yes • No
	Transient hepatic intensity difference	• Yes – wedge shaped • Yes – peri-lesional halo • No
	Internal arteries	• Yes • No
	Draining veins	• Yes • No
	Edema around lesion	• Yes • No
	Distance from nearest surface	Continuous
	Overall confidence for cancer	• 0 definitely not cancer • 1 probably not cancer • 2 possibly not cancer • 3 indeterminate • 4 possibly cancer • 5 probably cancer • 6 definitely cancer

6.11.4. Hepatectomy specimen handling and *ex-vivo* MR imaging acquisition

6.11.4.1. Overview.

Intraoperatively, the surgeon will place sutures on the hepatectomy specimen along its anatomic superior and inferior margins. The research technologist will place the specimen in saline in a sealed MR-compatible container and transport the container to the MR3T facility. Using the surgically placed sutures as a guide, the PI and research fellow will re-position the specimen within the container in an attempt to approximate the *in-vivo* anatomic alignment. Non-magnetic material will be used to secure the liver in position. An initial set of images will be obtained and compared to the pre-hepatectomy images on the scanner console.

Through an iterative process, the specimen will be re-imaged and re-positioned until satisfactory alignment with the pre-hepatectomy images is achieved. At this point, high-resolution 1-2 mm thick T1w and T2w images will be obtained of the entire specimen (Section 6.11.4.2) coronal to the scanning table. The PI and research fellow in consensus will review the *ex-vivo* and pre-hepatectomy images together, identify every nodule shown on those images, and, by using surface and intrahepatic landmarks, attempt to co-localize *ex-vivo* nodules and corresponding focal lesions depicted at pre-hepatectomy imaging. The specimen then will be bread-sliced into 5-mm sections sagittal to the scanner table, while leaving a thin rim of tissue intact so that the sections can be kept together.

The sectioned specimen then will be re-imaged in two planes: sagittal to the scanner table (ie, parallel to the cuts) and parallel to the scanning table. Preliminary studies have shown that some saline will fill the space between the sections and be visible as a high-signal intensity film of fluid that delineates the section interfaces on T2w images. The PI, research fellow, and pathologist will review the MR images of the sectioned specimen, number each section consecutively, re-identify the previously detected nodules in both imaging planes, and determine the exact location of each nodule relative to the sections.

After the imaging is completed, the study coordinator will photograph each pathology section in consecutive order. Photographs of both cut surfaces will be obtained and stored in JPEG format.

The study pathologist then will inspect each section grossly and, working together with the PI or radiology research fellow, locate, sample, and submit for histology every nodule detected at *ex-vivo* imaging. Any additional nodules visible on the cut surfaces not identified at *ex-vivo* imaging also will be sampled and submitted for histology. After all nodules are sampled, the tissue will be returned to pathology.

A cross-reference table will be generated of focal lesions depicted at pre-hepatectomy imaging, nodules identified at *ex-vivo* imaging, and nodules confirmed in the pathology specimen. Each lesion or nodule will be given a unique identifier for that subject. Representative screen capture MR images showing the location and identifier of each nodule will be exported in JPEG format.

Each cassette submitted to histology will be labeled with the subject's study identifier and focal lesion identifier. At the pathologist's discretion, some nodules will be sampled and submitted for clinical care; corresponding cassettes will be labeled with clinical identifiers. The processing of cassettes submitted for research will be considered a research expense and will be charged to the study. The processing of cassettes submitted for clinical care will be considered clinical expenses.

6.11.4.2. Specimen imaging.

Protocol details pending

Cardiac coil
Container
Localizers
3D T1w SPGR
2D T2w FSE
2D T1w SPGR

6.11.5. Imaging archival

MR images (pre-hepatectomy or *ex vivo*) will be saved in DICOM format. Screen capture images will be saved in JPEG format.

