Comparison of Endoscopic Visualization and CT Imaging of Head and Neck Cancers with Pathological Validation

UHN REB Protocol Number: TBD

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STATEMENT OF COMPLIANCE

The study will be conducted in compliance with the protocol, International Conference on Harmonisation [ICH] E6, applicable regulatory requirements, and carried out in accordance with Good Clinical Practice (GCP) as per the following:

- Health Canada Health Products and Food Branch [HPFB] Regulations
- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada
- Personal Information Protection and Electronic Documents Act, Bill C-6 [PIPEDA]
- USA Food and Drug Administration [FDA] Code of Federal Regulations [CFR] applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46
  http://www.fda.gov/cder/guidance/959fnl.pdf
  http://www.cancer.gov/clinicaltrials/learning/page3.
- National Institute of Health (NIH) Clinical Terms of Award;
  http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html

All key personnel (all individuals responsible for the design and conduct of this study) have completed GCP/Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and any attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal, regulatory requirements and applicable federal regulations and ICH guidelines.

Signed: _____   Date: _____

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CT	Computerized tomography
EM	Electromagnetic
FDA	Food and Drug Administration
FDG	Fluoro-deoxyglucose
GTV	Gross Tumour Volume
GTV-endo	Gross Tumour Volume - Endoscopic
GTV	Gross Tumour Volume - Standard
IGRT	Image Guided Radiation Therapy
IMRT	Intensity Modulated Radiation Therapy
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
OAR	Organ at Risk
OCI	Ontario Cancer Institute
OHRP	Office for Human Research Protections
PET	Positron emission tomography
PI	Principal Investigator
PIPEDA	Personal Information Protection and Electronic Documentation Act
PHIPA	Personal Health Information Protection Act
PMH	Princess Margaret Hospital
REB	Research Ethics Board
RMP	Radiation Medicine Program
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
STAPLE	Simultaneous Truth and Performance Level Estimation
UHN	University Health Network

PROTOCOL SUMMARY

Title	Comparison of Endoscopic Visualization and CT Imaging of Head and Neck Cancers with Pathological Validation
Population	• Age ≥ 18 years • Histologic diagnosis of squamous cell carcinoma • Primary H&N cancer • Disease visible on endoscopy • Intention to treat definitively using radical surgery therapy.
Number of Sites	One – Princess Margaret Cancer Centre, Toronto, Ontario
Study Duration	Accrual over 18 months years.
Description of Intervention	CT imaging immediately prior to surgery. Biopsy sampling of tissue samples using tracking and navigation technologies to register biopsy sampling to CT images
Objectives	Primary Objectives: • Pathological assessment of superficial extent of disease beyond CT-visible disease • Comparison of Gross Tumour Volume contours to pathological findings
Description of Study Design	This is a single centre, single arm feasibility study
Estimated Time to Complete Enrollment:	10 patients total, over 1.0 years

1   Key Roles

Principal Investigators	Dr. Jonathan Irish, MD MSc Dept. of Surgical Oncology University Health Network and Princess Margaret Hospital (UHN/PMH) 610 University Avenue, Toronto, Ontario M5G 2M9 Canada Tel: (416) 946-2149 FAX: (416) 946-2300 Email: jonathan.irish@uhn.on.ca Dr. Robert Weersink, PhD Medical Physicist Radiation Medicine Program (RMP) University Health Network/Princess Margaret Hospital (UHN/PMH)
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Research Ethics Board (REB)	University Health Network, Oncology Research Ethics Board Dr. J. Holland, Chair 700 University Avenue, 10th Floor, Toronto, Ontario M5G 1Z5 Tel. 416-581-7849 Fax: 416-946-2355 Email : jholland@uhnresearch.ca

2   BACKGROUND AND RATIONALE

2.1 Head and Neck Radiotherapy

Approximately half of cancer patients require radiation therapy (RT)* at some point during their care. Technological advances in RT, such as intensity modulation (IMRT) and image guidance (IGRT), allow radiation dose delivery with high accuracy and millimeter precision. RT planning can be thought of as a serial, step wise chain-like process where each link depends on the previous one. As these technical links are improved and strengthened, accurate definition of the target is now emerging as the weakest step in the RT process.[1] Accurate target definition is fundamental to all subsequent treatment planning and delivery and is critical for successful RT. Incorrect target definition can result in poorer outcomes through either undercontouring (less tumour control), overcontouring (more normal tissue toxicity), and/or both. For head and neck (H&N) cancer, the role of various combinations of radiological imaging in target delineation has been investigated with respect to target delineation at depth.[2-5] However, contouring with only standard radiological methods often misses superficial disease when compared to pathological sampling.[4, 5]

