The Sinai Robotic Surgery Trial in HPV Positive Oropharyngeal Squamous Cell Carcinoma (SCCA) (SIRS TRIAL)
Dr. Raymond Chai
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The Sinai Robotic Surgery Trial in HPV Positive Oropharyngeal SCCA
SIRS Trial

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1.0 INTRODUCTION

Study Design

Non-randomized Phase II de-escalation clinical trial to establish recurrence rates, site of recurrence, survival and quality of life outcomes for early T-stage HPV positive oropharyngeal SCCA treated with upfront surgery and reduced dose radiotherapy. Eligible, consented and registered patients will undergo transoral robotic surgery and selective neck dissection. After pathologic evaluation, patients with early stage disease as defined below will be placed into surveillance protocol as outlined or assigned to adjuvant therapy, depending on risk factors. Patients with intermediate risk factors will receive postoperative radiotherapy alone (5000 cGy). Patients with poor prognostic features will receive concurrent chemoradiotherapy (5600 cGy) with weekly cisplatin. Patients taken off study (based on Section 9.2 "Criteria from Removal of Study") will be followed for survival until the study ends. Any adverse events occurring thereafter in these patients will not be considered related to the study and will not be tracked or reported.

1.1 Primary Objectives

1.1.1 To determine the rate of local regional control (LRC) at 5 years in patients with early and intermediate stage HPV related oropharynx cancer treated with surgery alone.

1.1.2 To determine the rate of progression free survival (PFS) at 5 years in patients with early and intermediate stage HPV related oropharynx cancer treated with surgery alone.

1.1.3 To determine overall survival (OS) at 5 years in patients with early and intermediate stage HPV related oropharynx cancer treated with surgery alone.

1.1.4 To determine the rate of local regional control (LRC) at 3 years in patients with HPV related oropharynx cancer treated with a de-intensified adjuvant protocol.

1.1.5 To determine the rate of progression free survival (PFS) at 3 years in patients with HPV related oropharynx cancer treated with a de-intensified adjuvant protocol.

1.1.6 To determine overall survival (OS) at 3 years in patients with HPV related oropharynx cancer treated with a de-intensified adjuvant protocol.

1.1.7 To determine the rate of PFS (Ultimate Disease Control – UDC) and of OAS after secondary therapy for patients treated with surgery only who have local regional relapse at 5 years

1.1.8 To determine the rate of PFS (UDC) and OAS after secondary therapy for patients who relapse with distant disease after surgery only

1.1.9 To quantify the quality of life of patients treated with this protocol at 3 years

1.2 Secondary Objectives

Effective Date: 2/14/2022
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1.2.1 To determine the rate of local-regional control (LRC) over 5 years in patients with HPV related oropharynx cancer treated with a de-intensified adjuvant protocol.

1.2.2 To determine the rate of progression free survival (PFS) over 5 years in patients with HPV related oropharynx cancer treated with a de-intensified adjuvant protocol.