6.12. Histology analysis

Slides will be stained (haemotoxolin and eosin, trichrome, Prussian blue) at a histology lab. The study pathologist will review the slides and issue a dichotomous histological diagnosis for each submitted nodule (malignant or benign). Photographs of representative histology slides will be taken. One unstained slide will also be obtained as a precaution.

6.13. Generating a reference standard table for each lesion

The PI, research fellow, and research coordinator will review the pre-hepatectomy images, the ex-vivo images, the gross pathology photographs, the screen capture JPEGs, and the cross-reference tables, and create a final reference standard table for each lesion in each subject. Any lesion identified by the interpreting radiologist not visible on the *ex-vivo* images and not identified at pathology will be considered a false negative imaging finding.

7.0 DATA COLLECTION AND MANAGEMENT

The PI will supervise the data collection and management. The following types of data and materials will be collected:

7.0.1. Regulatory

A research chart will be created for each subject. The chart will include the signed consent form, a copy of the subject's experimental bill of rights, and a signed HIPAA form. Research charts will be kept in locked file cabinets.

An enrollment log will be maintained. The enrollment log will confirm that informed consent was obtained on each subject.

7.0.2. Parametrized data

Standardized data entry forms will be designed for each type of data being collected:

- Subject identifiers and demographics
- Subject lab results (e.g., eGFR, urine pregnancy test)
- List of sequences acquired and repeated during the pre-hepatectomy examination
- Adverse events occurring during the MRI appointment
- Adverse events occurring during first 24 hours after Gd injection as recorded by the study surgeon at subject admission for surgery.
- Lesion cross reference table
- Lesion reference standard table
- MRI features for each lesion

The research coordinator or study investigator will manually enter data into the corresponding data forms. Completed data entry forms will be duplicated. One set will be kept with each subject's research chart. One set will be kept in folders with other forms of the same type. The coordinator will transfer the data from the entry forms into an electronic database. The database is password protected, maintained by a data manager at the MR3T facility, stored on two servers, backed up to external hard-drives every 24 hours.

For statistical analysis, the database program will generate de-identified spreadsheet reports containing the variable of interest to the study statistician.

7.0.3. Images

Several types of images will be collected:

- MR images in DICOM format
- Screen-saved MR images in JPEG format
- Photographs of pathology sections in JPEG format.
- Photographs of histology specimens in JPEG format (select lesions)

DICOM format images will be stored on the hospital's password-protected PACS system. JPEG format images will be stored on two separate password protected hard-

drives in the MR3T facility. All images (DICOM or JPEG) will also be stored on CD in duplicate. Duplicated CDs will be kept in separate locked cabinets in the MR3T facility.

7.0.4. Histology slides and tissue blocks.

Histology slides and tissue blocks will be labeled with the subject ID and lesion ID and stored in a locked histology filing cabinet in the MR3T facility. Blocks will be kept as a precaution in case slides are damaged or lost.

8.0 ADVERSE EVENTS PROCEDURES

8.1. Definition of Adverse Events and Potential Risks

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

8.2. Definition of Serious Adverse Events (Serious Adverse Events List)

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- results in death, or
- is life-threatening (at the time of the event), or
- requires inpatient hospitalization or prolongation of an existing hospitalization, or
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

8.3. Adverse Events Characteristics

8.3.1. Grading of Adverse Events

Grade is used to denote the severity of the adverse event.

1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

8.3.2. Definition of Expected

MRI Scan

- Anxiety/Stress;
- Claustrophobia;
- Discomfort.

Contrast Agent (MultiHance)

- Nausea;
- Headache;
- Hives;
- Temporary low blood pressure;
- Allergic reaction.

Expected Adverse Events from Needle Placement

- Minor discomfort;

- Bleeding;
- Infection;
- Bruising.

8.3.3. Attribution of Adverse Events

Attribution of the AE:

- **Definite** – The AE is clearly related to the study treatment.
- **Probable** – The AE is likely related to the study treatment.
- **Possible** – The AE may be related to the study treatment.
- **Unlikely** – The AE is doubtfully related to the study treatment.
- **Unrelated** – The AE is clearly NOT related to the study treatment.

