



THOMAS JEFFERSON UNIVERSITY
Kimmel Cancer Center

Predictability of Carcinomatous Invasion of the Maxilla or Mandible: An Assessment of Radiologic Modalities with Histologic Correlation

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List of Abbreviations

OMFS or OMS: Oral and Maxillofacial Surgery
JHNS: Jefferson Head and Neck Surgery
SCC: Squamous Cell Carcinoma
CBCT: Cone Beam Computed Tomography

Study Summary

Title	Predictability of Carcinomatous Invasion of the Maxilla or Mandible: An Assessment of Radiologic Modalities with Histologic Correlation
Short Title	Prediction of Bone Invasion by Squamous Cell Carcinoma
Protocol Number	<i>The standard protocol number used to identify this study (e.g. CCRRC # and IRB #)</i>
Phase	<i>N/A, This is not a clinical trial, it is one of imaging modalities</i>
Methodology/Study Design	<i>Prospective, non-randomized, double blind study</i>
Study Duration	2 years
Study Center(s)	Single-center
Objectives	In this study, we aim to explore which imaging modality or combination of imaging methods, in conjunction with clinical and histological examination, will most accurately predict the presence or absence of invasion of the mandible or maxilla by intraoral squamous cell carcinoma (SCC)
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Inclusion: SCC of the oral cavity Exclusion: prior mandibular surgery, primary intraosseous carcinoma, prior history of radiation to the mandible, obvious finding of clinical invasion of the mandible, age under 18 years old
Study Therapy, Dose, Route, Regimen	N/A
Duration of administration and follow-up	N/A
Reference therapy	N/A
Statistical Methodology	Sensitivity and specificity of mandibular or maxillary invasion will be determined, in addition to true and false positive as well as true and false negative. Finally the positive and negative predictive values for each of the imaging modalities will be calculated based upon the previously mentioned statistical analysis.
Schema	See attached schema in the appendix section at the end

1.0 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Specific Aims and Hypothesis

There are newer imaging modalities that have not been studied sufficiently to determine whether intraoral SCC has or has not infiltrated a segment of the mandible or maxilla, necessitating partial or complete resection of the jaw. One such modality is cone beam CT (CBCT), which delivers approximately 1/6 the amount of radiation and is about 1/10 the cost of a multi-slice, helical CT¹. A previously published imaging protocol by Van Cann et al² used MRI, CT and bone SPECT to image the mandible. In contrast to the prior algorithm, this study aims to test newer modalities such as the CBCT, PET/CT and helical CT against more traditional imaging techniques, to attempt to detect neoplastic infiltration of the mandible and maxilla. We hypothesize that CBCT or a combination of the aforementioned modalities can be used in order to more accurately predict invasion of the maxilla or mandible by intraoral SCC.

The accurate prediction of the presence or absence of malignant invasion of the jaws greatly influences the surgical treatment plan. This is important for several reasons. First, it may change the staging of the disease, necessitating a more or less involved resection and reconstruction. Second, this knowledge will greatly benefit the surgeon, since the reconstruction of an extensive surgical defect will be more complex and require greater planning. In addition, occult infiltration of the jaws may be a source of locoregional regrowth and recurrence that may be detectable by such imaging, leading to a wider, more appropriate and oncologically sound resection. Third, if absence of mandibular or maxillary invasion can be proven statistically, it will permit “sparing” of complete or partial resection. Thus, the mandible and maxilla, which are critical to facial form and function, will be preserved in some form and improve the overall quality of life of the cancer patient.

1.2 Background and Rationale

In 2008, Van Cann et al² published a protocol of assessment of mandibular invasion by intraoral SCC. This algorithm involved using a combination of MRI, bone SPECT and helical CT. In 2010, Hendrikx et al³ examined CBCT to determine its ability to predict invasion of the mandible by carcinoma. They found that CBCT has the potential to obviate unnecessary mandibular resection and that it warranted further evaluation as such a tool. Review of CBCT literature shows two other studies that examined CBCT for the

detection of mandibular invasion by SCC^{1,4}. These studies have been retrospective in nature and none of them have examined the maxilla for possible invasion by SCC. Thus, this study will compare CBCT, PET/CT, and helical CT of the maxilla and mandible in a prospective manner with a larger study cohort than previous studies.