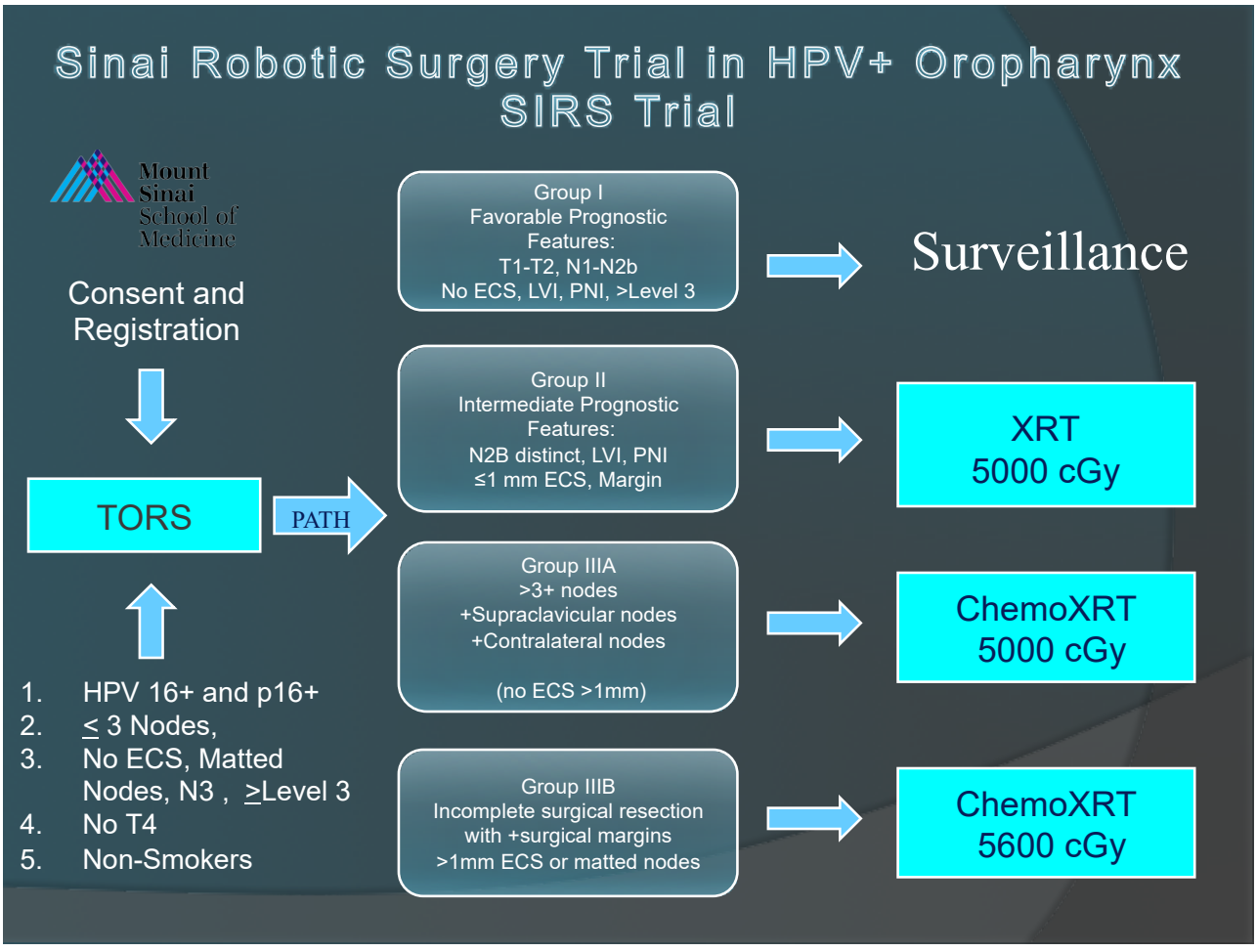
1.2.3 To determine the rate of Overall Survival (OS) at 5 years in patients with HPV related oropharynx cancer treated with a de-intensified adjuvant protocol.

1.2.4 To discover potential biomarkers predictive of local regional and distant failure.

1.2.5 To establish a tumor tissue, germline DNA and plasma bank for future studies of the protocol selected and treated populations.

