Evaluation of TraceIT® Tissue Marker to mark the primary resection bed margins of oropharyngeal cancers: a pilot study

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Protocol Revision History

Version Date	Revision Summary
08/15/18	*Initial Approval Version*
06/03/19	*Revise inclusion criteria to allow for confirmed or highly suspicious oropharyngeal cancer; clarify distant metastatic disease as exclusionary*
07/02/2019	*Revise the exclusion criteria to remove "5. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to TraceIT or other agents used in the study." According to the package insert there is no contraindication for this criteria.*
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1.0 BACKGROUND AND SIGNIFICANCE

1.1 Head and Neck Cancer

The pattern of spread of head and neck cancer for each anatomical subsite has been understood for many decades. Pioneering surgeons and radiation oncologists treating head and neck cancer used this knowledge to design appropriate surgical procedures and radiation fields to treat this disease. However, until the 1960s most patients were treated with either surgery or radiation initially, and then the other therapy for an attempt at salvage when they recurred. Resecting all of the potential sites of tumor spread was too morbid, and while radiation could reach all potential sites of spread, tumors often failed at the central bulky part of the tumor. Head and neck cancer patients benefited significantly when physicians started treating them with surgery followed by radiation therapy as a combined treatment. This sequence of treatment was confirmed in an early landmark RTOG clinical trial of preoperative radiation versus postoperative radiation versus radiation therapy alone. Postoperative radiation therapy proved to be most successful and has been a standard of care for head and neck cancer patients since that time. Unfortunately, the toxicity related to surgical therapy for oropharyngeal cancer was significant in that it often required a mandibulotomy approach and a mandatory free tissue transfer reconstruction and tracheotomy and long-term feeding tube requirements. With the increasing incidence of oropharyngeal cancer secondary to Human Papillomavirus (HPV), outcomes have significantly improved and have led to investigations aimed at decreasing toxicity while maintaining oncologic outcomes.[1-3]

1.2 Radiation Therapy and Surgery in the Treatment of Oropharyngeal Cancer

Since the publication of the RTOG trial in 1972, much advancement have been made in surgical and radiation therapy technique.[4-6] Surgery for oropharyngeal cancer has moved from morbid open procedures to transoral endoscopic laser surgery (TLM) and/or transoral robotic surgery (TORS).[7,8] TLM and TORS can be accomplished entirely transorally without the need for morbid approaches such as splitting the lip and mandible.[9] Therefore, it is rare today to perform reconstruction or tracheotomy in these patients and most patients receive oral nutrition immediately after the surgery or within a couple of weeks. In the era of HPV related oropharyngeal cancers, de-escalating therapy continues to be investigated. Radiation therapy has moved from treating the left and right sides of the head and neck with full dose to intensity modulated radiation therapy (IMRT) and proton beam radiation, both of which allow for reducing the dose of normal tissue treated. Reducing dose of normal tissue treated has been shown to reduce treatment-related toxicity and improve quality of life from both the physician's, and more importantly, the patient's perspective. At the advent of IMRT, there was concern that tighter radiation fields would spare not only normal tissue but also tumor cells and be less effective than 2D technology. Fortunately, patterns of failure data with IMRT have proven that not to be the case as shown in our prior publications.[10,11]

The change from 2D technology to IMRT required radiation oncologists to understand head and neck anatomy in 3 dimensions. To aid radiation oncologists in this transition,

several important international standards have been developed to aid in delineation of the potential patterns of tumor and lymphatic spread, as well as guidelines for contouring of normal tissues in the head and neck. These guidelines are by necessity population based. A member of the radiation oncology community will be assured of reasonable coverage of all potential patterns of tumor spread using these guidelines. It is understood that each individual patient's tumor may extend to only a fraction of the potential pattern of spread for a group of patients. It has not been possible to improve this situation because knowledge of individual patient's microscopic pattern of spread is elusive. Limiting radiation therapy to that required for each patient's individual tumor would represent a significant advance in treatment.

