Assessment of mandibular bone invasion with Magnetic Resonance Imaging (MRI) using SWeep Imaging with Fourier Transformation (SWIFT)

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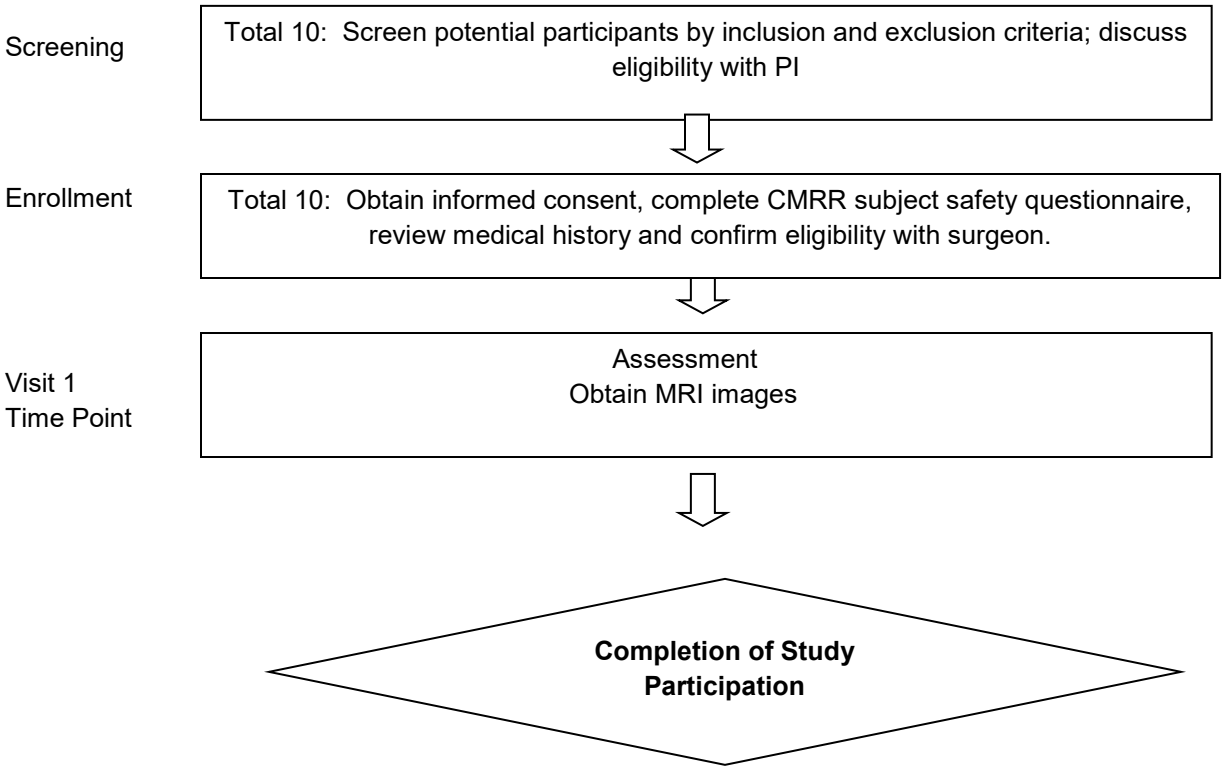
LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CMRR	Center for Magnetic Resonance Research
CRF	Case Report Form
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience

PROTOCOL SUMMARY

Title:	Assessment of mandibular bone invasion with Magnetic Resonance Imaging (MRI) using SWeep Imaging with Fourier Transformation (SWIFT)
Précis:	MRI scanning in 3T and 4T MR magnet will be performed on up to 20 patients with possible maxillofacial and/or mandibular bone invasion by applying newly developed sequences and clinically established MR sequences. We will then compare the conventional imaging results of the patients with 3T and 4T MRI results and post operative pathology results.
Objectives:	The primary objective of this study is to improve the diagnostic accuracy and specificity of MRI in detecting the degree of bone involvement and invasion in oral cancer. The presence and degree of bone invasion determines the extent of surgery and has great effect on the morbidity of patients with oral cancer and bone/soft tissue tumors. Primary: To demonstrate the efficacy of the MRI scanning in 3T and 4T MR magnet for patients with squamous cell carcinoma adjacent to, or involving, the mandible. Comparison will be made to histolopathological sections as the “gold standard.”
Population:	We plan to enroll 20 subjects with a diagnosis of advanced squamous cell carcinoma of the oral cavity or osteoradionecrosis. All of those subjects enrolled will have findings concerning for mandibular invasion on physical examination or computed tomography imaging. Prior to surgery, patients will be consented for SWIFT imaging. Imaging will be conducted during a seven-day period prior to surgery.
Number of Sites:	University of Minnesota- CMRR
Study Duration:	Four years
Subject Participation Duration:	1 ½ hours for the study visit with MRI
Estimated Time to Complete	3 Years

Schematic of Study Design:



1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information and Study Rational

The primary objective of this study is to improve the diagnostic accuracy and specificity of MRI in detecting the degree of bone involvement. The presence and degree of bone invasion determines the extent of surgery and has great effect on the morbidity of patients with oral cancer and bone/soft tissue tumors. The most important factor in the management is to accurately identify the presence of neoplastic invasion.

Unfortunately, detecting bone invasion and extension of bone involvement prior to surgery is often difficult with the currently available imaging techniques. MRI with high contrast resolution and the ability to perform multiplanar imaging plays an integral role in the delineation of tumoral involvement of the bone. Although MRI is an excellent tool in the assessment of bone invasion in carcinoma, its overestimation of cortical invasion and tumor extent to the bone marrow have been a diagnostic challenge, leading to false positive results. Like many of the musculoskeletal system tissues, cortical bone produces no signal with conventional MRI techniques, limiting the characterization of image contrast and differentiation of adjacent soft tissues.

A novel MRI technique called Sweep Imaging with Fourier Transformation (SWIFT) appears to be a suitable tool to overcome this challenge. The main advantage of SWIFT is to obtain signal from the cortical bone. We believe that the SWIFT technique will overcome the false positive results.

1.2 Potential Risks and Benefits

This study has the following risks:

1.2.1 Potential Risks

Screening Questionnaire

The questionnaire asks questions that are private in nature. Also, some people can be embarrassed by the questions. There is a risk that the information from the questionnaire could inadvertently be disclosed.

Magnetic Resonance Imaging (MRI)

MRI is routinely used in healthcare to look at tissues in the body. MRI scanners, the machines that take these images, have a strong magnetic field and have been cleared by the Food and Drug Administration (FDA) for routine use for patients. While there are no known health risks associated with these strong magnetic fields, some people report dizziness, mild nausea, headache, a metallic taste in the mouth, or sensations of flashing lights. These effects have been associated with movement of the head in a strong magnetic field. These symptoms, if present, disappear shortly after leaving the magnet. There are some risks linked with the MRI scanning procedure itself, which include:

1. Projectile Objects. Objects with magnetic properties, such as metallic objects, can be pulled into the magnet. These objects can be dangerous if they are brought into the magnet room. By keeping magnetic objects away from the magnet and by controlling access to the magnetic field area, we have minimized the chance of this occurring.

2. Claustrophobia. Some people may experience claustrophobia (fear of confined spaces), while inside the scanner. Once inside it is possible to stop the scanning and be removed at any time. Patients will be given a squeezable device, a bulb, which serves as an “emergency” button. The squeeze bulb will let MRI staff know immediately if the patient is experiencing claustrophobia, and they will terminate the scan. The MRI operators will be able to talk during the entire scanning process by two-way earphones and microphone communication system. Patients can also press a button inside the scanner to get their attention.

3. Energy waves. Another risk is presented by the energy waves used in the scanner. The power of the energy waves is well below the strength needed to heat the tissue in your body and cause harm, but any metal in contact with patient skin could heat up. This is why patients will be asked to remove all jewelry.

