University of Pennsylvania

A Single-arm Phase II Study of Post-Transoral Robotic Surgery (TORS) Alone to the Primary Tumor Site and Selective Neck Dissection (SND) Followed by Adjuvant Radiation Therapy (+/- Chemotherapy) to the Regional Nodes for Advanced Stage, Human Papilloma Virus (HPV) Positive, Oropharyngeal Cancer

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List of Abbreviations

Chemoradiotherapy	CTRT
External Beam Radiation Therapy	EBRT
Head and neck squamous cell carcinoma	HNSCC
Human Papilloma Virus	HPV
Intensity-modulated Radiation Therapy	IMRT
Lymphovascular Invasion	LVI
Perineural Invasion	PNI

Pencil-Beam Proton Radiation Therapy	PBRT
Quality of Life	QOL
Squamous Cell Carcinoma	SCCA
Transoral Robotic Surgery	TORS

Study Summary

Title	A Single-arm Phase II Study of Post-Transoral Robotic Surgery (TORS) Alone to the Primary Tumor Site and Selective Neck Dissection (SND) Followed by Adjuvant Radiation Therapy (+/- Chemotherapy) to the Regional Nodes for Advanced Stage, Human Papilloma Virus (HPV) Positive, Oropharyngeal Cancer
Short Title	Adjuvant Radiation Therapy Omitting Primary Tumor Bed in Resected HPV-positive SCCA of the Oropharynx
Protocol Number	
Phase	Single-arm phase II
Study Duration	1 year
Study Center(s)	Single-center
Objectives	**Primary:** To determine 2-year local (primary tumor site) control and toxicity rates in patients receiving adjuvant RT post-TORS, omitting the primary tumor bed, in patients with completely resected, HPV-positive SCCA of the oropharynx. To determine acute and long-term toxicity rates in patients receiving adjuvant RT post-TORS, omitting the primary tumor bed, in patients with completely resected, HPV-positive SCCA of the oropharynx. **Secondary:** To determine 2-year regional control, progression-free survival, metastasis-free survival, and overall survival. To determine differences in QOL between patients treated with intensity-modulated photon radiation therapy versus proton beam radiation therapy
Number of Subjects	60
Diagnosis and Main Inclusion Criteria	T1-2 N1-2 M0, stage III or IVa SCCA of the oropharynx, negative for PNI, negative surgical margins

Study Regimen	EBRT (via IMRT or PBRT) will be delivered to at-risk regional lymph nodes, per standard of care. This study will omit EBRT treatment of the primary tumor bed.
Statistical Methodology	This is a single-arm phase II study assessing the safety (evaluated as local control and toxicity) of omitting adjuvant RT to the primary tumor site for selected patients with HPV-positive SCCA of the oropharynx. The analysis will be stratified by type of RT — IMRT (photon) and PBRT (proton), with the patients distributed between strata in a 1:1 ratio. We will estimate the distributions of time to local recurrence and time to toxicity by the Kaplan-Meier curve, and two-year locoregional control proportion and proportions experiencing toxicities by 95% exact confidence intervals. We will compare mean values of health-related quality of life (HRQoL) measures between strata using linear statistical models.

1 Introduction

This is a single-arm, phase II study examining the safety of omitting postoperative RT to the primary tumor bed in completely resected patients with locally-advanced, HPV+ oropharynx cancer.

The primary objectives of the study will be to determine 2-year local (primary site) control at the primary tumor site, and to determine 2-year RT-associated toxicity (as measured by CTCAE, version 4.0 and patient-reported QOL).

Secondary objectives of this study include determining 2-year regional control, progression-free survival, metastasis-free survival, and overall survival. Differences between intensity-modulated radiation therapy and proton therapy with respect to disease-related outcome and toxicity/QOL will also serve as secondary objectives.