1.3 Towards Individualized Treatment of Oropharyngeal Cancer

Imaging technology has significantly advanced over the last several decades. CT, MRI, and CT/PET technology has been developed and each successive generation of technology results in improved resolution and accuracy of images. However, no imaging technology can define the microscopic extent of malignancy. PET imaging is complicated in the head and neck because the structures of the oropharynx (tonsils, base of tongue, and soft palate) all exhibit varying degrees of metabolic activity at baseline. Differentiating between tumor uptake and "normal" uptake is often not possible, especially with regards to the edge of even macroscopic disease.

TLM/TORS in conjunction with pathological sampling of resection margins during surgery is the only method by which microscopic margins of tumor resection can be defined. In addition, multiple investigations have shown that the distance of the cancer to the surgical resection margin is not necessarily a prognostic factor, as long as the surgical margin is clear of tumor cells.[12,13] This more binary approach to margin analysis implies that oropharyngeal cancers treated with transoral surgery are largely limited to the tumor bed within the resection margins. If the permanent sections are consistent with the frozen section margins, a complete resection of the tumor has been achieved with a microscopically clear margin. Radiation therapy to a small additional margin would be expected to eradicate any additional tumor cells that may yet exist with a tumor exhibiting perineural invasion, or an infiltrating tumor with separate nests of tumor cells. A number of retrospective studies have shown that with TLM/TORS and postoperative radiation using population based standardized radiation fields described above, tumor control is achieved in 95-100% of patients.[14] Reducing radiation volume to match the needs of an individual patient has not yet been possible because it has not been possible to define the exact position of negative surgical margins for the radiation oncologist. Even with detailed operative notes combined with pre- and post-operative imaging, the microscopic edge of the resected tumor is not clear.

Marking the edges of negative surgical margins during the TLM/TORS oropharyngectomy would be of immense benefit. These minimally invasive surgical procedures are an ideal setting as the surgical margins are mapped out intraoperatively using frozen section pathology and are more easily visible with the aid of operating microscopes and high definition 3- dimensional camera systems available. One group has a series of publications

describing the use of surgical clips for marking the margins of the oral cavity resection to reduce radiation therapy to their reconstruction of the defect.[15-18] In the oropharynx, we routinely use titanium clips to ligate intermediate to large vessels. Therefore, they would not be useful as a fiducial marker for that reason as well as they have a propensity to extrude over time. TraceIT Hydrogel is an injectable hydrogel that is visible with CT, CBCT, CT/PET, US, and MRI images. The hydrogel particles are visible through 3 months after which they liquefy and are cleared. TraceIT injection during TLM/TORS may be an ideal solution for transmitting the exact location of negative tumor margins to the radiation oncologist, allowing a customized treatment volume for each individual head and neck cancer patient.

1.4 TraceIt Hydrogel Preclinical Studies

TraceIT Tissue Marker has 510K clearance (Approval) from the FDA. It was shown that TraceIT is substantially equivalent to a product that is already on the market in its intended use and principle of operation. Both *in vivo* and *in vitro* (bench, cadaver, and animal) testing were performed to verify and validate the safety and effectiveness profile of TraceIT. It has been approved in both the US and Europe. Investigations using TraceIT have been performed to use as a spacer between normal tissue and tissue undergoing radiation in the pancreas,[19] submandibular gland,[20] rectum and bladder,[21] and as a fiducial marker for gynecologic malignancies.[22] No adverse events related to the product in these investigations would prohibit its use in the proposed investigation.