1.2.6 To quantify the quality of life of patients treated with this protocol at 5 years

1.3 Treatment Schema



2 BACKGROUND

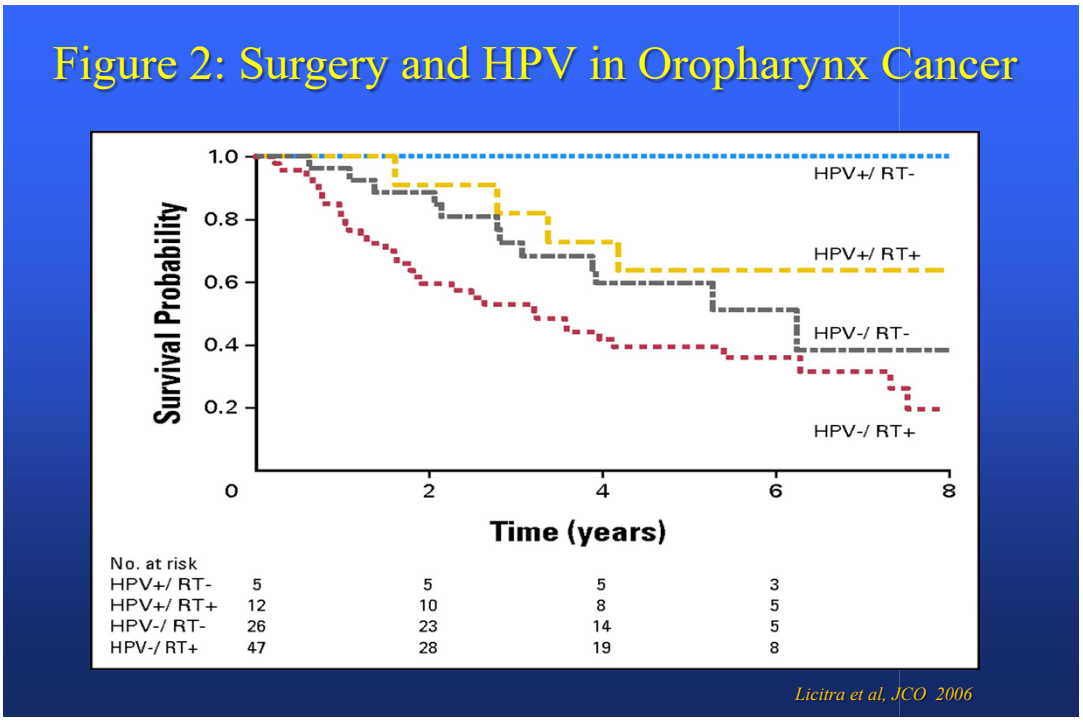
2.1 HPV – Related Oropharynx Cancer

The demographics and excellent prognosis of HPV related oropharyngeal squamous cell cancer (HPVOPC) has called into question the rational for aggressive concurrent chemoradiotherapy for intermediate stage HPV related oropharyngeal SCCA. Epidemiologic evidence has revealed a significant increase in the incidence of oropharynx cancer (OPC) in North America and Europe. Molecular studies of oropharyngeal tumors have revealed that this increase is due to an increase in the incidence of tumors which contain Human Papillomavirus (HPV), most specifically HPV16 and for which there is direct evidence that HPV16 is the molecular cause mechanistically driving the development and viability of the cancer cells. HPV-related oropharynx cancer (HPVOPC) now accounts for almost 60% of OPC seen in the USA and an increasing fraction of these malignancies in Europe [1-3].

Based on the existing data from clinical trials and patient material through retrospective analysis, it is now understood that there are two dominant carcinogenic and biologic pathways where oropharynx cancer develops: Environmentally related OPC (EROPC), caused principally by smoking and alcohol, and HPV related OPC (HPVOPC). The relative paucity of genetic changes in HPV-positive head and neck cancer is in sharp contrast to what is observed in HPV-negative head and neck cancer and is mechanistically related to the direct effects of viral proteins in inactivating regulators of key cellular processes[4-7]. In the typical EROPC, mutations and deletions of p53 have very frequently been demonstrated. In contrast, HPVOPC do not contain p53 mutations. Similarly, p16 in the Rb pathway of cell growth is frequently mutated, deleted or silenced in EROPC but is often up-regulated in HPVOPC as a consequence of viral alterations in Rb function. Up regulation of p16 can be seen in up to 20% of non-HPV related cancers including other sites in the head and neck, however, p16 appears to be up-regulated in >95% of HPVOPC making it a good screening tool[8].

Studies in unselected patients suggest that patients with HPVOPC have a better prognosis than patients with HPV-negative, predominantly environmentally related OPC (EROPC) [9-11]. In one retrospective study of radiotherapy as sole therapy from Denmark, p16 was used as a surrogate for HPV. In this randomized study of a radiation sensitizer, the control arm of radiotherapy only was analyzed for p16 expression. There was 62% 5-year survival among p16+ patients compared to 26% in p16- patients. LRC was 58% vs. 28%, respectively (Figure 1). A significant fraction of p16+ tumors were not of oropharyngeal origin [12].

A second trial, Licitra et al retrospectively evaluated surgery in the HPV positive and negative cases. Surgery alone was effective therapy for a small group of patients. Patients who underwent surgery as a single modality were spared the long term consequences of radiation. However, selection criteria for surgery alone was not well explained[13].



Recently, results of retrospective analyses of survival and HPV status were reported from two International Phase III trials comparing chemoradiotherapy (CRT) regimens in locally advanced HNC. In both trials there were insufficient patient numbers to report a treatment effect; however the impact of HPV on survival, regardless of therapeutic assignment, was highly significant [8,14]. The RTOG (R) 01-29 has the most extensive data and retrospectively analyzed on 323 out of 433 OPC cases. In RTOG 01-29, patients were randomized between CRT with accelerated fractionation with cisplatin versus regular fractionation and cisplatin. The overall survival (OS) and progression free survival (PFS) at three years were 82%and 74% in HPVOPC compared to 57% and 43% for EROPC, respectively. A careful analysis of failure and death revealed a LRF rate of 14% versus 35% for HPVOPC versus EROPC and a second primary tumor rate of 6% versus 15% respectively. Non-cancer deaths also occurred in 9% and 19% respectively. All these data support a better outcome for HPVOPC, much of which is found in improved LRC, some of which is explained by less co-morbidity.

2.2 Transoral Surgery and HPV Related Oropharynx Cancer

Robotic surgery has been widely applied in the medical field and the FDA has approved several applications including: laparoscopic surgery (2000), prostate surgery (2001), thorascopic surgery (2001), mitral valve surgery (2002). More recently, investigators began exploring the feasibility of transoral robotic surgery in the oropharynx. Hockstein et al. studied the use of the robot in an airway mannequin and determined that it was feasible to access both the oropharynx and the larynx using the Da Vinci robot and both the 5 mm and 8mm instrument arms.[15] In a subsequent report, the same group demonstrated that several surgical procedures including a tongue base resection and several laryngeal procedures were technically feasible using the Da Vinci robot system.[16] Hockstein further demonstrated that effective hemostasis of the extensive pharyngeal vasculature was achievable using a combination of cautery and robotically applied hemoclips to control the lingual artery.[17]