Background, Preliminary Data, and Significance

Standard options for advanced-stage, HPV+, oropharyngeal cancer include either definitive chemoradiation or surgery followed by adjuvant radiation (+/- chemotherapy). The approach using TORS for the primary tumor resection followed by staged SND and adjuvant RT to the primary tumor bed and bilateral neck nodes has been pioneered at the University of Pennsylvania (1, 2). Disease outcomes are generally favorable, with overall survival of 90% (3), and locoregional control of 95–100% with either organ preservation RT (4), or with the TORS-based approach (5, 6); however, treatment-related morbidity can be significant. Definitive chemoradiation can result in long-term feeding tube use in up to 20% of patients (7), while 1 out of 4 patients who receive post-op RT after TORS resection experience ulceration and tissue breakdown at the primary resection bed as a late consequential effect of severe, acute mucositis (8). Approaches to decrease toxicities are therefore warranted.

One potential approach may be to omit post-op RT to the primary resection bed. A study from our group of 30 patients with oropharynx cancer (T1-2 in 83%) treated with surgery alone (TORS + SND) who refused adjuvant RT revealed a local control of 97% with surgery alone (9), calling into question the need to radiate the primary tumor bed in such patients. We will therefore conduct a pilot study of TORS alone to the primary tumor and SND followed by adjuvant RT (+/- Chemotherapy) to the regional nodes. The decision to add concurrent chemotherapy to postoperative radiation will be based on current standards of care, which recommend the addition of chemotherapy for the presence of either nodal extracapsular extension or positive margins (10). Margin positivity is an exclusion criterion for this study; therefore, the only indication for concurrent chemotherapy for this phase II study would be for nodal extracapsular extension.

This study is the first of its kind exploring such an approach in this patient population, and if high rates of locoregional control are obtained with less toxicity, it would potentially represent a paradigm shift in how patients with locally-advanced oropharynx cancer are managed.

This study will allow for RT to be given with either IMRT or PBRT (decision to treat with IMRT vs. PBRT not based on clinical features, but rather, insurance approval). Our initial patient experience with pencil-beam proton therapy reveals significant decreases in doses to critical organs at risk with no differences in coverage of radiation dose to at-risk tumor sites. For example, doses delivered to the oral cavity have consistently been reduced 10-fold with proton therapy compared to IMRT, with the first 2 patients reporting no changes in taste sensation near the end of their proton course.

We expect robust accrual to this protocol, as the Department of Otolaryngology performs over 800 resections annually for head and neck cancer, and the Department of Radiation Oncology treats over 200 patients annually with head and neck cancer. The majority of the patients receiving radiation do so after TORS and SND. We expect that approximately 150 patients annually will be eligible to participate on this study. Of these patients, based on current experience, approximately half will end up receiving IMRT, and half receiving PBRT, based solely on patient insurance carrier approval/denial of request for proton therapy (patient are not randomized to IMRT vs. PBRT).

We will prospectively administer patient-reported questionnaires to evaluate toxicity and quality of life to all patients, representing the first direct comparison of photon versus proton therapy for patients receiving head and neck radiation, and may potentially help define the standard RT modality for such patients.

2 Study Objectives

2.1 Primary Objective

2.1.1 Determine 2-year local control with omission of primary tumor bed RT.

2.1.2 Determine 2-year toxicity, as measured per CTCAE, version 4.0 and patient-reported HRQoL.

2.2 Secondary Objectives

2.2.1 Determine 2-year regional control, progression-free survival, metastasis-free survival, and overall survival

2.2.2 Determine differences between IMRT and proton therapy with respect to disease-related outcomes and toxicity/QOL

3 Study Design

3.1 General Design

This is a single-arm phase II study of post-op RT in the setting of locally-advanced HPV(+) oropharynx cancer. Only patients with small volume primary site disease (T1 or T2), resected with negative margins (2 mm or greater), without PNI, will be eligible.

- Patients will undergo post-op RT (+/- chemotherapy) to 60-66 Gy, per established clinical guidelines (10-12)
- P16 positivity via immunohistochemistry will be used as a surrogate for HPV positivity (standard of care practice at Penn)
- Regional nodes will be included in the RT field, as per current practice standards
- The primary tumor bed will be excluded from the RT field
- Platinum-based chemotherapy will be required for patients with evidence of extracapsular extension, based on current clinical guidelines (10-12)

3.2 Primary Study Endpoints

- 2 year local control
- 2 year toxicity

3.3 Secondary Study Endpoints

- 2 year regional control
- 2 year progression-free survival
- 2 year metastasis-free survival
- 2 year overall survival
- Differences in toxicity/QOL between IMRT and PBRT