In order to determine the feasibility of injecting TraceIT hydrogel during TORS surgery, identifying the marker with CT simulation images, and contouring individual target volumes, we performed a study using cadaver heads. The heads were imaged preoperatively and had a TORS procedure during which 0.2 – 0.3 ml TraceIT were injected at the superior, inferior, medial, lateral, and deep margins of resection, respectively. More volume than that did not stay in the tissue but began to extrude through the needle insertion site. A total of 4 cadaver heads were used; two had base of tongue resections and two had tonsil resections. Postoperative imaging was performed and the CT information was transmitted to an Eclipse (Varian Corp) treatment planning workstation. The markers were clearly visible on the CT images. Standard population-based tumor treatment volume and lymphatic treatment volumes were contoured, as well as an individual marker-based tumor treatment volume. Standard and individualized treatment plans were developed. Depending on the resection location, DVH curves for the individualized plans were significantly improved relative to the standard plans (see table on following page). In keeping with the sigmoidal shape of the normal tissue complication probability (NTCP) curves, the esophageal and pharyngeal constrictor doses dropped below the range where one would expect permanent swallowing problems and/or esophageal strictures in the individualized plan relative to the standard plan. Oral cavity and lip dose were significantly improved as well, and one would expect less acute morbidity and less permanent xerostomia due to damage to the tiny salivary gland tissue which carpets the oral cavity. Parotid and submandibular gland tissue dose was decreased as well, with results differing with respect to location of resection. Depending on the size and extent of tumor, these results should be typical for patients with cancer in the oropharynx. The preliminary

preclinical data are compelling and warrant further study in patients with oropharyngeal carcinoma.

1.5 Dose Limits to Head and Neck Subsites

Reduction in radiation dose and volume is important to maintain function of normal structures while still adequately treating the oropharyngeal cancer.[23,24] The percent reduction, though, is only significant if it reduces toxicity to these structures. For instance, toxicity rates at a given dose has been well studied and is well documented in the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) guidelines.[25] For example, patients have approximately a 20% risk of symptomatic dysphagia and aspiration if the mean dose to the pharyngeal constrictors is 50 Gy. In our pre-clinical cadaveric study, the standard treatment plans delivered doses 55 Gy to the ipsilateral and contralateral pharyngeal constrictor muscles while the marker-based treatment plan was only 42 and 39 Gy, respectively. This reduction would be clinically significant for reducing toxicity related to swallowing dysfunction, which is incredibly important in patients receiving surgery and radiation for oropharyngeal cancer. In addition, dose and volume reduction may have more implications than just limiting toxicity. For example, if surrounding tissue has less overall radiation exposure, this could allow future re-irradiation of overlapping sites in the instance of treatment failure in patients that currently may not tolerate re-irradiation.

	Cadaver A Markers	Cadaver A Standard	% Difference	Cadever B Markers	Cadaver B Standard	% Difference	Cadaver C Markers	Cadaver C Standard	% Difference	Cadaver D Markers	Cadaver D Standard	% Difference
	cGy	cGy		cGy	cGy		cGy	cGy		cGy	cGy	
Brain	372	438	-15	158	383	-59	219	257	-15	1521	1805	-16
Brainstem	662	865	-23	646	1682	-62	1835	2038	-10	1809	2072	-13
Spinal cord + 5	2663	2672	0	2642	2411	10	2836	3051	-07	2433	2755	-12
Mandible	2715	3413	-20	3176	3469	-08	2347	3080	-24	2114	2819	-25
Oral Cavity	3439	4458	-23	3517	3949	-11	2596	4013	-35	2408	3712	-35
Lips	1532	1988	-23	1500	1396	7	1237	1715	-28	871	1199	-27
ParynCont R	3921	5538	-29	5094	5638	-10	3025	4665	-35	3128	3513	-11
PharynContL	4205	5499	-24	5617	6002	-6	5550	6032	-8	5507	5959	-8
Esophagus Upper	4635	6077	-24	4668	5961	-22	3742	4439	-16	3799	4060	-6
Parotid L	2628	2670	-2	2834	3155	-10	4319	4589	-6	4689	5001	-6
Parotid R	1894	1935	-2	4396	4505	-2	656	807	-19	871	920	-5
Submandib L	5591	5660	-1	5951	5919	1	5154	5752	-10	-	-	-
Submandib R	3806	4252	-10	4499	4513	0	1301	1465	-11	-	-	-
Supraglottic Larynx	-	-	-	3635	5380	-32	-	-	-	-	-	-
Arytenoid L	-	-	-	1479	4001	-63	-	-	-	-	-	-
Arytenoid R	-	-	-	1733	3122	-44	-	-	-	-	-	-
Glottis	-	-	-	835	3378	-75	-	-	-	-	-	-
Total Sum	38063	45465	-16	52380	64864	-19	34817	41903	-17	29150	33815	-14
Total Mean	2927.92	3497.31	-16	3081.18	3815.53	-19	2678.23	3223.31	-17	2650	3074.09	-14