The accurate prediction of the presence or absence of mandibular or maxillary infiltration by SCC will allow use of 3-D surgical planning models for the immediate reconstruction of the defect and preclude prolonged loss of function that patients may experience post-resection.

1.3 Study Therapy

This is a study comparing radiologic modalities already in use as the standard of care in order to determine bone invasion by oral squamous cell carcinoma.

1.4 Preclinical Data

Summarize the available non-clinical data (published or available unpublished data) that could have clinical significance.

Refer to section 1.2 “Background and Rationale”

1.5 Clinical Data to Date

Summarize the available clinical study data (published or available unpublished data) with relevance to the protocol under construction.

Refer to section 1.2 “Background and Rationale”

2.0 STUDY OBJECTIVES

2.1 Primary Objective:

To determine which imaging modality or combination of imaging methods, in conjunction with clinical and histological examination, will most accurately predict the presence or absence of invasion of the mandible or maxilla by intraoral squamous cell carcinoma (SCC).

2.2 Secondary Objective:

To compare the histopathologic findings to the radiologic findings

3.0 STUDY DESIGN

3.1 General Design

Prospective, non-randomized, double blinded study

3.2 Primary Study Endpoints

The primary endpoint is to determine if any one or combination of imaging modalities can accurately predict the presence or absence of bone invasion by oral squamous cell carcinoma

3.3 Secondary Study Endpoints

The secondary endpoint would be to more accurately plan the resection of mandibular or maxillary bone if invasion is predicted. If invasion is not predicted based upon the imaging modalities, then the secondary endpoint would be to spare resection of uninvolved bone

3.4 Primary Safety Endpoints

As this study compares radiologic modalities of diagnosis that are currently used for standard of care practice, there is no safety risk.

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

- Age 18-90
- Diagnosis of squamous cell carcinoma of the oral cavity
- Able to read and sign and informed consent

4.2 Exclusion Criteria

- prior mandibular surgery,
- primary intraosseous carcinoma,
- prior history of radiation to the mandible,
- obvious finding of clinical invasion of the mandible

4.3 Gender/Minority/Pediatric Inclusion for Research

All ethnicities will be included in this study of both male and female gender. The patients will be adults, 18 years of age or older and have a biopsy proven squamous cell carcinoma of the oral cavity.

While men have an increased incidence of oral SCC by 2:1 as compared to women, there will be no preference for one gender or another. Also, the ratio of men: women in the study will be monitored and all patients that meet the inclusion criteria will be added regardless of gender

4.4 Subject Recruitment and Screening

All patients will be from the Dept of OMS or JHNS practice. The patients will have a Cone Beam CT which will be used in the detection of mandibular or maxillary invasion by the oral squamous cell carcinoma as well as the evaluation of the dentition prior to possible radiation therapy.

4.5 Early Withdrawal of Subjects

4.5.1 When and How to Withdraw Subjects

Early withdrawal from the study is not foreseen as this study does not use any therapies of treatment, only radiologic tools for diagnosis

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

Not applicable

5.0 STUDY DRUG/THERAPY

N/A

5.1 Description

Cone beam CT scan

5.2 Treatment Regimen

This study will compare helical, medical grade CT, PET/CT and CBCT for the ability to predict invasion of the maxilla or mandible. Currently, helical CT and PET/CT are routinely used. Currently, panoramic radiographs are taken for patients with oral SCC necessitating therapeutic radiation. These radiographs on average emit 24 Micro Sieverts of absorbed radiation to the patient. The CBCT which provides three dimensional imaging of the teeth and jaws yield approximately 85 Micro Sieverts, which is only a small increase of 60 Micro Sieverts, with the benefit being the ability to more accurately predict invasion or absence of extension of the carcinoma with the hope of more accurate surgical margins and the sparing of uninvolved tissue when invasion is absent.