8.4. Adverse Event Documentation and Reporting

8.4.1. Assignment of attribution and grades

The PI will assign the grade and attribution for each AE/SAE.

8.4.2. Documentation

The PI will document all Adverse Events (AEs) that within the first 24 hours following contrast injection. This time period exceeds 10 elimination half-lives of gadebenate dimeglumine [MulthiHance product insert]).

AEs will be recorded within the study participant's chart within one week of the PI becoming aware of the event. The nature of each event, date and time (when appropriate) of onset, outcome, frequency, maximum intensity, action taken, and attribution will be recorded.

8.4.3. Expedited or Routine Adverse Event Reporting

8.4.2.1. Definitions

Expedited reporting is defined as immediate notification of the IRB within the specified timeframe outlined in the protocol. Routine reporting requirements also apply.

Routine reporting is defined as documentation of adverse events on source documents and submission to the local IRB.

8.4.2.1. Instructions

1. Grade 3 unexpected adverse events with hospitalization that are possible, probable, or definite require a complete SAE report to be submitted within **10 calendar days** of first knowledge of the event. **Routine reporting procedures also apply.**

2. Grade 3 expected adverse events with hospitalization that are possible, probable, or definite will be reported by **routine reporting procedures only.**

3. Grade 3 unexpected and expected adverse events without hospitalization that are possible, probable, or definite will be reported by **routine reporting procedures only.**

4. Grade 4 unexpected and expected adverse events that are possible, probable, or definite require a complete SAE report to be submitted within **10 calendar days** of first knowledge of the event. **Routine reporting procedures also apply.**

5. Grade 5 unexpected and expected adverse events that are possible, probable, or definite will be reported via phone report within a **24-hour** time period to the IRB by the investigator or investigator-designee. In addition, a complete SAE report is due to the IRB within **10 calendar days** of the initial 24-hour telephone report. **Routine reporting procedures also apply.**

6. Expedited adverse event reporting must be completed within 10 working days of first knowledge of the event.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design and Endpoints

9.1.1. General study design.

This is a prospective cohort pilot study assessing 3T MRI for diagnosis of CRC metastases to the liver in pre-hepatectomy patients. Consecutive eligible subjects with CRC metastases to the liver will undergo a research MRI of the liver within one week prior to curative hepatectomy done for clinical care. One radiologist will review the MR images and, for each focal lesion (benign or malignant) identified at imaging on each subject, assess 21 imaging features such as size, shape, margination, heterogeneity, kinetic enhancement pattern, and overall confidence for malignancy. Features will include binary, categorical, ordinal, and continuous variables. Sixteen features will be standard and five (T2*, ADC, shear modulus, late venous phase signal intensity, and hepatocellular phase signal intensity) will be experimental. The MR sequences used to obtain the three quantitative experimental lesion features (T2*, ADC, shear modulus) will be acquired twice for each subject. The radiologist also will assess two-per patient imaging features (abdominal AP diameter at the level of the portal vein bifurcation and the presence of ascites). Three demographic features (subject age, gender, ethnicity) will be available for the multivariate analyses; of the three, age will potentially be known to the radiologist as the scans will include the subject's date of birth.

For each subject, the lesions included in the analysis will be those identified at pre-hepatectomy imaging, *ex-vivo* imaging, pathology, or any combination of the three. The reference standard for each lesion will be the dichotomized histological diagnosis (malignancy versus other). Subjects are expected to have between one and ten CRC metastases in the hepatectomy specimen (average of three) and zero to five benign lesions (average of one). Subjects are not expected to have any malignancies other than CRC metastases.

9.1.2. Endpoints.

9.1.2.1. Primary endpoint.

The primary endpoint is the per-lesion sensitivity and specificity for binary and dichotomized categorical features and the area under the ROC curve for ordinal and continuous features for the diagnosis of CRC metastases.