2.0 OBJECTIVES

2.1 Primary Objective

To evaluate the reduction in clinical target volumes (CTV) for the primary resection bed between the standard of care treatment plan and the treatment plan based on the TraceIT hydrogel markers.

2.2 Secondary Objectives

1. To describe the anatomic localization relative to standard treatment fields based on anatomy.

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

1. Pathologically confirmed (by routine H&E staining) or highly suspicious for oropharyngeal squamous cell cancer.

2. Planned treatment includes transoral surgery followed by adjuvant IMRT.

3. At least 18 years of age.

4. Ability to understand and willingness to sign an IRB approved written informed consent document.

3.2 Exclusion Criteria

1. Distant metastatic disease at the time of definitive treatment, and thus study, initiation.

2. History of major head & neck surgery or previous head & neck irradiation.

3. History of or current oral disease that may interfere with interpretation of study outcomes.

4. Currently enrolled in another radiation therapy trial that has not completed its primary endpoint or that clinically interferes with this study.

5. Poor surgical candidate.

7. Prisoners.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 STUDY DESIGN

Study participants will be recruited from the head and neck oncology clinic at Washington University/Barnes Jewish Hospital. Patients will be offered participation if they are being offered a minimally invasive transoral surgery as part of their standard treatment for their head and neck malignancy. These are patients that would be recommended transoral surgery despite this investigation and this investigation will have no influence on treatment recommendations.

Consenting and eligible patients will be scheduled for standard of care surgical resection of the primary tumor. Following successful tumor resection, TraceIT Tissue Marker will be applied in 0.2 to 0.5 mL injections at 5 locations to mark the tumor bed: superiorly, inferiorly, laterally, medially, and center of resection. The marginal injections will be within 3 mm of the resection edge and within 5 mm deep. The center of the resection bed will be injected within 5 mm deep if possible (i.e., no critical structure in this region). Patients will be monitored for adverse events following injection of the TraceIT Tissue Marker intraoperativelyby the operating surgeon/principle investigator.

Within 6 weeks after surgery, a CT simulation scan will be performed per normal protocol for patients receiving surgery followed by adjuvant therapy. This scan will be used to generate the IMRT treatment plan. Participants will begin IMRT per standard of care following surgery in most instances, recognizing that some patients may be delayed due to wound healing, infection, etc. These delays will not have impact on this investigation as our end-point is the CT simulation scans and treatment planning, not the actual start date of therapy.

Two treatment plans per patient will be performed using the simulation CT scan. One will be the standard of care treatment plan and will be the basis of the actual radiation treatment they receive. The second treatment plan (research purposes only) will be based on utilizing the TraceIT hydrogel markers as a guide for the resection bed. These two treatment plans will then be used to generate clinical target volumes and a comparison per patient will be performed between standard target volumes and marker-based target volumes. This will be used to generate radiation dose to regions of interest for simulation purposes only. The study does not interfere with the clinical care treatment plan. Regions of interest will include the brain, brainstem, oral cavity, lips, pharyngeal constrictor muscles, upper esophagus, parotid glands, submandibular glands and laryngeal structures.