For head and neck cancers, endoscopy is invaluable in visualizing the superficial, radiographically occult extent of disease. Relation of these findings to the planning environment, however, is based primarily on the treating clinician's recall of the endoscopically visible disease relative to anatomical landmarks, a process subject to substantial contouring bias, error, and uncertainty in delineating the target or gross tumour volume (GTV).

Endoscopic examination of involved endothelial surfaces plays a critical albeit qualitative role in target delineation revealing superficial visible tumour extending beyond the invading disease apparent on volumetric imaging studies. In current practice, the clinician integrates the endoscopic findings into the treatment plan using their clinical judgment, recollection of anatomical landmarks and experience to define a target volume. Although clinical practice may vary, permanent records of the endoscopic procedure such as screen captures are not typically stored in the medical record. The subjectivity of this practice is evident in the large inter-observer variations observed in most contouring studies that include the physical exam.[5, 26]

2.2 Spatially Registered Endoscopy

To address these issues and improve contouring of superficial disease, we have designed and prototyped a novel platform that uses endoscopic tracking and image analysis tools for the accurate registration of endoscopic images to the treatment planning CT.[12, 13] Disease visible on endoscopy can then be contoured and registered to the planning CT, allowing inclusion of superficial disease invisible on the volumetric CT image dataset into the treatment plan.

Specifically, contouring can be performed on 2D endoscopic images, projected into 3D image space and imported into the treatment planning software. Our "optical simulation" (or endoscopic contouring) technology employs 3 fundamental technologies: an optical imaging

system, tracking technology, and image registration software. These technologies have been integrated into a single platform developed primarily for image-guided surgery[14, 15] which has been used in other REB-approved trials. The optical systems used in our initial studies were flexible endoscopes typically used in patient physical exams. Both real and virtual endoscopic images can be simultaneously displayed or, using various transparent display techniques can be overlaid on each other. Orthogonal views are also displayed showing the camera coordinates and contours.

The endoscopic contouring was demonstrated in pilot clinical studies with accuracies of ~3 mm on patients each with early stage (T1) glottic cancer. Endoscopic imaging was performed shortly after acquisition of the planning CT images. Patients were examined in the same position as the CT imaging, including fixation mask. Video and tracking information was recorded, allowing retrospective analysis. The 15 minute procedure was well tolerated by all subjects. Clinicians reviewed the video for frames displaying the tumour. Concordance between the endoscopic contours and those generated by the CT images alone were excellent along the superficial extent of the disease.

These cases were selected deliberately to be visible on both the optical and CT imaging, providing confirmation of contour concordance and as proof of concept. In contrast to this protocol, no suspicious submucosal extension was allowed in these patients. The study concluded optical simulation was feasible in these patients.

We currently have a clinical trial examining the impact on contouring accuracy by including spatially registered endoscopic imaging to the planning CT. Despite limited enrollment, several of the cases have shown large discrepancies between the CT visible GTV and the GTV contoured when endoscopic information is included.

The proposed study will examine the necessity of endoscopic contouring by comparison with pathology in a limited number of patients with oral cancer that are scheduled for surgical resection. Using image-guided surgery tools very similar to those used in the endoscopic contouring, we will compare GTV delineation of H&N cancers with and without the use of endoscopic contouring to pathologic findings. The study will use resources available in the GTx-OR (described below) to perform endoscopic contouring on oral cancer patients during the surgical procedure, immediately prior to resection.

The resected samples will be processed using whole mount pathology methods. Images of the whole mount tissue sections will be registered with the CT images acquired before and during surgery so that the pathology findings can be spatially correlated with the CT and endoscopic imaging. The pathology findings will also aid in defining the superficial extent of the disease and if these findings correlate with the region defined by the endoscopic imaging.

3   Objectives

3.1 Primary Objectives

3.1.1   To compare the location of lesions visible on the tissue surface with standard CT imaging and pathology

3.2 Secondary Objectives

3.2.1   To determine the registration accuracy of spatially navigated endoscopy in a controlled surgical setting.

4   Study Design

4.1 Overview

4.1.1   This is a single centre, single arm feasibility study comparing target delineation of GTV for H&N cancer to pathology using either standard CT-based contouring or spatially registered endoscopy combined with CT-based contouring.