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

4.1.1 Patients ≥ 18 years old.

4.1.2 Histologically confirmed diagnosis of squamous cell carcinoma of the oropharynx, stage III or IVa, p16-positive on immunohistochemistry (determination of HPV status using p16 as surrogate is standard of care)

4.1.3 Pathologic T1 or T2 disease, resected with negative margins (≥ 2mm)

4.1.4 Pathologic N1,N2a, N2b, or N2c disease

4.1.5 ECOG Performance Status 0-1

4.1.6 Patients must sign an informed consent document that indicates they are aware of the investigational nature of the treatment in this protocol as well as the potential risks and benefits.

4.1.7 Ability to understand and the willingness to provide written informed consent.

4.2 Exclusion Criteria

4.2.1 Prior radiation therapy to the head and neck

4.2.2 Prior chemotherapy within the past 5 years

4.2.3 Presence of T3 or T4 disease

4.2.4 Presence of close (<2 mm) or positive margins

4.2.5 PNI on TORS resection of the primary cancer

4.2.6 LVI on TORS resection of the primary cancer

4.2.7 Presence of N0 disease in neck dissection

4.2.8 Presence of distant metastatic (M1) disease

4.2.7 Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, connective tissue disease or psychiatric illness/social situations that would limit compliance with study requirements.

4.3 Inclusion of Women and Minorities

The University of Pennsylvania Medical Center serves the metropolitan Philadelphia area, the surrounding suburban counties, southern New Jersey, and northern Delaware.

Inclusion of minorities: The University of Pennsylvania Cancer Center reports that minorities accounted for 14% of all patients (adult and pediatric) enrolled on therapeutic clinical trials. Furthermore, it is estimated that approximately 30% of cancer patients admitted to the Hospital of the University of Pennsylvania are minorities (source: University of Pennsylvania Cancer Center Grant). Female and male patients of all ethnic groups will be eligible for treatment in these protocols. Protocol accrual will be reviewed annually to include a determination of minority representation. An attempt will be made to enroll patients with larynx cancer in a distribution that matches the frequency of incident larynx cancer in the general population. The minority accrual estimates for our trial are based upon the total number of patients, the incidence rates of head and neck cancer, and estimates in the literature regarding minority accrual in clinical trials. A study by Tejeda and Brawley (13) found that the accrual of American cancer patients to NCI-sponsored

treatment trials paralleled the incident disease burden among minorities. A report by Sikora et al. (14) indicates the distribution of incident head and neck squamous cell carcinoma to be 81.8%, 21.1%, 11.9%, 5.2%, 3.7%, 0.3%, and 0.8% among whites, all minorities, blacks, Asians, Hispanics, others and unknowns, respectively. The Philadelphia metropolitan area does not have a large American Indian or Alaskan population; therefore, no patients are estimated for this group.

Inclusion of women: Recruitment of patients will be through the University of Pennsylvania Cancer Center, Department of Radiation Oncology. All patients meeting study requirements will be approached for participation without discrimination. According to Cancer Facts and Figures (2011) from the American Cancer Society (15), new cases of larynx cancer were divided approximately 4:1 among male and female patients. Based on these and the above minority data, we estimate the accrual distributions for this trial shown below:

Ethnic Category	Males	Females	Total
Hispanic or Latino	2	1	3
Not Hispanic or Latino	46	11	57
Ethnic Category Total of All Subjects	48	12	60
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	0	2
Native Hawaiian or other Pacific Islander	0	0	0
Black or African American	12	2	14
White	34	10	44
Racial Categories: Total of All Subjects	48	12	60

Proposed Outreach Programs

The University of Pennsylvania Cancer Center has developed a number of minority outreach strategies. These include development of relationships with local community organizations, presentations or distribution of materials to local groups regarding trials, advertisements in minority newspapers and magazines, and presentations to professional organizations. If under-accrual of minority subjects is determined to be a problem, we will employ these methods to improve accrual. We will also make an effort to educate radiotherapists, surgeons, and medical oncologists who are working within our network and who serve minority populations about this trial.