5.3 Risks

Formerly, patients received a panoramic radiograph in the OMFS Department for evaluation of dentition prior to radiation. The experimental procedure will now include CBCT in place of a panoramic x-ray which will more accurately predict invasion of the maxilla or mandible, and give better resolution concerning the risk of osteoradionecrosis of the jaw, should radiation therapy be used in the future. Although CBCT has slightly more radiation as compared to

the panoramic radiograph (87 Micro Sieverts vs 24 Micro Sieverts), it has the ability to yield more information relevant to patient diagnostic benefit and as such these benefits outweigh the approximate 60 Micro Sievert increase in absorbed radiation dose.

Risk will be minimized by using the smallest field of view necessary to provide diagnostic benefit of the CBCT. In addition, patients will be adequately shielded using a lead apron and thyroid collar.

The relative increase in absorbed radiation dose between the panoramic radiograph and the CBCT is small in comparison to the potential improvement in quality of life for these patients if they can avoid locoregional recurrence, tracheotomy, feeding tubes, cosmetic deformity and loss of masticatory function and speech function. In addition, the increase of approximately 40 micro sieverts from the panoramic radiograph to the CBCT gives the image greater resolution and contrast as well as 3-dimensional representation of the image, greatly increasing the accuracy of the image.

5.4 Method for Assigning Subjects to Treatment Groups

This study will not be randomized. All patients will received a helical CT, PET/CT and CBCT

5.6 Subject Compliance Monitoring

In this study, compliance is minimized in that once the imaging is completed and the surgical treatment carried out, the patient will have little commitment to the study.

5.7 Prior and Concomitant Therapy

In this section, describe:

- What prior and/or concomitant medical therapy will be collected (if applicable):
 - None
- Which concomitant medicines/therapies (including rescue therapies) are permitted during the study:
 - Any that are prescribed by the medical oncologist, given that the imaging is unrelated
- Which concomitant medicines/therapies are not permitted during the study (if applicable):
 - Radiation to the mandible or maxilla

6.0 STUDY PROCEDURES

6.1 Study Visit Schedule

Screening: Once patients are referred to the OMFS or JHNS departments with oral SCC, they will be evaluated to see if they meet the inclusion criteria and do not satisfy the exclusion criteria. Once they are deemed a candidate for the study by one of the involved doctors, they will have an appointment setup for a CBCT

Visit 1: CBCT in OMFS Office

Visit 2: Surgical planning in JHNS office, blinded to the result of the CBCT

Definitive Surgical Treatment

Follow-up: The patient will follow up in the JHNS department for necessary adjuvant therapies and post-surgical care when surgical treatment is carried out.

Please see the appendix for an outline of the study and also a card that will be posted in both JHNS and OMFS office to be used when evaluating patients for inclusion

Procedures, situations, or materials that may be hazardous to personnel and the relevant precautions, should also be outlined here.

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

Sample size was based upon the average number of cases per year that meet inclusion for the study based upon previous diagnostic and surgical logs

7.2 Statistical Methods

Sensitivity and specificity of the clinical exam, CBCT, helical CT, PET/CT, MRI and any other imaging modality used in detection of bone invasion will be calculated, as compared to the histological examination of the specimens.

Sensitivity: $[TP / (TP + FN)] \times 100$

Specificity: $[TN / (FP + TN)] \times 100$

Also, the confidence interval will be determined for the sensitivity and specificity.

True positive (TP): pts with histologic and radiographic evidence of invasion

True negative (TN): pts without histologic or radiographic evidence of

invasion

False Positive (FP): pts with positive radiologic evidence of invasion without histologic evidence

False Negative (FN): Those without radiographic evidence of invasion, but with histologic invasion present

In addition, the positive and negative predictive value will be calculated for each modality using the true positive and negatives as well as false positive and negative values.