9.1.2.2. Secondary endpoints.

9.1.2.2.1. The areas under the ROC curves of multivariate models for diagnosis of CRC metastases.

9.1.2.2.2. Intraclass correlation coefficient between repeated quantitative measurements.

9.2 Specific Aims and Analysis Plans

9.1.3.1. Primary aim.

9.1.3.1.1. Aim: For each MRI feature, estimate the per-lesion sensitivity and specificity (binary and dichotomized categorical features) or the area under the ROC curve (ordinal and continuous features) for the diagnosis of CRC metastases.

9.1.3.1.2. Analysis plan:

Frequency tables of the per-lesion MR features will be generated for non-continuous features. Descriptive statistics (e.g., mean, median, variance) will be used to summarize continuous features.

For each binary or dichotomized categorical feature, lesions will be classified as:

- True positive: lesion feature is positive and lesion histology is malignant
- False positive: lesion feature is positive and lesion histology is benign
- True negative: lesion feature is negative and lesion histology is benign
- False negative: lesion feature is negative and lesion histology is malignant

From this classification, the per-lesion sensitivity and specificity for the diagnosis of malignancy will be estimated. Corresponding 95% confidence intervals will be calculated using clustered data methods that can accommodate multiple lesions per patient and multiple observations per lesion.

For ordinal and continuous features, the ROC curve for the per-lesion diagnosis of malignancy will be generated and the area under the ROC curve calculated using empirical method. Corresponding 95% confidence intervals will be calculated using clustered data methods that can accommodate multiple lesions per patient and multiple observations per lesion. If the 95% confidence interval for the AUC contains the null hypothesis value of 0.5, then we will conclude that the corresponding feature does not have discriminatory ability.

9.1.2.2. Secondary aims.

9.1.2.2.1. Secondary aim 1.

9.1.2.2.1.2. Aim.

Estimate and compare the per-lesion area under the ROC curve of a multivariate model that uses experimental as well as standard MRI features versus that of a model that uses only standard MRI features for the diagnosis of CRC metastases. Both models may use per-patient features such as age, gender, ethnicity, ascites, and anterioposterior diameter.

9.1.2.2.1.2. Analysis plan for secondary aim 1.

Using all available per-lesion MRI features (standard and experimental), per-subject MRI features (anterioposterior diameter and ascites), and per-subject clinical features (age, gender, ethnicity), multivariate models will be constructed to assess the discriminatory ability of each MRI feature after adjusting for the other features.

Other multivariate models will be constructed after excluding experimental features from consideration.

The area under the ROC curves corresponding to these models will be compared. To account for clustering due to multiple lesions for some patients and multiple observations per lesion, generalized estimating equation techniques will be used. The model with the largest area under the ROC curve will be identified.

9.1.2.2.2. Secondary aim 2.

9.1.2.2.2.1. Aim: Estimate the intraclass correlation coefficient of repeated quantitative measurements (T2*, ADC, and shear modulus) on each lesion.

9.1.2.2.1.2. Analysis plan for secondary aim 2. The intra-class correlation coefficient between repeated measures will be calculated.

9.3 Sample Considerations

With an accrual of 30 subjects, this study will provide a worst-case precision (i.e., confidence interval half width) of ± 18% at a sensitivity of 50% and 5% significance level. The precision will improve the larger the observed sensitivity is from 50%. Furthermore, the observed precision will be better than 18% because some subjects will have multiple lesions.

Assuming 75% of lesions are malignant, an average of four lesions per subject, and a moderate correlation (0.5) between measurements within subjects, this study will have 80% power at a significance level of 0.05 to detect an AUC of 0.7 or higher.

9.4 Randomization schema and stratification factors

This is a cohort study. There will be no randomization or stratification of subjects.

9.5 Study monitoring, interim analyses, and early stopping rules

Because this is a small pilot study with minimal risk, the PI will monitor the study for accrual and AEs. Every three months, the research coordinator will generate a summary report on accrual and participant demographics.