4.4 Subject Recruitment and Screening

Patients will be recruited for possible participation in this study when they have been referred to the Department of Radiation Oncology at Penn for post-TORS adjuvant radiation therapy (+/- chemotherapy). The radiation oncologist will discuss participation in this study. The patient will be given an opportunity to read the consent form, ask questions and have them answered to their

satisfaction by the investigator or sub- investigator. At that time, if the patient indicates willingness to participate, the consent is signed by the patient and the investigator or sub-investigator obtaining consent. An eligibility checklist will be completed by the CRC to verify patient eligibility based on the criteria outlined in Section 4.1 and Section 4.2 and a subject ID number will be issued.

4.5 Clinical Evaluation and Staging Criteria

- History and Physical Examination
- Laboratory studies: pregnancy tests for women of child bearing age or potential prior to simulation for radiation therapy. (an urine pregnancy test prior to any radiation exposure is standard of care in the Department of radiation Oncology) .
- Staging studies are to include a chest x-ray, chest CT, or FDG PET/CT scan to evaluate for systemic metastases, performed 3 months prior to study entry. (standard of care)

4.6 Off-Study Criteria

- Extraordinary Medical Circumstances. If at any time the constraints of this protocol are detrimental to the subject's health, the subject will be removed from protocol therapy. In this event, the reasons for withdrawal will be documented.

- Subject's refusal to continue treatment. In this event, the reasons for withdrawal will be documented.

- Patients may be taken off study at any time at the discretion of the Principal Investigator

- Every effort will be made to follow subjects off study for toxicity and disease-related outcome

4.7 Study Duration

With an estimated accrual of 67 subjects per year, it is anticipated that accrual will continue for approximately 1.0 years. We believe this to be a conservative estimate, given the following:

5 . Study Procedures

The Department of Otolaryngology performs over 800 resections annually for head and neck cancer, and the Department of Radiation Oncology treats over 200 patients annually with head and neck cancer. The majority of the patients receiving radiation do so after TORS and SND. We expect that approximately 150 patients annually will be eligible to participate on this study.

5.1 General study design

Sixty subjects will be enrolled on this single-arm Phase II study investigating the efficacy and safety of omitting postoperative RT to the primary tumor site in patients with locally-advanced (stage III or IVa) HPV+ oropharynx cancer who undergo TORS resection and neck dissection. Patients will be required to have a negative surgical margin (defined as 2mm or greater) after

resection of the primary site for a pathologic T1 or T2 cancer, with no evidence of perineural invasion.

Patients will be treated to the regional nodes, per current clinical standards, to a total dose of 60-66 Gy over 30-33 fractions, as determined by current clinical guidelines for postoperative radiation therapy (10-12). Both IMRT and PBRT will be allowed. Platinum-based chemotherapy will be delivered concurrently with RT, as clinically indicated for ECE (10-12).

Clinical, toxicity and QOL evaluations will be obtained at baseline (prior to RT), and completion of RT, and then at approximately 3, 6, 12, 18 and 24 months after completion of RT, during routine clinical follow-up appointments. Routine clinical follow-up will continue after this time point, at the discretion of the treating physicians.

Local recurrence will be defined as biopsy-proven recurrent squamous cell carcinoma at the original, primary tumor site.

Study Visit Schedule & Procedures

	*Baseline	End RT	**3mo. post RT	**6mo. post RT	**12mo. post RT	**18mo. post RT	**24mo. post RT
ICF	x						
Eligibility	x						
PE	x	x	x	x	x	x	x
QOL form	x	x	x	x	x	x	x
Tox. Assessment		x	x	x	x	x	x

*prior to RT ** approximately

5.2 Chemotherapy Administration

See above in section 5.1. Standard indications for the use of chemotherapy will be applied, as no part of this study will be examining any "off-label" uses of chemotherapy (including cetuximab, which is off-label in the adjuvant setting).

5.3 Radiation Therapy

Simulation for treatment is required. CT-based treatment planning is required. Treatment with either IMRT or PBRT is allowed. All fields will be treated every session. Interruptions in therapy should be discussed with the principal investigator but will be instituted at the discretion of the attending radiation oncologist.