The treatment planning studies performed in each participant will be performed using an identical technique and similar setup, with the test group using the TraceIT hydrogel markers as a guide for the resection bed. Target volume definitions and critical structure contouring will be performed using the same methods for treatment planning for any given participant. The radiotherapy prescription will be standardized to the use of image-guided IMRT consisting of the high risk planned target volume, and the low risk or elective PTV. The marker-based treatment plans will be used as a theoretical treatment to compare to the standard treatment plan. The standard treatment plan will be used for the patients actual radiation treatment, thus no deviation from standard of care treatment will be prescribed. The international standard plan volumes for tonsil, base of tongue, and soft palate will be contoured, as well as by a volume determined from the markers.

5.1 Evaluability

All patients are evaluable for the primary endpoint (evaluate the volume reduction in drawing CTV for the primary resection bed) provided they have had the TraceIT injections and undergone the post-op treatment planning study.

Patients who receive the TraceIT injections are evaluable for toxicity related to the tracer even if they don't receive IMRT. Patients are evaluated during the intraoperative period

only for TraceIT-related Adverse Events.

5.2 Duration of Participation

Participation includes the injection of the TraceIt fiducial marker and the RT simulation planning post-surgery. The patient will be withdrawn from the study if:

- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue participation for any reason will be followed as indicated in the study calendar.

5.3 Duration of Follow-up

Patients will return for standard of care follow-up visits approximately 14 days after completion of their surgical procedure and injection of the TraceIT fiducial markers. They will then follow up with their radiation oncologist for a treatment planning session for which their standard of care treatment plan and their marker-based treatment plans will be completed. This will occur approximately 6 weeks after surgery. They will continue to be treated and followed as per standard of care, but no further follow-up will be necessary for the purposes of this investigation.

6.0 PHARMACEUTICAL INFORMATION

6.1 TraceIT

6.1.1 TraceIT Description

TraceIT Tissue Marker is a sterile, single use product consisting of a pre-filled glass syringe containing the synthetic, radiopaque cross-linked PEG hydrogel with an endcap. The pre-filled glass syringe, sterile plastic luer-luer connector, plastic receiving syringe, and a 1" needle are packaged inside a poly-Tyvek pouch within a larger poly-Tyvek pouch. As some hydrogel/carrier separation can potentially occur during storage, two syringes are provided to allow for mixing (by injecting back and forth 5 times between the syringes so the material ends up inside the plastic receiving syringe) immediately prior to use. TraceIT Tissue Marker is provided in a 1mL and 3mL configuration.

The maximum injection volume of TraceIT hydrogel, for a single location, is 1mL. TraceIT hydrogel is visible on ultrasound, computed tomography (CT), and Magnetic Resonance Imaging (MRI) for approximately three (3) months and is absorbed and cleared from the body within approximately seven (7) months of implantation. TraceIT hydrogel implant is MR Safe. The 304-stainless steel

applicator needle is MR Unsafe; all other TraceIT Tissue Marker delivery components are MR Safe.

TraceIT Tissue Marker is indicated for use to radiographically mark soft tissue during a surgical procedure or for future surgical procedures. TraceIT hydrogel is intended to mark tissue for at least 3 months after injection.

TraceIT Tissue Marker has been cleared by the FDA for the indication stated above. TraceIT Tissue Marker has completed all testing required for an implantable medical device.

6.1.2 Supplier

Augmenix (201 Burlington Rd, Bedford, MA 01730 p: 781-902-1624)

6.1.3 Dosage Form and Preparation

It is provided in a 1 mL and 3 mL configuration.

6.1.4 Storage and Stability

TraceIT Tissue Marker should be stored at room temperature, 15° C – 25° C (60° F – 77° F).

6.1.5 Administration

See TraceIT Tissue Marker Instructions for Use

6.1.6 Side Effects

Potential side effects from the administration of TraceIT:

1. Injection site pain
2. Vascular occlusion
3. Local inflammatory response
4. Embolic phenomena
5. Bleeding

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below. Events that are temporally related to the TraceIT injection (beginning at time of injection through the intraoperative period) will be evaluated for regulatory reportability as per the criteria in this section.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does

not include a reaction that, had it occurred in a more severe form, might have caused death.