10.0 Regulatory and Ethical Considerations

10.1 Protection of Patient Rights

The PI, a liver radiologist, will monitor MR examinations and report any major, unexpected findings that may alter clinical management to the surgery team. The PI and the surgery team in consensus will formulate a list of findings to be reported. Patients will be informed of this possibility at the time of consent.

10.2 Confidentiality

Subjects will be assigned unique study identifiers. The link to subject identity will be stored securely and separately from personal health information. MR images will be generated using only the subject's study ID and date of birth.

All study data will be kept confidential. No publication or written reports will link subject data with a name or any individual protected health information. Computer data file entry and access will require a password.

10.3 Inclusion of Women and Minorities

Distribution of subjects: There will be no sexual, racial, religious or other discrimination. San Diego County demographics are shown in the Table below.

Table. San Diego County Demographics

Gender	Alaskan or American Indian	Asian or Pacific Islander	Black	Hispanic	White	Other	Total
Female	<1	3.6	3	10	32	0.4	**49**
Male	<1	3.8	3	10.4	33.4	0.4	**51**
Total	**<1**	**7.4**	**6**	**20.4**	**65.4**	**0.8**	**100.0**

Relative to national averages, black patients are somewhat under-represented in San Diego County (6% vs. 11.8%). However, Hispanic and Asian patients are over-represented in comparison to national averages. Furthermore, these figures are based upon the 1990 Census and it is highly likely that the representation of minorities in San Diego County has increased since that time relative to the representation of Caucasian patients. Also, UCSD treats a greater proportion of black patients than other healthcare programs in San Diego County. The University of California does not discriminate in any of its policies, procedures, or practices on the basis of race, ethnicity, national origin, region, gender, sexual orientation, disability, age, veteran status, medical condition (defined in Section 12926 of the California Government Code), ancestry, or marital status, nor does the University discriminate on the basis of citizenship within limits imposed by law or University policy. It is the policy of the University of California that all research involving human subjects be conducted in compliance with policy concerning inclusion of minorities and women in research.

CRC metastases affect both sexes and all ethnicities. Therefore, subjects will be recruited from the surgery clinic without regard to sex/gender or racial/ethnic group. The population sample selected for this study will be representative of the population sample followed at the surgery clinic.

10.4 Audit and Monitoring

The PI will permit study-related auditing and inspections of all study-related documents by the IRB and government regulatory agencies. The PI will ensure the capability for inspection of all participating site's study-related facilities (e.g. imaging center). The PI will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits.

10.5 IDE / IND / etc.

Not applicable.

11.0 REFERENCES (see below)

1. *Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57(1):43-66.*
2. *Nordlinger B. Indications for and use of neoadjuvant chemotherapy before resection of hepatic colorectal metastases. Invited lecture at the American Society of Clinical Oncology.*
3. *Yabroff KR, Mariotto AB, Feuer E, Brown ML. Projections of the costs associated with colorectal cancer care in the United States, 2000-2020. Health Econ 2007.*
4. *Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239(6):818-825; discussion 825-817.*
5. *Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235(6):759-766.*
6. *Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg 2004;240(3):438-447; discussion 447-450.*
7. *Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 2005;241(5):715-722, discussion 722-714.*
8. *Antoniou A, Lovegrove RE, Tilney HS, et al. Meta-analysis of clinical outcome after first and second liver resection for colorectal metastases. Surgery 2007;141(1):9-18.*
9. *Adam R, Pascal G, Azoulay D, Tanaka K, Castaing D, Bismuth H. Liver resection for colorectal metastases: the third hepatectomy. Ann Surg 2003;238(6):871-883; discussion 883-874.*
10. *Malik HZ, Gomez D, Wong V, et al. Predictors of early disease recurrence following hepatic resection for colorectal cancer metastasis. Eur J Surg Oncol 2007;33(8):1003-1009.*
11. *Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. Ann Surg 1997;225(1):51-60; discussion 60-52.*
12. *Nomura K, Kadoya M, Ueda K, Fujinaga Y, Miwa S, Miyagawa S. Detection of hepatic metastases from colorectal carcinoma: comparison of histopathologic features of anatomically resected liver with results of preoperative imaging. J Clin Gastroenterol 2007;41(8):789-795.*
13. *Matsuda K, Hotta T, Uchiyama K, et al. Repeat reduction surgery after an initial hepatectomy for patients with colorectal cancer. Oncol Rep 2007;18(1):189-194.*
14. *Petrowsky H, Gonen M, Jarnagin W, et al. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. Ann Surg 2002;235(6):863-871.*
15. *Ahmad A, Chen SL, Bilchik AJ. Role of repeated hepatectomy in the multimodal treatment of hepatic colorectal metastases. Arch Surg 2007;142(6):526-531; discussion 531-522.*