It is also possible that the scanner will cause peripheral nerve stimulation (stimulation of the nerves or muscles). If patients feel any tingling or unusual

sensations during the scan, or muscle contractions, they can use the squeeze bulb to alert the researcher immediately.

4. Loud Sounds. The MRI scanner makes loud banging noises during operation. Patients will be given earplugs to reduce the noise level. The noise generated by the operation of the scanner during a study is loud enough to cause hearing damage if patients do not wear hearing protection, which we will provide. If, even with the hearing protection we give patients, patients may find the noise from the scanner to be uncomfortable or painful, and can ask the scanner operator to stop the experiment immediately.

5. In addition, there is a risk of unknown effects related to participation in T4 tesla level MRI research. Long-term effects of exposure to high magnetic fields are unknown. Short term most people experience no ill effects from the strong magnetic field, but some people report dizziness, mild nausea, headache, a metallic taste in their mouth, or sensations of flashing lights.

6. The risks of exposure to high magnetic fields are unknown for fetuses. Therefore, if the participant is a female who is capable of becoming pregnant, and has any reason to believe that they might be pregnant, they should not participate in this study. The effects of taking MRIs on an unborn baby have not yet been proven to be safe or unsafe. If they think they may be pregnant, they must inform the investigator. The investigators strongly recommend that participants do not participate in this study if the participant thinks that they may be pregnant. Participants are ultimately responsible for their own decision to participate or not to participate in this study.

Potential Benefits

There are no direct benefits to participation. However, if anything abnormal is found and is considered to be a significant finding it will be reported to the patient's surgeon prior to surgery.

2 OBJECTIVES

2.1 Study Objectives

To demonstrate the efficacy of the MRI scanning in 3T and 4T MR magnet for patients with mandibular bone invasion. Comparison will be made to histolopathological sections as the “gold standard.”

2.2 Study Outcome Measures

To determine how well the MR images will predict the presence of mandibular invasion, we will compare our results with clinical, operative, radiological and pathological findings (gold standard). Thus, patients will be asked to give permission to the investigators to access the relevant medical records.

3 STUDY DESIGN

This is a cross-sectional study to be conducted at the University of Minnesota. For this study we will enroll patients with possible maxillofacial and/or mandibular bone invasion. Patients 18 and older with oral cancer or osteoradionecrosis will be recruited for the study prior to their surgery. Subjects will be identified by their physician while seeking care for oral cancer or osteoradionecrosis in the Otolaryngology/Head and Neck Surgery clinic. Eligible patients will be recruited and consented in the Otolaryngology/Head and Neck Surgery clinic during their scheduled appointment. This appointment will occur before the patient undergoes surgery for their oral cancer or osteoradionecrosis. Patients that are deemed eligible, after reviewing their medical records, will complete the CMRR subject safety screening questionnaire.

All eligible and consented participants will have MRI scans obtained at the CMRR using the 3T and 4T magnet. Patients will also be asked to sign a HIPPA waiver allowing researchers to access their medical records including their clinical, operative, radiological and pathological findings.

4 STUDY ENROLLMENT AND WITHDRAWAL

Patients 18 and older with oral cancer or osteoradionecrosis will be recruited for the study prior to their surgery. Subjects will be identified by their physician while seeking care for oral cancer or osteoradionecrosis in the Otolaryngology/Head and Neck Surgery clinic. Eligible patients will be recruited and consented in the Otolaryngology/Head and Neck Surgery clinic during their scheduled appointment. Consent will take place in the privacy of an exam room and consent will be obtained by a member of the research team that is familiar with the study. This appointment will occur before the patient undergoes surgery for their oral cancer.

Patients will have the study explained to them, will be given a full explanation of the risks of the study and the measures that will be taken to minimize them. Only individuals involved with this study will be obtaining consent from patients. The research staff will explain that the study is optional and participation will not influence the participant's treatment or relationship with the doctor of the University.

At any time during the course of the study participants can withdraw their consent and terminate their participation.