4.1.2   Oral cancer surgery will be performed under image-guidance, including a standard contrast-enhanced CT scan immediately prior to the resection procedure. This CT scan will replicate the standard radiation planning CT scan and will be used for delineation of the GTV-std. External fiducial markers will be placed on the patient for registration of the navigation tools to the CT image coordinate system.

4.1.3   During surgery, the superficial lesion will be mapped using either a standard pointing tool that will be used by the surgeon to outline the lesion or navigated endoscopy will be performed of the superficial disease visible in the oral cavity. The endoscopic video will be spatially registered to the prior CT scan and used post-procedure for endoscopic contouring as an aid in delineation of the GTV.

4.1.4   The tissue will be marked along all planned excisions and resected using standard protocols. The surgical specimen will be mounted and scanned fresh in the OR using the CT scanner and a small animal MRI for correlative pathology. The sample will be prepared for whole mount pathology mapping by embedding the fixed tissue in a gel. The sample will be imaged again using the small animal MRI. It will then be delivered to pathology whole-mount section and identification of disease margins, both superficial and at depth. Details of the pathology workflow are in Section 7.6.

4.1.5   Following the procedure, contouring of the GTV will be performed by a radiation oncologist unfamiliar with the surgery and using only the CT image. The mapping

of the superficial lesion (from 4.1.3) will be added to the CT image and the errors between the standard CT-based contouring and the extent of the superficial lesion will be measured. The standard contours and lesion mapping will be compared to pathology for concordance and volume.
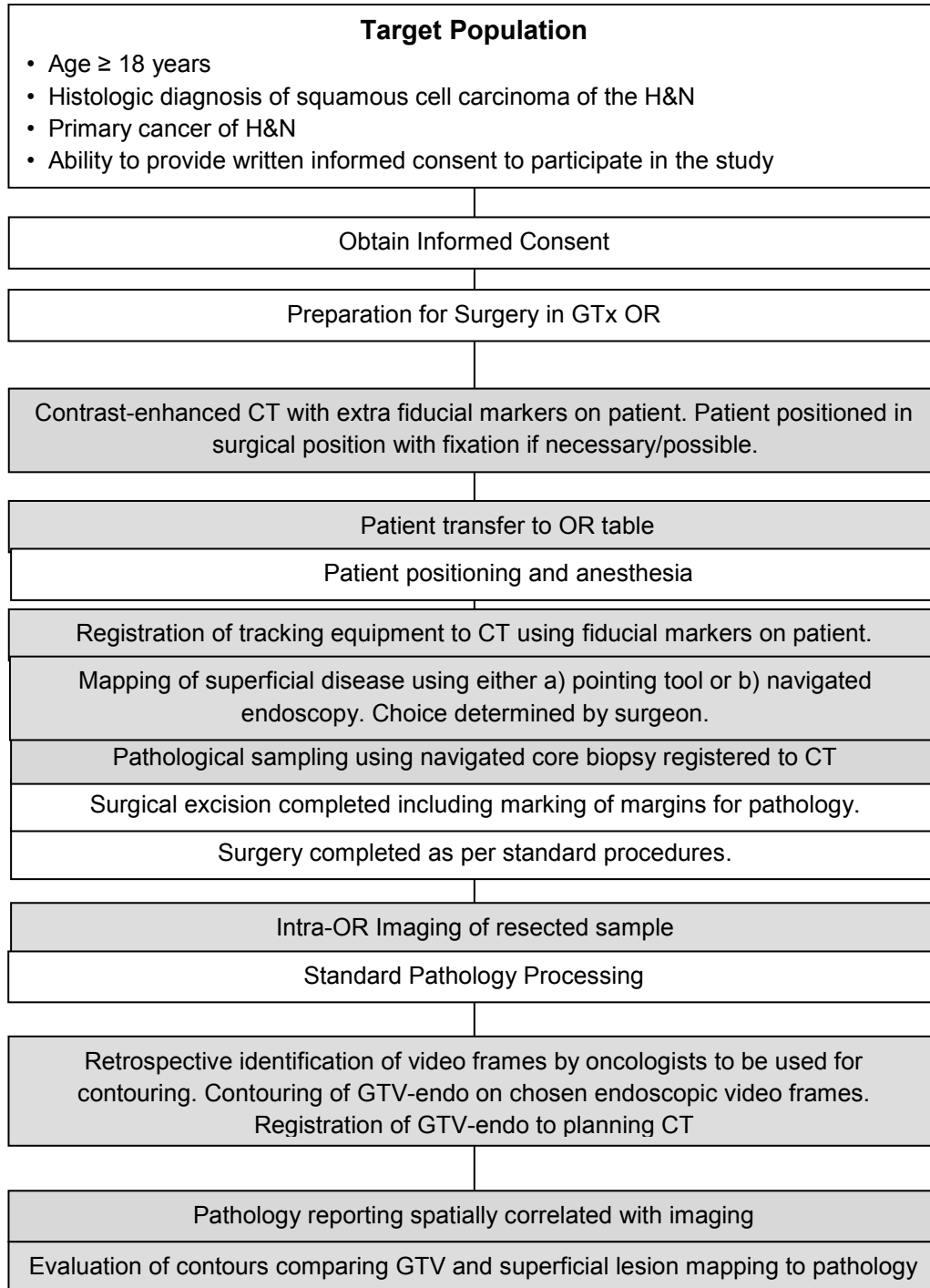
4.2 Integration with Standard Treatment of H&N Cancer