These pre-clinical studies conducted by Hockstein and the University of Pennsylvania group led the way for several preliminary clinical cohort studies. O'Malley et al. described the first series of TORS tongue base resections for squamous cell carcinoma.[18] In this report, he outlined the surgical technique and advantages and disadvantages of the multiple retraction systems used during transoral tongue base surgery. All three patients were eating a full diet within 6 weeks. Weinstein et al. subsequently reported the use of the robot for supraglottic surgery with a series of 3 patients undergoing robotic supraglottic laryngectomy.[19] Solares et al. followed shortly thereafter with a report of a supraglottic laryngectomy performed using a CO2 laser.[20] The University of Pennsylvania group also reported the first series of TORS cases for radical tonsillectomy on 27 patients.[21] The technical aspects of the surgery were described to allow for negative margin resection of tonsil malignancies while protecting the internal carotid artery in the parapharyngeal space. In this early series, all patients had gastrostomy tubes inserted prophylactically and one patient had planned tracheostomy. An additional patient had unexpected tracheostomy following exacerbation of pre-existing obstructive sleep apnea. The surgical complication rate was 19% including one mucosal hemorrhage requiring a return to the operating room, one tracheostomy, two patients developed trismus, and one patient developed hypernasality requiring an outpatient procedure for correction. Genden et al. and the Mount Sinai group published their institutional experience with their first 20 transoral robotic surgery cases.[22] Two cases were aborted due to inadequate access and the remaining 18 cases consisted of 7 tonsil lesions, 4 tongue base lesions, 4 supraglottic lesions, 2 parapharyngeal lesions and 1 palate lesion. Patients did not require prophylactic gastrostomy tubes, and oral diet was achieved on 1.4 days after surgery on average. Patients were discharged on average 1.7 days after surgery.[23] These investigations lead to FDA approval of transoral robotic surgery in 2009.

Functional Outcomes

Proponents of transoral robotics surgery for oropharynx cancer contend that it offers improved functional outcomes when compared to non-surgical treatment with radiation therapy with or without chemotherapy. Many of the functional limitations incurred by chemoradiotherapy are related to long term toxicities. A recent retrospective analysis of three RTOG trials suggested that the rate of severe late toxicities in patients receiving chemoradiotherapy is 43% for all subjects, and 35% for patients with oropharyngeal cancer.[24] This group defined late toxicities as grade 3 or 4 pharyngeal/laryngeal toxicity, feeding tube dependence at 2 or more years from treatment, and/or treatment related death (grade 5 toxicity). Another prospective study of 104 patients (72 oropharyngeal cancers) found that 26.4% of patients are feeding tube dependent at one year, and 13.8% were tracheotomy dependent (although less commonly for oropharyngeal cancers).[25] These numbers are considerably better in modern practice, and only 5-12% of patients remain PEG dependent in more recent studies. In patients undergoing TORS and selective neck dissection, pathologic data can provide staging information that may allow for tailoring treatment to the individual and obviate the need for unnecessary toxic adjuvant treatments. Additionally, patients with unfavorable pathologic criteria are identified and more intense adjuvant therapy may be applied more appropriately.

Several studies report favorable swallowing outcomes using TORS for resection of oropharyngeal cancers.[21,22,26-29] Genden et al. reported all patients (n=20) tolerated an oral diet at a mean 1.4 days after surgery without any patients requiring gastrostomy tubes, in patients who did not receive adjuvant CCRT.[22] Iseli et al. performed TORS on 54 patients, and 83% of their patients were tolerating a diet within 14 days, 17% required a feeding tube at 12 months follow-up, and 5.6% of patients demonstrated signs or symptoms of aspiration.[29] Moore et al. performed TORS on 45 patients, and 82% of patients were tolerating an oral diet by the first post-operative visit. Seventeen percent of patients required a feeding tube, but none required assistance with feeding at one year follow-up.[28] Hurtuk et al also described an early return to oral diet with all 54 patients in their study tolerating oral diet on the day of surgery.[27] They reported, 20% of their patients requiring feeding tubes mainly during adjuvant therapy. In these studies, tracheostomy rates varied from 0-31% of patients requiring temporary tracheostomy tubes, more commonly for supraglottic or laryngeal malignancies.[21,22,28,29] However, the majority of patients were decannulated within two weeks and no patients required tracheotomy tubes at one year follow-up.