Dose calculation should be performed using inhomogeneity corrections to account for differences in tissue density across the head and neck region. The total dose to regional lymph nodes will be 60-66 Gy to high-risk regions over 30-33 fractions, and 54 Gy to low-risk regions over 30 fractions. The primary tumor bed will be excluded from receiving high-dose radiation. Treatment will be continuous, 5 days per week for 6-7 consecutive weeks.

5.4 Study Visit Schedule

Please see above in section 5.1. Patients will be followed on study for a period of approximately 2 years after completion of RT, after which time, routine follow-up will continue "off-study" per the discretion of the treating physicians. Patients will be followed for short and long term RT-associated toxicity and local and /or regional recurrence.

6 Statistical Plan

Study design

A total of 60 patients will be accrued over a total of 1.0 year. Patients will be followed on study for a period of approximately 2 years after completion of RT. After this time, patients will continue to be seen in follow-up by their treating physicians, per physician discretion according to physician and institutional practices.

Patients will be enrolled into two non-randomized treatment strata: IMRT (photon) and PBRT (proton). We anticipate enrolling approximately 30 subjects in each stratum given our recent experience with patterns of insurance approval for PBRT versus IMRT (please see rationale described above in the introduction regarding IMRT vs. PBRT. Patients will not be randomized to IMRT vs. PBRT, but rather the decision to treat with one modality versus another is based on insurance carrier approval status. .

Data analysis plan

The primary objectives of the study are to estimate the 2-year local (primary site) control rate at the primary tumor site, and 2-year rates of RT-associated toxicities (as measured by CTCAE, version 4.0 and patient-reported QOL). We will estimate the distributions of time of loss of local control and time to RT-associated toxicity by exact 95% confidence intervals. We will compare the distributions of time to local recurrence and time to toxicity between strata by the logrank test.

Secondary objectives include determining 2-year regional control, progression-free survival (PFS), metastasis-free survival (MFS), and overall survival (OS). Differences between intensity-modulated radiation therapy and proton therapy with respect to disease-related outcomes and toxicity/HRQoL will also serve as secondary objectives. We will summarize data on regional control, PFS, MFS and OS using Kaplan-Meier curves; estimate proportions of toxicities by 95% exact confidence intervals; and make comparisons between treatment strata by the logrank test.

HRQoL evaluations will be obtained at baseline and completion of RT, and then approximately at 3, 6, 12, 18 and 24 months after completion of RT. We will estimate mixed linear models predicting HRQoL from treatment stratum, demographic and baseline clinical criteria. It is necessary to adjust for these factors to reduce potential confounding bias, as the treatments will not be randomized.

Sample size justification

With 30 patients per stratum, we will have 78% power to detect a difference in failure of 2-year local control, assuming a null rate of 5% and an alternative rate of 17.5%, using a one-tailed exact binomial test with type I error rate 10%.

Also with 30 patients per stratum, we will have 90% power to detect a difference in stratum means of HRQoL outcomes, provided that the effect size (absolute difference in means divided by common standard deviation) is larger than 0.86. This calculation assumes a two-tailed Student *t* test with type I error rate 5%.

Given that the decision to treat with IMRT vs PBRT is not randomized, but rather based on current insurance approval/denial patterns, we expect there to be an approximate 1:1 ratio of IMRT:PBRT; however, this study will not obligate 1:1 IMRT:PBRT. The comparison of IMRT to PBRT is a secondary objective of the study, and inability to populate the strata in a 1:1 ratio will not impede evaluation of the data for the primary objective. If recruitment goals are not met for each stratum, adjustments will be made to the data analysis as it pertains to the secondary objective of comparing IMRT to PBRT.

Interim analysis

We anticipate enrolling roughly 60 subjects over a period of 12 months, following each subject for up to 24 months. Because no patient will have reached the 24-month follow-up limit by the time enrollment ends, interim safety analyses will rely on model-based estimates of the rate of local recurrence using available time-to-event data. We will conduct an interim analysis for safety at the one-year mark (one year after completion of enrollment), when the median follow-up is 1.5 years (minimum = 1 and maximum = 2 years). We will fit an exponential model to the data on time to local recurrence. We will estimate the overall exponential hazard rate, comparing it to the null hazard rate of 0.00214 (predicting 5% recurrence at 24 months) in a two-tailed test with type I error rate 2.5% (to adjust for multiplicity). Should the estimated hazard rate significantly exceed the null rate, we will consider halting the trial for concern about safety. We will conduct the test when follow-up is complete (two years after completion of enrollment), again at the 2.5% type I error rate.