4.2.1 The patient will undergo standard clinical assessment and preparation for surgical resection of oral lesions.

4.2.2 A standard contrast-enhanced CT scan will be added to the standard surgical procedure, with fiducial markers placed on the patient's skin and with the patient in same position as used during surgery.

4.2.3 During the surgery, the superficial disease will be delineated using either a pointing tools tracking the outline of the tumour or using navigated endoscopy. The delineated disease will be registered to the initial CT scan using fiducial markers placed on the patient prior to the CT scan.

4.2.4 Patients will receive standard treatment for oral H&N cancer with surgery according to the UHN H&N oncology site policies. Treatment will not be modified based on the results of this study.

4.2.5 The radiation oncologist(s) will use the intra-operative CT scan to delineate the GTV as per standard clinical practice.

4.2.6 The overlap and differences between the mapped superficial disease and the GTV will be measured.

4.2.7 The locations of the disease identified by the CT scanning and the superficial lesion mapping will be correlated with the pathology reports. (See Sections 7.2 and 7.6 below for details)

4.3 Integration with Other Studies in Patients with H&N Cancer

4.3.1 Patients who participate in this study will be also be eligible to participate in other biomarker or therapeutic studies aimed at better characterizing the biologic behavior of H&N cancer or improving clinical outcome. Patients will be consented separately for these other studies.

5   Study Schema

Target Population
- Age ≥ 18 years
- Histologic diagnosis of squamous cell carcinoma of the H&N
- Primary cancer of H&N
- Ability to provide written informed consent to participate in the study

Obtain Informed Consent

Preparation for Surgery in GTx OR

Contrast-enhanced CT with extra fiducial markers on patient. Patient positioned in surgical position with fixation if necessary/possible.

Patient transfer to OR table

Patient positioning and anesthesia

Registration of tracking equipment to CT using fiducial markers on patient.

Mapping of superficial disease using either a) pointing tool or b) navigated endoscopy. Choice determined by surgeon.

Pathological sampling using navigated core biopsy registered to CT

Surgical excision completed including marking of margins for pathology.

Surgery completed as per standard procedures.

Intra-OR Imaging of resected sample

Standard Pathology Processing

Retrospective identification of video frames by oncologists to be used for contouring. Contouring of GTV-endo on chosen endoscopic video frames. Registration of GTV-endo to planning CT

Pathology reporting spatially correlated with imaging

Evaluation of contours comparing GTV and superficial lesion mapping to pathology

Tasks highlighted in grey are additional steps not part of standard clinical practice.