Quality of Life

Patient reported quality of life may be the next most important outcome besides survival and in many instances patients are willing to trade-off a longer life for a better quality of life. Treatment for cancer often entails some negative effects on quality of life during the treatment period which may improve over time. Leonhardt et al. prospectively administered the Performance Status Scale, a disease-specific questionnaire, and the SF-8, a generic questionnaire, to 34 patients with TORS surgery and followed these patients for a year.[30] They observed that the swallowing domains in the PSS, eating and diet, suffered and experienced significant decreases which returned to normal at the 1 year time point. The speech domain, however, was significantly reduced at both the 6 month and the 1 year time-points. They also noted that patients who had TORS with chemoradiation had significantly lower swallowing scores compared to those without. Genden et al. performed a case-control study to compare quality of life for patients undergoing TORS compared to those undergoing primary chemoradiotherapy. In the swallowing domains, eating and diet, TORS patients had significantly better scores immediately post-treatment (72 vs. 43; p=0.008 and 43 vs. 25; p=0.01).[31] While TORS patients had a return to baseline in all domains at 12 months, patients who had chemoradiotherapy did not have a return to baseline in the diet domain.

Oncologic Outcomes

The retrospective oncologic outcomes from TORS surgery for oropharyngeal cancer are slowly emerging, and early outcomes are promising. Recent studies have reported local failure rates which varied between 0-3% with median follow-up rates ranging from 18 months to two years.[26,31-33] Regional recurrence rates in the same studies varied between 2-8%, while distant disease was identified in 1-9% of patients.[26,31-33] Eighteen month overall survival was 90% in one study[31], and two-year overall survival was 82% and 80.6% in two other studies.[26,32] While many investigations include large proportions of HPV+ oropharyngeal malignancies, Cohen et. al. stratified survival by HPV status and there were no differences with an overall survival of 81% in the HPV+ group and 80% in the HPV-. Two year disease-specific survival rates were 90% and 92.6%, respectively .[26,32] Meanwhile 18 month recurrence free survival rates were 78% and two year rates were 79% and 86.3% respectively.[26,32,33] These early figures compared favorably to existing reports of oropharyngeal cancer treated with chemoradiotherapy.[34-38] While patients who receive concurrent chemoradiotherapy can be stratified based on HPV and smoking status into a de-intensification or intensification regimens, staging information regarding their disease is lost. Furthermore, patients treated non-surgically require high-dose radiation to definitively treat the primary tumor and metastatic cervical nodes. There is definitive evidence that radiation effects on critical structures such as the pharyngeal constrictors are dose dependent and reduced dosage may reduce the risk of chronic dysphagia, feeding tube dependence, and aspiration risk.[39-42] By physically removing tumor, one can theoretically offer a lower or dose or entirely eliminate primary radiation reserving it for salvage and confer better swallowing and QOL outcomes.

Following the data published by Ang et al. demonstrating that survival and local regional control is better amongst HPV positive patients, new studies are underway to evaluate the role of de-intensification of therapy.[43] The Easter Cooperative Oncology Group (ECOG) and the Radiation Therapy Oncology Group (RTOG) both have studies investigating de-intensified therapy. The former group is investigating the role of induction therapy with dose-reduced radiation while the latter group is conducting a phase III randomized controlled trial comparing standard chemoradiation with cisplatin to radiation and cetuximab in HPV positive patients.

In addition, more recent data has prompted changes in the AJCC staging system for HPV related oropharyngeal squamous cell carcinoma.[44] This data has indicated that the prognostic impact of the number of cervical lymph nodes appears less important than previously realized. This has prompted the addition of a cutoff group of >6 nodes (as proposed in the new AJCC staging system, see SIRS Groups IIIA,IIIB) for a marker for more advanced disease, thereby warranting the addition of chemotherapy. In addition, this proposed staging system which will be implemented in 2018 has now been validated by analysis of additional

cohorts.[45,46] Additional data indicates a low rate of contralateral node failure in this population further supporting an upfront surgical approach in order to spare patients uncessesary adjuvant radiation.[47]

Amidst these trials there is a clear need to study the use of surgery alone to replace radiation for local regional control, reserving "salvage" chemoradiotherapy for local regional failure and sparing a large fraction of patients the morbidity and mortality of radiotherapy.

2.3 Rationale for Single Modality Treatment of Early stage HPV related OPSCC

In general, patients with HPVOPC are young and will live for prolonged periods. They are at high risk for long-term toxicity and mortality from therapy[24]. While the long-term consequences of chemotherapy for head and neck cancer are relatively constrained, high-dose radiotherapy (RT) and chemoradiotherapy substantially impact on local tissues and organ function and result in a significant rate of late mortality and morbidity in patients[48-51]. Studies are now being designed to reduce the impact of RT and CRT for patients.

There are currently few trials examining the role of de-escalation using surgery alone in early T-stage HPV related disease or reduced radiotherapy in intermediate risk patients. New surgical techniques have broadened the range of patients capable of achieving a complete resection and the functional outcomes in such patients. Furthermore, the sensitivity of HPVOPC to chemotherapy and radiotherapy raise the possibility that delayed or salvage treatment in early stage patients would be highly effective, would result in similar survival outcomes and could be applied to a much smaller population then current standards call for. Looked at from a different perspective, the need for post-operative radiotherapy in this younger, HPV+ and more functional population have not been validated in clinical trials to date.