7 Safety and Adverse Events

7.1 Definitions

Adverse events (AE) and Serious Adverse Events (SAE) will use the descriptions and grading scales found in the revised **NCI Common Terminology Criteria for Adverse Events (CTCAE)**. This study will utilize the CTCAE v4.0 for adverse event reporting. All appropriate treatment areas will have access to a copy of the CTCAE v4.0 and a copy can be accessed at the web site: http://ctep.cancer.gov/.

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. 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)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

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. Concurrent 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 <u>any one of the following</u> 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.

Expedited Adverse Event Reporting

Common Toxicity Criteria

Toxicity will be evaluated with the NCI Common Toxicity Criteria (CTCAE) v. 4.0.

Serious Adverse Events

A SAE is defined as any of the following:
- Fatal or life-threatening (real risk of dying) event
- Requires or prolong hospitalization
- Causes persistent or significant disability/incapacity
- Results in a birth defect or congenital anomaly
- Causes cancer

All hospitalizations or prolongation of existing hospitalization for medical events regardless of phase of study, expected or unexpected attributions are SAE's.

Serious, unexpected drug-related adverse events will be reported to the University of Pennsylvania IRB, and the University of Pennsylvania Cancer Center Data and Safety Monitoring Committee (DSMC) using the expedited reporting guidelines as is required by each board.

The toxicities that develop during the standard chemotherapy portion of this trial will not require reporting in an expedited manner.

DSMC Adverse Event reporting requirements

All events meeting the DSMC reporting requirements must be entered into the mandatory Velos AE/SAE form. A study CRF does not replace the ACC central reporting form.

Once an event is entered, please send an e-mail alert to the current designee at the DCOM for events as follows:

1. All grade 3 or higher events (AE or SAE) within five business days of knowledge.
2. All unexpected deaths within 24 hours of knowledge.
3. All others deaths within 30 days of knowledge. Deaths of subjects off-study for greater than 30 days from the last study treatment/intervention are not reportable with the following exceptions:
    a) Deaths on in-house gene or cellular-therapies
    b) Deaths on in-house studies utilizing on-campus manufacturing of the study agent(s) or components of the study agent(s)
    c) Deaths on first-in-human studies

7.2 Stopping Rules

As noted in section 6.0, based on results of an interim analysis for safety at the one-year mark, we will consider halting the trial for safety if the estimated hazard rate significantly exceeds the null rate.

8 Data Handling and Record Keeping

8.1 Records

All patients must have a signed Informed Consent Form and an On-study (confirmation of eligibility) form filled out and signed by a participating investigator prior to entering the study.

Confidential research charts will be kept in locked cabinets at each participating institution. Subjects will be assigned a study number at the time of study enrollment. This study number and not the subject's name will be used on all case report forms.

HIPAA Compliance:

Patients will be asked to read and sign a separate consent form acknowledging the uses and disclosures of protected health information (PHI) in this study as required by The Health Insurance Portability and Accountability Act (HIPAA). PHI will not be shared with any outside institution except as required by law. Any reporting of the results of this study will be done only with de-identified patient data. Confidentiality will be protected as outlined below.

- Each subject will sign a study informed consent and a study-specific HIPAA authorization form prior to surgery.
- Each subject will be assigned a study number. All research-related material (to include specimens for research) will be labeled with the subject study number and the subject's initials.
- A list of the subject names with the associated subject numbers will be maintained in a locked cabinet and computer by the principal investigator and study coordinator.
- All research subject records will be kept in a study chart.
- An electronic database will be maintained. No subject names will be used in this database. Study numbers will be used. Only data which constitutes a limited data set (as defined by the University of Pennsylvania Health System in the HIPAA Privacy Education website) will be used.

8.2 Data Entry

All patients must have a signed Informed Consent Form and an On-study (confirmation of eligibility) form filled out and signed by a participating investigator prior to entering the study.

An electronic case report forms (eCRFs) will be used to standardize data keeping and allow entry to a computerized data base (Velos).