6   Study Enrollment and Withdrawal

6.1 Inclusion Criteria

Patients will be eligible for inclusion in this study if they meet all of the following criteria:

6.1.1   Age ≥ 18 years

6.1.2   Histologic diagnosis of oral squamous cell carcinoma

6.1.3   Primary cancer of the H&N

6.1.4   Intention to treat using surgery.

6.1.5   Ability to provide written informed consent to participate in the study

6.2 Exclusion Criteria

6.2.1   Prior complete or partial radiation therapy to H&N

6.2.2   Prior complete or partial surgery of the tumour

6.2.3   Concurrent illness or condition that precludes subject from undergoing endoscopy or CT scanning

6.2.4   Psychiatric or addictive disorders that preclude informed consent or adherence to protocol

6.3 Criteria for Withdrawal

6.3.1   Subject requests withdrawal from study for any reason

7   Study Schedule and Procedures

7.1 Clinical Evaluation and Informed Consent

7.1.1   Eligible patients are required to provide written, informed consent prior to study participation.

7.1.2   The start of treatment for H&N cancer will not be delayed by participating in this study. Surgery will proceed as schedule.

7.2 Design & Methodology

7.2.1   Using the Somatom FLASH CT scanner in the OR, a contrast-enhanced CT scan using standard Radiation Medicine protocols will be performed minus the use of a head fixation mask. The contrast agent will be Visipaque. The patient will be awake and generally positioned as they would be for the surgery/endoscopy procedure. Fiducial markers will be added to the patient's surface to be used for the registration of the endoscopy to the CT imaging.

7.2.2   The patient will be transferred to the operating table that is part of the ZEEGO robotic imaging device. In this transfer, the Zeego table is rotated and extended so that it aligns with the table of the CT scanner tables. A thin carbon fiber board under the patient is lifted and the patient moved to the Zeego table. A similar procedure has been used in other protocols in the GTx OR.

7.2.3   Patient is prepared for surgery.

7.2.4   Prior to tumour excision, surgeon defines the observable superficial extent of the disease one of two methods, determined at the discretion of the surgeon. One option uses a tracked pointing tool to record its position as the surgeon moves the pointer around the outline of the superficial disease. The other option is to use navigated endoscopy to record video of the superficial disease. (See Section 7.5) The endoscopes used here can be either rigid (with optical tracking) or flexible (using EM tracking)

7.2.5   The surgical procedure will continue using standard of care. Immediately prior to resection of the visible tumour, the tissue will be marked to identify visible extent of the superficial disease and the added margin. The navigated endoscopy will be repeated so that it includes these markings.

7.2.6   After surgical resection, a cone-beam CT scan will be acquired to define the location of the resected tissue. The cone-beam CT scan will be registered to the pre-resection CT scan for comparison of the resected volume and the disease contoured by the radiation oncologists. (See 7.2.9 below).

7.2.7 The resected tissue sample will be imaged again using a small field of view MRI scanner (0.5T) located in the OR. The tissue sample will then be sent to pathology for standard assessment. See Section 7.6 below for details of pathology handling.

7.2.8 Following the surgical procedure, the pre-operative CT scan will be evaluated by 3 observers. Each will independently perform contouring of the GTV. These observers will be practicing radiation oncologists at Princess Margaret Cancer Centre.

7.2.9 The shape and position of the superficial lesion defined by the tool tracking or navigated endoscopy (7.2.4) will be registered to the CT scan.

7.2.10 Pathology reporting will be correlated to the CT image set, allowing for measurements of the correspondence between the pathology and the contouring of the disease using the CT scan and the superficial disease.

7.3 Intraoperative CT Scanning

7.3.1 The CT scan will be an additional scan of the patient beyond standard of care. The typical dose for a CT scan of the head is 2-3 mSv. This is similar to the annual background radiation exposure in Canada. The contrast agent is Health Canada approved.

7.4 Equipment and Software for Endoscopic Contouring

7.4.1 The navigation tools and image guidance software platform used in this protocol have been developed within UHN. The tools include real-time optical and electromagnetic tracking (using commercially available equipment from NDI, Waterloo, ON) of surgical instruments and endoscopes co-registered to CT and MR imaging and display of the imaging information using augmented visualization methods. The necessary functions include:

- reading of CT images and data,

- tracking of EM sensors, calibration of endoscopic images,

- registration of CT image and EM coordinate spaces,

- registration of video images to CT images,

- selection of video frames for contouring,

- contouring on endoscopic images and

- export of endoscopic contours for reading by the treatment planning system.