2.4 Histological Requirements

Patient selection for the SIRS trial will include squamous cell carcinomas of head and neck classified as oropharynx that are both positive for HPV16 or any high risk HPV subtype (i.e. 18, 33, 35, etc.) by PCR and p16 positive[1,52]. Tissue for confirmation of p16 status and confirmatory HPV-PCR and will be required and analyzed at a central laboratory. Although p16 has been found to be a potential independent risk factor for prognosis, and a negative p16 is highly predictive of a negative HPV test, about 20% of HNC tumors are p16 positive independent of HPV presence. Because the biologic behavior of this population may be heterogeneous and is less well understood, p16- or p16+ HPV- patients will be excluded from the trial. Similarly, 90% of HPV positive oropharynx cancer is HPV16+, and the behavior of other serotypes is unknown. Hence this study will be limited to HPV16+ cancers, and cancers from high risk HPV subtypes will be analyzed in a separate group. Testing for p16 will be performed and/or reviewed in the central laboratory.

In addition, smoking has been shown to be a prognostic factor in HPVOPC[53]. In the SIRS trial, patients with a history of > 20 pack years and recent (within 5 years) tobacco abuse will be excluded, as this is a known negative prognostic factor and the role of adjuvant therapy in smoking related HPVOPC is currently being examined in other investigations.

2.5 Correlative Studies Background

It is still not well understood as to what biological factors influence the growth and response to treatment of HPVOPC tumors. Current research strongly suggests that there are multiple pathways that may account for the difference in growth and treatment response between HPVOPC and non-HPVOPC tumors. Furthermore, there are several mechanisms reported in the literature that may account for differences in survival within the HPVOPC subset of patients. The advantage of surgical trials in this arena is the availability of high quality tissue specimens for analysis.

This study will collect blood and tumor samples in order to further quantify such mechanisms. Studies will be performed on samples in order to analyze expression of p16, p53, cMET in tumor, and HPV copy number among others. Serial blood samples will be collected to measure sequential serum anti-HPV antibody titers to HPV16 proteins, cytokines, HGF and quantification of circulating tumor cells, MDSC, and other immune function cells. Additionally, studies will be performed to quantify tumor EGFR copy number and Bcl-xL expression, in order to further study the relationship between these proteins and survival of HPVOPC patients. Finally, HPV related signaling pathways will be analyzed using such markers as NFκβ and STAT3 in tissues or a high throughput screening system. Antibodies the HPV16 early antigens are elevated in HPVOPC and may prove to be a useful biomarker for assessing risk of recurrence and response to therapy[54].

Kumar, et. al. reported that low EGFR and high p16 expression are markers of good response to treatment [55]. Other studies have also shown HPV copy number to be linked to better response to treatment and improved OS[7]. p16 will be measured as a marker for HPV status, as it is a cyclin-dependent kinase inhibitor, which acts to inhibit pRb phosphorylation, thus blocking cell cycle progression. The inactivation of pRb by HPV leads to overexpression of p16, making it a good marker for HPV status. Additionally, high EGFR expression, low p53, as well as high Bcl-xL (an antiapoptotic protein) expression are factors that may indicate poor response to treatment and poor outcomes. This study will seek to analyze these factors, as well as proteins that are often mutated in cell signaling pathways, such as cMET, in order to further correlate these proteins with treatment response.

3.0 PARTICIPANT SELECTION

All patients will be evaluated and consented in the multidisciplinary head and neck cancer clinic where eligibility criteria, entry and disease parameters will be evaluated and documented. Subjects who enroll on this study must be diagnosed with HPV related squamous cell carcinoma in the oropharynx, and must not have received any prior chemotherapy, radiotherapy or surgery for their cancer. Potential participants will be screened based on their past medical history, the results of their radiological scans, blood work, as well as a number of other required studies that will determine their eligibility. To be screened and consented on this study subjects must have had a biopsy and must display clinical features that are consistent with p16 positivity (i.e., no history of smoking/alcohol, age range, etc.). To be assigned to a group and participate in the experimental portion of the trial, surgery must be performed at MSSM, tumor tissue must be available, and both p16 and HPV status must be assessed and proven to be positive for HPV 16 or any high risk HPV subtype (i.e., 18, 33, 35, etc.) by PCR and p16 positive by IHC.