8.3 Flow of Subject Data

Study entry: Each patient will be screened and evaluated for this study based upon the inclusion and exclusion criteria. If a patient is found to be potentially eligible for the study the patient will be approached for participation in this study, and if they are interested, they will be asked to sign an informed consent form. An eligibility checklist will be completed and signed by the PI verifying eligibility. The patient will be assigned a study number. A list of the subjects with the assigned study numbers will be kept in a locked cabinet with the study charts as well as on a confidential computer file in the Department of Radiation Oncology, University of Pennsylvania. The study coordinator and principal investigator will maintain the locked cabinet. All study forms: eligibility forms, on study forms, case report forms (CRF), toxicity forms, and data entry forms will be coded with the subject's study number to protect subject confidentiality.

Treatment: After study enrollment, the subject will undergo treatment planning for radiotherapy as per standard clinical care. The principal or a co-investigator will fill out a radiotherapy prescription form as per routine clinical care. A hard copy of the radiotherapy prescription form, radiotherapy treatment plan, and dose-volume histograms will be placed in the subject's study chart.

Follow-up: The clinical status of the subjects will be recorded on a flow sheet and on the CRF and maintained in the subject's study chart. QOL forms and toxicity grading will be performed at baseline, at end of treatment, at approximately 3, 6, and 12, 18, and 24 months after treatment. At approximately 24 months after completion of RT, the subject will be considered "off-study", but will continue routine clinical follow-up as per routine clinical guidelines.

9 Data and Safety Monitoring Plan

9.1 Overview

This study will be audited by the ACC Department of Compliance and Monitoring on behalf of the Data and Safety Monitoring Committee (DSMC). The investigators on this study are responsible for the continuous, close monitoring of subjects enrolled on this trial.

9.2 Study Audits

The study has been designated high risk by the CTSRMC using the criteria defined in the NCI approved Institutional Data and safety Monitoring Plan (DSMP). Risk is not synonymous with the intervention. High risk studies will be audited by the DOCM on behalf of the DSMC in accordance with the DSMP. The DSMC reserves the right to modify auditing requirements of this study at any time.

9.3 Study Monitoring

A Medical Monitor, Bruce J. Giantonio, MD, FACP, Associate Professor of Medicine, who is not directly involved in this trial and is not collaborating with the Sponsor-investigator in any other trials, has been selected for this trial. The Medical Monitor will review adverse events, safety data, and activity data observed in the ongoing clinical trial. The Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported, and

may recommend suspension or termination of the trial. Meetings with the Medical Monitor will occur biannually or more frequently if necessary. The meetings will take place in person or via telephone. The minutes of the PI and Medical Monitor discussion along with the agenda will be maintained in the regulatory binder. A report from the Medical Monitor following each review will be sent to the DSMC within 10 business days of study team receipt.

The Principal Investigator or his/her designee of the trial will present to the Medical Monitor all adverse events observed in patients, any activity data obtained, and whether those data invoked any stopping criteria in the clinical protocol. Adverse event reporting will follow the NCI guidelines. Results of the data from toxicology or other animal studies that are relevant will be discussed. Other information related to the safety and efficacy of the clinical study will be discussed. This includes information of similar investigational materials used in different studies.

Definitions Exceptions and Deviations

Exception

A one time, **intentional** action or process that departs from the IRB and CTSRMC approved study protocol, intended for **one** occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, **advance** documented IRB and DSMC approval is required. No exceptions to eligibility will be requested.

- For exceptions on Industry or Cooperative group sponsored protocols, written approval must be obtained from the Sponsor prior to submitting your exception request to the DSMC.
- For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the DSMC.

Deviation

A one time, **unintentional** action or process that departs from the IRB and DSMC approved study protocol, involving one incident and **identified retrospectively**, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the DSMC within 5 business days and the IRB within 10 business days.

10 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 Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal

prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. 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.

11 Study Finances

11.1 Funding Source

This study is financed through the Department of Radiation Oncology at the University of Pennsylvania, via an intra-departmental pilot funding grant.

11.2 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 University of Pennsylvania investigators will follow the University conflict of interest policy.

12 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor (PI). Any investigator involved with this study is obligated to provide the sponsor (PI) with complete test results and all data derived from the study.