7.3 Subject Population(s) for Analysis

This section should be very specific in defining the subject populations whose data will be subjected to the study analysis – both for the primary analysis and any applicable secondary analyses.

The data from all of the subjects that are enrolled and have consented to be a part of the study will be analyzed.

8.0 SAFETY AND ADVERSE EVENTS

8.1 Definitions

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious.

A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay

- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse

event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Unblinding Procedures

If it is found that any one or combination of imaging studies is able to accurately predict the presence or absence of bone invasion, this information will be unblinded to the oncologic surgeon, thereby allowing them to use the information in planning their surgical resection

8.4 Stopping Rules

If it is determined that this study is unsafe or of little clinical efficacy, then it will be stopped. As there are no drugs or other therapies being tested, stopping the study should not be necessary.

8.5 Data and Safety Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the compliance and implementation of the KCC data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events by both the assigned Medical Monitor and the KCC DSMC.

8.5.1 Medical Monitoring and AE/SAE Reporting

A Medical Monitor is assigned to this study at the Thomas Jefferson University. This is a physician/pharmacist who is not directly involved in the trial, and is not currently collaborating with the sponsor/investigator on any other trial. The role of the Medical Monitor is to review all reportable AEs/SAEs (in real-time) including grading, toxicity assignments, non-reportable AEs (quarterly), protocol violations/deviations, as well as all other safety data and activity data observed in the ongoing clinical trial occurring at Thomas Jefferson University. The Medical Monitor may recommend reporting of adverse events and relevant safety data, and may also recommend suspension or termination of the study to the DSMC and TJU IRB.

Every KCC investigator initiated protocol includes requirements for reporting of adverse events based on CTC 4.0. All events are reported to the IRB and Medical Monitor using a password protected web-site. In addition all unexpected and serious adverse events (SAEs) are reported to the TJU IRB and to the Food and Drug Administration (FDA) if applicable. The investigator is required to submit all unexpected and serious adverse events to the TJU IRB and the Medical Monitor within the timeframes outlined in the below table. All AE/SAEs will be reported to the DSMC at the quarterly DSMC review meetings; however, if the Medical Monitor determines corrective action is necessary, an "ad hoc" DSMC meeting will be called.

Fatal adverse events related to treatment which are unexpected must be reported within 24 hours to the TJU IRB and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days. A summary of the reporting requirements for KCC investigator initiated Phase I and Phase II studies are presented below.

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 and 5
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 - 48 Hours (Death: 24 Hours) Phase 2 - 5 Working Days
Possible Probable Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 working days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase 1 - 48 Hours Phase 2 - 5 Working Days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 and Phase 2 - 48 Hours (Death: 24 Hours)

****NOTE:** This table is based on the NCI AE/SAE reporting Guidelines and the TJU IRB Policy and Procedures. Please follow the individual protocol AE/SAE reporting guidelines if more stringent reporting procedures are specified.

8.5.2 Data and Safety Monitoring Committee

Data and Safety Monitoring Committee (DSMC) is the Data and Safety Monitoring Board (DSMB) for the KCC. The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials at the Thomas Jefferson University KCC. The committee meets quarterly to review the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

- The DSMC meets quarterly. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC meets (by conference call) within 24

hours following the notification of an unexpected adverse event felt to be related to the study drug.

- Prior to each DSMC meeting, each board member, is provided a printout of all reported AEs and SAEs occurring during the reporting period for this clinical trial. The principal investigator provides a detailed and comprehensive narrative assessment of current adverse events to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. DSMC members are provided with the principal investigator's assessment, a written report summarizing adverse events, safety data, and activity data observed during the specified time period described in each protocol, as well as recommendations from the Medical Monitor. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study.
- A summary of the board's action is sent to each investigator, the CCRRC and TJU IRBs. The DSMC actions may include recommendations/requirements that will lead to improved patient safety and/or efficacy, significant benefits or risks that have developed, or other changes determined to be necessary. The DSMC may also take note of slow accrual or lack of scientific progress, and refer such issues to the CCRRC. The DSMC provides the investigator with the rationale for any decision made.