7.4.2 This package has been demonstrated in several previous and current REB protocols:

UHN REB 11-0660-CE, Localized Intraoperative Virtual Endoscopy (LIVE) for Surgical Guidance in Sinus and Skull Base Patients

UHN REB 12-5315: The Translational Research Image-Guided Operating Room (TRIGORA): Intraoperative 3D Imaging for Head & Neck Surgical Patients

UHN REB 13-5914-C: Comparing Target Delineation of Head and Neck Cancers With and Without the Aid of Spatially Registered Endoscopy

UHN REB 15-9147-CE: Intraoperative 3D Imaging and Navigation for Patients with Benign Bone Tumours

7.5 Endoscopy Procedures

7.5.1 The endoscopy procedure will follow the CT scan and patient transport, which will be within 30-40 minutes following the CT scan. If necessary, immobilization devices may be used to fix the patient in the same position for endoscopy as used during the CT scan. Small plastic fiducial markers will be temporarily added to the patient using double sides tape. Once the patient is in place on the surgical table, CT to EM registration will be performed. The fiducial markers placed on the patient will be identified and located in both the CT image and in real space using the EM secondary pointing tool.

7.6 Pathology Correlation Procedures

Specifics of tissue handling:

Notification of a case pathologist (Drs. Bayardo Perez-Ordonez or Doaa AlGhamdi) and Surgical Pathology Laboratory Grossing room at UHN by Dr. Irish of name, MRN and date of surgery of patient scheduled for oral/tongue resection.

2. Sample taken by GTx staff to Pathology on 2nd floor TGH. Accessioning of surgical specimen by technologist upon arrival from OR and verification of the specimen by case pathologist. . Inform biobank personnel that the case may not be biobanked.

3. Fresh sample taken by GTx staff to small animal MRI on 7th floor Princess Margaret Discovery Tower (PMDT). T2-weighted (T2) and T1-weighted imaging of fresh sample within 2 hours of surgery.

4. Sample returned by GTx staff to Pathology on 2nd floor TGH. No incisions in the specimen are allowed to preserve the anatomy. Fixation and processing of the surgical specimen with neutral buffered formalin then overnight fixation of the specimen immersed in formalin. This may include injection of formalin into the specimen.

5. Gross description, including inspection orientation and measuring of the specimen and inking (with multiple colors to determine margin status and to aid in orientation) according to standard operating procedure. Recording of data on a requisition sheet.

6. Removal of stitches and/or sutures of specimen by Head and Neck pathologists/pathology fellow.

7. Gel embedding of sample, including MR visible markers to aid in identifying slice location. Once complete, fixed sample taken by GTx staff to small animal MRI on 7th floor PMDT for T2 and T1-weighted imaging.

8. Sample returned by GTx staff to Pathology on 2nd floor TGH. Sectioning at a 3mm interval will be done by a head and neck pathologist/fellow. Gross digital pictures of each section will be taken. Sections will then be sent for paraffin infiltration by UHN pathology.

9. Histologic wholemount processing (further sectioning to 4-6μm thickness, mounting of sections on slides, staining with hematoxylin and eosin (H&E) stain). Each paraffin bock and slide will contain a label that includes the accession number and a number for identification of a section.

10. Return of stained sections to UHN pathology. An e-mail of acknowledgement of receipt will be sent to Dr. Irish and Dr. Weersink by the receiving pathologist. Slides will be taken by GTx staff to Advanced Optical Microscopy Facility on 15th floor PMDT and scanned at histologic resolution (20x) with an Aperio scanner.

11. Outlining of malignant and ablated areas of surgical section in marker to be completed by the head and neck pathologist. The marked histologic slides will then be digitized and reconstructed into whole mount sections. Slides with outlined tumours will be digitized using a flat-bed scanner at 300dpi.

12. All cancerous regions marked and contoured on pathology will be registered on the corresponding parametric maps from each MRI data set. The MRI data will be registered to the post-resection cone-beam CT scan and the original planning CT image. This will register the pathological contours with those contoured by the radiation oncologists in step 7.2.9.

7.7 Metrics

7.7.1   Analysis will correlate the pathological sampling to the imaging. Specifically, we will compare the number of samples that show superficial disease and how this matches the location of the GTV as determined by CT imaging alone (GTV-std)

and the location of the GTV as determined by the combination of CT imaging and navigated endoscopy (GTV-endo).

7.7.2   Analysis will correlate the pathological sampling to the imaging. Specifically, we will measure the overlap of the pathology with the tumour defined using CT imaging alone, and the overlap of the pathology with the mapping of the superficial extent of the disease determined during surgery using either the pointing tool or navigated endoscopy.