7.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Timeframe for Reporting Required Events

Events that are temporally related to the TraceIT injection (beginning at time of injection through the intraoperative period only) will be monitored. For the purposes of this protocol, adverse events related to surgical complications will not be collected and documented on CRFs.

8.0 STUDY CALENDAR

	Screening	Surgery	6 wks post-op
Informed consent	X		
H&P	X		
Tumor staging	X		
Resection		X	
TraceIT hydrogel placement		X	
IMRT treatment planning session			X
AE assessment		X	

9.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Surgery Form	Time of surgery
Treatment Planning Form	Time of IMRT treatment planning
AE Form	Time of surgery

10.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual

- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

11.0 STATISTICAL CONSIDERATIONS

Our pilot data from 4 cadavers show effect sizes ranging from 0.57 and 1.68 for the reduction in radiation dose/volume to critical structures. With this, using the lowest effect size of 0.57, a one sided alpha error of 0.05 and 80% power, we will need 21 subjects to detect this effect size.

Standard descriptive statistics will be used to describe study population as well as volume and planned treatment dosimetry using the standard approach and based on the margins defined by fiducial marker. Variables will include patient age and gender, tumor pathologic diagnosis and tumor characteristics such as anatomic subsite, stage, and size. Paired samples t-test or its nonparametric equivalent Wilcoxon signed rank test will be used to compare the tumor volume and planned dose of treatment under each approach. Histograms and Shapiro-Wilks test will be used to explore normal distribution of the data. Stratified analysis will be performed to compare treatment plans between the 2 approaches for each main cancer site. Secondary endpoints, such as adverse events, will be described as frequency and percentage of patients experiencing an adverse event.

12.0 REFERENCES

1. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J. Clin. Oncol.* Nov 10 2011;29(32):4294-4301.

2. Kelly JR, Husain ZA, Burtness B. Treatment de-intensification strategies for head and neck cancer. *Eur. J. Cancer.* Nov 2016;68:125-133.

3. Arnaoutakis D, Sumer BD. Treatment Deintensification for Human Papillomavirus-Associated Oropharyngeal Cancer. *Ann. Surg. Oncol.* Nov 2017;24(12):3463-3465.

4. Eisbruch A, Foote RL, O'Sullivan B, Beitler JJ, Vikram B. Intensity-modulated radiation therapy for head and neck cancer: emphasis on the selection and delineation of the targets. *Semin. Radiat. Oncol.* Jul 2002;12(3):238-249.

5. Gregoire V, Ang K, Budach W, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother. Oncol.* Jan 2014;110(1):172-181.

6. Guerrero Urbano MT, Clark CH, Kong C, et al. Target volume definition for head and neck intensity modulated radiotherapy: pre-clinical evaluation of PARSPORT trial guidelines. *Clin. Oncol. (R. Coll. Radiol.).* Oct 2007;19(8):604-613.

7. Steiner W, Fierek O, Ambrosch P, Hommerich CP, Kron M. Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue. *Arch. Otolaryngol. Head Neck Surg.* Jan 2003;129(1):36-43.

8. Weinstein GS, O'Malley BW, Jr., Cohen MA, Quon H. Transoral robotic surgery for advanced oropharyngeal carcinoma. *Arch. Otolaryngol. Head Neck Surg.* Nov 2010;136(11):1079-1085.

9. Williams CE, Kinshuck AJ, Derbyshire SG, et al. Transoral laser resection versus lip-split mandibulotomy in the management of oropharyngeal squamous cell carcinoma (OPSCC): a case match study. *Eur. Arch. Otorhinolaryngol.* Feb 2014;271(2):367-372.