13 References:

1. Weinstein, G.S., O'Malley, B.W., Jr., Cohen, M.A., and Quon, H. 2010. Transoral robotic surgery for advanced oropharyngeal carcinoma. Arch Otolaryngol Head Neck Surg 136:1079-1085.

2. Weinstein, G.S., Quon, H., O'Malley, B.W., Jr., Kim, G.G., and Cohen, M.A. 2010. Selective neck dissection and deintensified postoperative radiation and chemotherapy for oropharyngeal cancer: a subset analysis of the University of Pennsylvania transoral robotic surgery trial. Laryngoscope 120:1749-1755.

3. Ang, K.K., Harris, J., Wheeler, R., Weber, R., Rosenthal, D.I., Nguyen-Tan, P.F., Westra, W.H., Chung, C.H., Jordan, R.C., Lu, C., et al. 2010. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363:24-35.

4. O'Sullivan, B., Huang, S.H., Siu, L.L., Waldron, J., Zhao, H., Perez-Ordonez, B., Weinreb, I., Kim, J., Ringash, J., Bayley, A., et al. 2013. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol 31:543-550.

5. Cohen, M.A., Weinstein, G.S., O'Malley, B.W., Jr., Feldman, M., and Quon, H. 2011. Transoral robotic surgery and human papillomavirus status: Oncologic results. Head Neck 33:573-580.

6. Quon, H., Cohen, M.A., Montone, K.T., Ziober, A.F., Wang, L.P., Weinstein, G.S., and O'Malley, B.W., Jr. 2013. Transoral robotic surgery and adjuvant therapy for oropharyngeal carcinomas and the influence of p16 INK4a on treatment outcomes. Laryngoscope 123:635-640.

7. Ingle, C.J., Yip, K., Caskie, V., Dyson, C., Ford, A., and Scrase, C.D. 2010. Intensity modulated radiotherapy (IMRT) in the management of locally advanced oropharyngeal squamous cell carcinomata (SCC): disease control and functional outcome using the therapy outcome measure (TOM) score--report from a single U.K. institution. Head Neck Oncol 2:28.

8. Lukens JN, L.A., Grover S, McMenamin EM, Weinstein GS, O'Malley BW, and Quon H. 2012. Late Consequential Surgical Bed Soft-tissue Necrosis in Advanced Oropharyngeal Squamous Cell Carcinomas (OP-SCC) Treated With Transoral Robotic Surgery (TORS) and Postoperative Radiation(PORT). Int J Radiat Oncol Biol Phys 84:S62.

9. Weinstein, G.S., Quon, H., Newman, H.J., Chalian, J.A., Malloy, K., Lin, A., Desai, A., Livolsi, V.A., Montone, K.T., Cohen, K.R., et al. 2012. Transoral robotic surgery alone for oropharyngeal cancer: an analysis of local control. Arch Otolaryngol Head Neck Surg 138:628-634.

10. Bernier, J., Cooper, J.S., Pajak, T.F., van Glabbeke, M., Bourhis, J., Forastiere, A., Ozsahin, E.M., Jacobs, J.R., Jassem, J., Ang, K.K., et al. 2005. Defining risk levels in locally advanced head and neck cancers: a comparative

analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 27:843-850.

11. Bernier, J., Domenge, C., Ozsahin, M., Matuszewska, K., Lefebvre, J.L., Greiner, R.H., Giralt, J., Maingon, P., Rolland, F., Bolla, M., et al. 2004. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 350:1945-1952.

12. Cooper, J.S., Pajak, T.F., Forastiere, A.A., Jacobs, J., Campbell, B.H., Saxman, S.B., Kish, J.A., Kim, H.E., Cmelak, A.J., Rotman, M., et al. 2004. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 350:1937-1944.

13. Tejeda, H.A., Green, S.B., Trimble, E.L., Ford, L., High, J.L., Ungerleider, R.S., Friedman, M.A., and Brawley, O.W. 1996. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. J Natl Cancer Inst 88:812-816.

14. Sikora, A.G., Toniolo, P., and DeLacure, M.D. 2004. The changing demographics of head and neck squamous cell carcinoma in the United States. Laryngoscope 114:1915-1923.

15. Society, A.C. 2011. Cancer Facts and Figures 2011.