7.7.3   Concordance of GTV-std and GTV-endo using conformity indices[22] such as DICE[23], or STAPLE.[24] These metrics estimate the differences between the GTV contours.

7.8 Data Collection

For each patient, a single anonymized identifier will be used. The following data will be collected:

- Date of surgery
- Tumour site
- Tumour type
- CT images (from 7.2.1)
- Intraoperative cone beam CT (from 7.3.1)
- Endoscopic video (from 7.5.1)
- Pathology data, including whole mount images (7.6) and tumour classification from pathology reports

A data collection summary sheet will be stored for each patient.

8   Safety

8.1 CT Scan

8.1.1   An additional contrast-enhanced CT scan will be required. The additional dose to the patient resulting from this scan is minor. The routine CT Head & Neck scan conducted as standard of care at UHN delivers ionizing radiation of 3.0-5.0 mSv to the patient. For comparison, this exposure is equivalent to about one year of background radiation exposure from living in North America (2.0 - 3.0 mSv), while for people living on the plateaus of Colorado or New Mexico, the annual background radiation exposure is 3.5 - 4.5 mSv. REB 11-0192-C was granted to image a very similar patient population to the present study, with similar demographics and the same diagnosis.

9   STATISTICAL CONSIDERATION

9.1 Sample Size

9.1.1   This study will accrue up to 10 patients with H&N cancer, leading to 10 whole mount pathology samples in total. The reporting of the pathology findings will be spatially correlated to the imaging. If possible, other pathological findings will be used in the analysis if sufficient spatial correlation can be recovered based on tissue markings used with the excision.

9.1.2   The number of H&N oral cancer cases that proceed to surgery is ~5 per week, Assuming an accrual of 10%, this would average approximately 1-2 cases per month.

10   SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Appropriate documentation will be maintained for this trial, in compliance with ICH E6, Section 4.9 and OCI/PMH institutional requirements for the protection of confidentiality of subjects. The documentation will be stored for a period of 25 years in accordance with Health Canada Regulations.

Only designated personnel will have access to records. Only authorized representatives of the sponsor or regulatory agencies will be allowed to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, or evaluation of the study safety and progress.

11 ETHICS/PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Standard

The PI will ensure that this study is conducted in full conformity with the principles set forth in the Declaration of Helsinki, CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of 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; 62 Federal Regulations 25691 (1997).

11.2 Institutional Review Board

The institution must provide for the review and approval of this protocol and the associated informed consent documents, and relevant recruitment material by an appropriate independent research ethics board [REB]. Any amendments to the protocol or informed consent materials must also be approved before they are placed into use.

11.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms, separate from the protocol document, describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product (see Appendix for sample of Informed Consent Form). Consent forms will be REB-approved and the subject will be asked to read and review the document. Approved consent forms may be available translated into other languages, as applicable.

Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The privacy, rights and welfare of the subjects will be protected by emphasizing, to them, that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.4 Subject Confidentiality

Subject confidentiality will be strictly held in trust by the participating investigators, their staff, and the sponsor and their agents, and will be in compliance with the Personal Health Information Protection Act (PHIPA) and other applicable legislation.

All study related documentation, data, and all other information will be held in strict confidence in accordance with the Personal Information Protection and Electronic Documentation Act (PIPEDA) and other applicable regulation.

Authorized representatives may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and other relevant records for the subjects in this study.

In the event of personal information disclosure to an unauthorized party, any further release of information will be stopped, as much information as possible will be retrieved, UHN REB and UHN Privacy Office will be contacted, and then further actions will be taken based on their recommendations.

12   DATA HANDLING AND RECORD KEEPING

The PI is responsible to ensure 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.

12.1 Data Management Responsibilities

All source documents must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the site PI or medical designate.

Data collection is the responsibility of the clinical research staff at the site under the supervision of the site PI. During the study, the investigator must maintain complete and accurate documentation for the study.

12.2 Study Records Retention

As per Health Canada regulations, study documents will be retained for a minimum of 25 years. No clinical trial records will be destroyed without the written consent of the sponsor and PI, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.3 Protocol Deviations

The site PI and study staff are responsible for knowing and adhering to the study protocol and to the reporting requirements of relevant regularity agencies (e.g. UHN REB, Health Canada as applicable). A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), The noncompliance may be either on the part of the subject, the investigator, or the study site staff. All deviations from the protocol must be addressed in study subject source documents. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6.

13   References

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