16. *Yan TD, Sim J, Black D, Niu R, Morris DL. Systematic review on safety and efficacy of repeat hepatectomy for recurrent liver metastases from colorectal carcinoma. Ann Surg Oncol 2007;14(7):2069-2077.*
17. *Bipat S, van Leeuwen MS, Ijzermans JN, et al. Evidence-base guideline on management of colorectal liver metastases in the Netherlands. Neth J Med 2007;65(1):5-14.*
18. *Bipat S, van Leeuwen MS, Comans EF, et al. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis--meta-analysis. Radiology 2005;237(1):123-131.*
19. *Conlon R, Jacobs M, Dasgupta D, Lodge JP. The value of intraoperative ultrasound during hepatic resection compared with improved preoperative magnetic resonance imaging. Eur J Ultrasound 2003;16(3):211-216.*
20. *Kulig J, Popiela T, Klek S, et al. Intraoperative ultrasonography in detecting and assessment of colorectal liver metastases. Scand J Surg 2007;96(1):51-55.*
21. *Cervone A, Sardi A, Conaway GL. Intraoperative ultrasound (IOUS) is essential in the management of metastatic colorectal liver lesions. Am Surg 2000;66(7):611-615.*
22. *Schmidt J, Strotzer M, Fraunhofer S, Boedeker H, Zirngibl H. Intraoperative ultrasonography versus helical computed tomography and computed tomography with arterioportography in diagnosing colorectal liver metastases: lesion-by-lesion analysis. World J Surg 2000;24(1):43-47; discussion 48.*
23. *Rydzewski B, Dehdashti F, Gordon BA, Teefey SA, Strasberg SM, Siegel BA. Usefulness of intraoperative sonography for revealing hepatic metastases from colorectal cancer in patients selected for surgery after undergoing FDG PET. AJR Am J Roentgenol 2002;178(2):353-358.*
24. *Benoist S, Nordlinger B. Neoadjuvant treatment before resection of liver metastases. Eur J Surg Oncol 2007.*

12.0 APPENDICES

12.1 Glossary of Abbreviations and Acronyms

12.2 Case Report Forms -- PENDING

12.3 Informed Consent Document -- PENDING

GLOSSARY OF ABBREVIATIONS AND ACRONYMS

Acronym	Definition
ADC	Apparent diffusion coefficient
AE	Adverse event
AUC	Area under the curve
CRC	Colorectal cancer
CT	Computed tomography
DICOM	Digital imaging and communications in medicine
DW	Diffusion weighted
DWI	Diffusion-weighted imaging
eGFR	Estimated glomerular filtration rate
EPI	Echo-planar imaging
FA	Flip angle
FOV	Field of view
FSE	Fast spin echo
ID	Identifier or identification
JPEG	Joint Photographic Experts Group
LAVA	Liver Acquisition with Volume Acceleration
MR	Magnetic resonance
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
PACS	Picture archiving and communications system
PI	Principal investigator
ROC	Receiver operator characteristics
SAE	Serious adverse event
SCIC	Surface coil intensity correction
SPGR	Spoiled gradient recalled echo
SSFSE	Single shot fast spin echo
TE	Time to echo
TR	Time to repetition
US	Ultrasound