10. Chin RI, Rao YJ, Hwang MY, et al. Comparison of unilateral versus bilateral intensity-modulated radiotherapy for surgically treated squamous cell carcinoma of the palatine tonsil. *Cancer.* Sep 07 2017.

11. Chin RI, Spencer CR, DeWees T, et al. Reevaluation of postoperative radiation dose in the management of human papillomavirus-positive oropharyngeal cancer. *Head Neck.* Nov 2016;38(11):1643-1649.

12. Hinni ML, Ferlito A, Brandwein-Gensler MS, et al. Surgical margins in head and neck cancer: a contemporary review. *Head Neck.* Sep 2013;35(9):1362-1370.

13. Hinni ML, Zarka MA, Hoxworth JM. Margin mapping in transoral surgery for head and neck cancer. *Laryngoscope.* May 2013;123(5):1190-1198.

14. Jackson RS, Sinha P, Zenga J, et al. Transoral Resection of Human Papillomavirus (HPV)-Positive Squamous Cell Carcinoma of the Oropharynx: Outcomes with and Without Adjuvant Therapy. *Ann. Surg. Oncol.* Aug 14 2017.

15. Bittermann G, Ermer M, Voss P, et al. Comparison of virtual and titanium clip marking of tumour resection margins for improved radiation planning in head and neck cancer surgery. *Int. J. Oral Maxillofac. Surg.* Dec 2015;44(12):1468-1473.

16. Bittermann G, Voss P, Duttenhoefer F, Zimmerer R, Vach K, Metzger MC. The validity of surgical clips as radiographic markers for the tumour resection cavity in head and neck cancer treatment. *J. Craniomaxillofac. Surg.* Jul 2015;43(6):758-762.
17. Bittermann G, Wiedenmann N, Bunea A, et al. Clipping of tumour resection margins allows accurate target volume delineation in head and neck cancer adjuvant radiation therapy. *Radiother. Oncol.* Jul 2015;116(1):82-86.
18. Bittermann G, Wiedenmann N, Voss P, Zimmerer R, Duttenhoefer F, Metzger MC. Marking of tumor resection borders for improved radiation planning facilitates reduction of radiation dose to free flap reconstruction in head and neck cancer surgery. *J. Craniomaxillofac. Surg.* May 2015;43(4):567-573.
19. Rao AD, Feng Z, Shin EJ, et al. A Novel Absorbable Radiopaque Hydrogel Spacer to Separate the Head of the Pancreas and Duodenum in Radiation Therapy for Pancreatic Cancer. *Int. J. Radiat. Oncol. Biol. Phys.* Dec 1 2017;99(5):1111-1120.
20. Rao AD, Coquia S, De Jong R, et al. Effects of biodegradable hydrogel spacer injection on contralateral submandibular gland sparing in radiotherapy for head and neck cancers. *Radiother. Oncol.* Oct 3 2017.
21. Damato AL, Kassick M, Viswanathan AN. Rectum and bladder spacing in cervical cancer brachytherapy using a novel injectable hydrogel compound. *Brachytherapy.* Sep - Oct 2017;16(5):949-955.
22. Bair RJ, Bair E, Viswanathan AN. A radiopaque polymer hydrogel used as a fiducial marker in gynecologic-cancer patients receiving brachytherapy. *Brachytherapy.* Nov-Dec 2015;14(6):876-880.
23. Ferris MJ, Zhong J, Switchenko JM, et al. Brainstem dose is associated with patient-reported acute fatigue in head and neck cancer radiation therapy. *Radiother. Oncol.* Jan 2018;126(1):100-106.
24. Monroe AT, Reddy SC, Peddada AV. Dorsal vagal complex of the brainstem: conformal avoidance to reduce nausea. *Pract. Radiat. Oncol.* Jul-Aug 2014;4(4):267-271.
25. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. *Int. J. Radiat. Oncol. Biol. Phys.* Mar 1 2010;76(3 Suppl):S10-19.