3.1 Inclusion Criteria

Participants must meet the following criteria to be eligible to participate in the study. Patients may be screened and consented if they display clinical features that are consistent with p16 positivity, but not yet tested for p16 by IHC and for HPV by PCR and if they meet the other eligibility criteria. They will enter the experimental post-surgical portion of the study if they have surgery performed at MSSM and surgical specimens or biopsies proven to be both p16+ on IHC testing and HPV+ on PCR testing:

3.1.1 Participants must have histologically or cytologically confirmed and identified resectable primary squamous cell carcinoma of the oropharynx that is HPV 16 positive or positive for any high risk HPV subtype (i.e., 18, 33, 35, etc.) as determined by PCR at the central laboratory. Patients must have p16+ status as determined by IHC performed or reviewed at the central laboratory. Both p16 and HPV status must be determined prior to post-surgical adjuvant treatment assignment. Tissue from the primary site must be available for biomarker studies after surgery. Patients with an unknown primary site may be

enrolled if the primary site is identified as a result of the definitive surgical intervention and meets criteria in 3.1.2 and 3.1.1 with confirmation of p16 positivity.

3.1.2 Stage 1, 2, 3 or early and intermediate stage IVa (T1N0-2B, T2N0-2B) (Level 2, non-matted) disease without evidence of distant metastases or extracapsular extension. Primary site must be lateralized for a functional dissection.

3.1.3 Age $\geq$ 18 years.

3.1.4 No previous surgery, radiation therapy or chemotherapy for SCCHN (other than biopsy or tonsillectomy) is allowed at time of study entry.

3.1.5 ECOG performance status of 0 or 1.

3.1.6 No active alcohol addiction (as assessed by medical caregiver).

3.1.7 No active tobacco use ($\geq$1cigarette or cigarette-equivalent per day within the last 5 years) and no cumulative smoking history of >20 pack years

3.1.7.1 1 cigar = 4 cigarette-equivalent exposure (http://www.smoking2.nes.scot.nhs.uk/module4/working-out-cigarette-equivalents.html)

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.1.9 Participants must have adequate bone marrow, hepatic and renal functions as defined below:

3.1.9.1 Hematology:

- Neutrophil count $\geq$ 1.5 x 10^9/l.
- Platelet count $\geq$ 100 x 10^9/l.
- Hemoglobin $\geq$ 10 g/dl (may achieve by transfusion).

3.1.9.2 Renal function: $\geq$ 60 ml/min (actual or calculated by the Cockcroft-Gault method) as follows:

$$\text{CrCl (mL/min)} = \frac{(140\text{-age})\ (\text{weight kg})}{72 \times \text{serum creatinine (mg/dL)}}$$

N.B. For females, use 85% of calculated CrCl value.

Or a Creatinine $\leq$ the upper limits of normal

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Patients < age 18.

3.2.2 Pregnant or breast feeding women.

3.2.3 Previous or current malignancies at other sites, with the exception of adequately treated in situ carcinoma of the cervix, basal or squamous cell carcinoma of the skin, thyroid cancer, prostate cancer treated with surgery/radiotherapy, or other cancer curatively treated by surgery and with no current evidence of disease for at least 5 years.

3.2.4 Other serious illnesses or medical conditions including but not limited to:

3.2.4.1 Unstable cardiac disease despite treatment, myocardial infarction within 6 months prior to study entry.

3.2.4.2 History of significant neurologic or psychiatric disorders including dementia or seizures

3.2.4.3 Active clinically significant uncontrolled infection

3.2.4.4 Active peptic ulcer disease defined as unhealed or clinically active

3.2.4.6 Active drug addiction including alcohol, cocaine or intravenous drug use defined as occurring within the 6 months preceding diagnosis

3.2.4.7 Chronic Obstructive Pulmonary Disease, defined as being associated with a hospitalization for pneumonia or respiratory decompensation within 12 months of diagnosis. This does not include obstruction from tumor

3.2.4.8 Autoimmune disease requiring therapy, prior organ transplant, or known HIV infection

3.2.4.9 Interstitial lung disease

3.2.4.10 Hepatitis C by history

3.2.4.11 Concurrent treatment with any other anticancer therapy.

3.2.4.12 Participation in an investigational therapeutic drug trial within 30 days of study entry. Participation in additional investigational radiation studies will exclude participation in SIRS. Participation in non-therapeutic, non-oncologic investigational studies (i.e. pain control studies, nutritional studies, etc.) will be allowed amongst SIRS participants, provided there is no alteration of treatment planning, oncologic therapy, or surveillance, and additional studies comply with SIRS safety criteria and stopping rules as outlined in the SIRS protocol.

3.2.5 Advanced Stage III,IV (N2C, N3) or surgically unresectable disease or disease that cannot be fully resected, obvious radiologic ECS, supraclavicular or matted metastatic disease, >3 cervical nodes. (These patients will be placed on the Quarterback trial due to advanced state of disease and poor prognostic features)

3.2.6 p16 or HPV negative OPSCC as determined by IHC and PCR, respectively.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

The inclusion and exclusion criteria do not affect enrollment of women, minorities, or other under-represented populations.