9.0 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. **DO NOT ERASE OR WHITE OUT ERRORS.** For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.0 STUDY MONITORING, AUDITING, AND INSPECTING

10.1 Study Monitoring Plan

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related

documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the funding sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10.2.1 Independent External and Internal Audits

In addition to review by the DSMC, all studies initiated by KCC investigators are audited by an independent auditor once they have achieved 10% of target accrual. However, a study can be audited at any time based on recommendations by the IRB, DSMC, CCRRC and/or the Director of Clinical Investigations, KCC. Studies are re-audited once they have achieved 50% of target accrual. Special audits may be recommended by the IRB, DSMC or CCRRC based on prior findings, allegations of scientific misconduct and where significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

In addition to the audits at 10 and 50%, the CRMO randomly audits at least 10 percent of all patients entered into therapeutic KCC trials and other trials as necessary, on at least a bi-annual basis, to verify that there is a signed and dated patient consent form, the patient has met the eligibility criteria, and that SAEs are documented and reported to the TJU IRB.

All audit reports are submitted to the DSMC for review and action (when appropriate). A copy of this report and recommended DSMC action is sent to the CCRRC and TJU IRB. The committee regards the scientific review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The TJU IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

11.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on

Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for 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 commencement of this study.

All subjects for this study will be provided a consent form that is compliant with local and federal regulations, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.0 STUDY FINANCES:

12.1 Funding Source

Departmentally funded.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

13.0 PUBLICATION PLAN

Once imaging and histologic data have been collected from the target sample size, the information will be compiled for publication. This information will not be published in any manner prior to official publication

14.0 REFERENCES

- ¹ Closmann, James J., and Schmidt, Brian L.. "The use of cone beam computed tomography as an aid in evaluating and treatment planning for mandibular cancer." *Journal of Oral and Maxillofacial Surgery* 65.4 (2007): 766-771.
- ² Van Cann, E. M., et al. "Assessment of mandibular invasion of squamous cell carcinoma by various modes of imaging: constructing a diagnostic algorithm." *International journal of oral and maxillofacial surgery* 37.6 (2008): 535-541.
- ³ Hendriks, A. W. F., et al. "Cone-beam CT in the assessment of mandibular invasion by oral squamous cell carcinoma: results of the preliminary study." *International Journal of Oral and Maxillofacial Surgery* 39.5 (2010): 436-439.
- ⁴ Momin, Mohammad A., et al. "Diagnostic accuracy of cone-beam CT in the assessment of mandibular invasion of lower gingival carcinoma: comparison with conventional panoramic radiography." *European journal of radiology* 72.1 (2009): 75-81.
- ⁵ Smith, Jonathan C., et al. "Quality of life, functional outcome, and costs of early glottic cancer." *The Laryngoscope* 113.1 (2003): 68-76.

15.0 APPENDICES

To be posted in OMFS and JHNS office:

Prediction of Bone Invasion by Squamous Cell Carcinoma:

Inclusion: SCC of the oral cavity

Exclusion:

1. prior mandibular surgery
2. primary intraosseous carcinoma
3. prior history of radiation to the mandible
4. obvious finding of clinical invasion of the mandible,
5. age under 18 years old

Visit I: Screening visit

Visit II: Referral to OMS department for CBCT

Visit III: Definitive Surgical Treatment Plan

Goal:

To determine if any imaging modalities or combination of studies can accurately predict the presence or absence of maxillary or mandibular invasion by oral SCC. The diagnostic imaging will be compared to the histologic investigation of the resected specimens in order to determine their accuracy.

Patient Cohort
(N=10)