4.1 Subject Inclusion Criteria

1. Patients with a diagnosis of oral cancer with clinical or imaging findings suggestive of maxillofacial or mandibular bone invasion. **OR**
2. Patients with a diagnosis of osteoradionecrosis
3. Patients who will be undergoing surgery as treatment for their oral cancer.
4. Age is over 18 years olf

Subject Exclusion Criteria

1. Pregnancy
2. Ferromagnetic implant
3. History of shotgun wounds and shrapnel
4. Obesity (>250 pounds)
5. Cardiac pacemaker
6. MR incompatible medical device
7. Severe claustrophobia
8. Surgeries with potential ferromagnetic implants
9. Metallic ink tattoo in close proximity to area of interest.

4.2 Subject Withdrawal

Subjects may withdraw voluntarily from the study or the investigator may terminate a subject's participation at any point during the course of the study

4.2.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study subject’s participation in the study if:

- Any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

4.3 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for suspension or termination.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.

5 STUDY SCHEDULE

5.1 Screening/ Prior to Enrollment

- Review of medical records of any potentially eligible participants scheduled for a clinic visit. (Potentially eligible participants are also identified during tumor board.)
- Discuss the identified potential participant with PI to ensure eligibility prior to approaching participant about study.
- Introduce the study to the participant prior to their surgery. This usually needs to be done at least a week before surgery to ensure that the MRI can be scheduled.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.

5.2 Enrollment

- Obtain and document consent from participant on study consent form and HIPAA authorization form.
- Verify inclusion/exclusion criteria with surgeon.
- Complete the CMRR Subject Safety Screening Questionnaire. The requirements of the CMRR Subject Safety Screening Questionnaire must be met prior to the participant's MRI visit.
- Review medical history with physician if indicated by CMRR Subject Safety Questionnaire (example: surgical implants, etc).
- Schedule study visits with CMRR for individuals who are eligible and available for the duration of the study.
- Provide potential participants with instructions needed to prepare for first study visit including directions to the CMRR at the University of Minnesota.
- Contact participant the day before their study visit to confirm their participation.

5.3 MRI Visit (Visit 1)

- Review CMRR Subject Safety Screening Questionnaire to ensure that nothing has changed between enrollment and visit 1. If something has changed, check with CMRR staff to make sure participant is still eligible.
- Review MRI procedure with participant and answer any final questions.
- Target gift card is given to participant.

- CMRR staff will obtain MRI scans. The total time required for scanning will be about 1 hour

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6 STUDY PROCEDURES/EVALUATIONS

6.1 Study Procedures/Evaluations

The subject will be taken to the room where the magnet is located. As MRI scanning is noisy, subjects will be given ear plugs and will be shown how to place them. Subjects will be asked to lie on his/her back on the scanner table. He/she will be moved into the magnet while lying on his/her back. Brief scans will be obtained (less than 1 minute) to localize the area of interest. We will then obtain longer MRI scans (around 5-15 minutes each). The total time required for scanning will be about 1 hour.

6.2 Questionnaire Administration

Prior to obtaining the MRI images all participants will complete, with the research staff, the CMRR subject safety screening questionnaire.

7 ASSESSMENT OF SAFETY

7.1 Specification of Safety Parameters

Safety monitoring for this study will focus on unanticipated problems involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event.

7.1.1 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.2 Reporting Procedures

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

8 STUDY OVERSIGHT

The investigator will be responsible for study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. The PI will review the data for safety concerns and data trends at regular intervals, and will promptly report to the IRB any Unanticipated Problem (UP), protocol deviation, or any other significant event that arises during the conduct of the study.

9 ETHICS/PROTECTION OF HUMAN SUBJECTS

9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

9.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

9.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence. The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

10 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

10.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems must be reviewed by the investigator or designee.

10.2 Study Records Retention

Study records will be maintained for at least five years from the study close out.

10.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

APPENDIX A: Schedule of Events

Procedures	Enrollment (Day –X to –Y)	Study Visit 1 (Day 0)
Signed Consent Form	X	
Assessment of Eligibility Criteria	X	
Review of Medical History	X	
Completion of CMRR safety	X	
Review of CMRR Safety Form		X
MRI performed		X