4.0 REGISTRATION PROCEDURES

After the patient signs the informed consent the patient will be registered for screening and once the investigator has verified that the patient meets all inclusion/exclusion criteria, the patient will be registered for and started on the protocol. Patients who lack p16 and HPV PCR may proceed to surgery however they will not be assigned to an experimental group and registered on the protocol until p16 IHC and HPV PCR are completed and positive. The verification of patient's eligibility and screening completion will be performed centrally after the receipt of the patient primary post-surgical registration form. It is mandatory not to exceed 21 days between the date of registration for screening and the start of the study treatment (surgery). In any case, all events occurring after the registration for therapy must be recorded in the case report form and will be taken into account in the analysis, whether the patient received the study treatment or not. Patient must receive surgery and be p16 IHC and HPV PCR positive to be included in the intent to treat analysis. Patients found to not meet entry criteria will be offered best therapy.

4.1 General Guidelines

Clinicians will register eligible participants with the Clinical Trial Office. Registration must occur prior to the initiation of screening, again prior to therapy, and finally at completion of therapy for assignment. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist for final registration.

Following registration for therapy, participants will have surgery on study and following surgery re-registration and assignment to treatment group. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy and assignment treatment following registration, the participant's protocol status must be changed to registered not treated. Notify the registrar of participant status changes as soon as possible. Patients who are eligible and do not receive study surgery will be analyzed in a separate cohort.

4.2 Registration Process

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related screening procedures or assessments and register consent and register the patient for screening.

2. Complete the protocol-specific screening and eligibility checklist using the eligibility assessment documented in the participant's medical/research record. To be eligible for registration to the surgery on study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist, however p16 and HPV PCR results need not be necessary.

3. Patients will be re-registered for post-surgical adjuvant treatment assignment as per the protocol design and will require final p16 IHC and HPV PCR for this. Pathologic criteria as outlined in the protocol will determine the post-surgical adjuvant arm assignment.

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

5.0 TREATMENT PLAN

Determination of Stage

Clinical stage will be based on clinical exam, and office based endoscopic evaluation with flexible endoscopy of the upper aerodigestive tract as well as radiographic evaluation with CT and/or MRI in conjunction with CT/PET. Formal operative endoscopy with biopsy under general anesthesia will be performed as indicated when diagnostic or staging dilemma occurs. A preoperative tissue biopsy will be taken and used for histopathological analysis and assignment of p16 status and, if possible, HPV status. All biopsies performed outside the institution will be internally reviewed by pathology department according to protocol guidelines and repeat biopsies will be obtained if there is inadequate tissue for analysis. All patients will be presented and reviewed at multidisciplinary tumor board. Final staging will be performed according to standard 8th Edition AJCC TNM criteria.

Surgical Intervention

Patients who meet inclusion criteria and are surgical candidates will be consented for primary surgical therapy. Surgery will include transoral robotic resection of the tumor with negative intraoperative frozen section margins. Selective neck dissection of levels II-IV will be performed routinely ipsilateral to the primary tonsillar tumors. Bilateral selective neck dissection of levels II-IV will be performed for all tongue base tumors. Additional levels (i.e. I,V) will be performed at the discretion of the operating surgeon if indicated on the size and location of the primary tumor. Appropriate reconstruction will be performed at the time of tumor resection as deemed necessary by the operating surgeon.

Pathological Evaluation/Criteria and Post-Operative Treatment Assignments

Group I:

- Complete resection (margins: tonsil >1mm, tongue >3mm, pT1-2, pN0-2B),
- No LVI, no PNI, <3 positive nodes.
- No ECS, No matted or Level ≥III,

Group I Protocol

- No adjuvant therapy
- Clinical evaluations every 3-4 months the first year

PET or CT at 4 months, 12 months, 24 months. 36 months 48 54, and 60 months unless clinically indicated

Group II

- Complete resection (margins: tonsil <1mm, tongue <1mm, pT1-2, pN0-2B),
- +LVI, +PNI, <3 positive nodes, or ≤1mm ECS.

Group II Protocol

- Postoperative XRT 5000 cGy

- Clinical evaluations every 3-4months during the first year
- PET or CT at 4 months, , 12 months, 24 months. 36 months 48 54, 60 unless clinically indicated. (Newer data suggests we can substitute quarterly cfDNA after initial clear PET through year 2 and then q 6 months through year 4 and then yearly through year 6. Physicians have the option to follow with cfDNA in all groups, but with imaging, as indicated).

Group IIIA

- ≥3+ nodes (without ECS ≥1mm)
- +Supraclavicular nodes (without ECS ≥1mm)
- +Contralateral nodes (without ECS ≥1mm)

Group IIIA Protocol

- CCRT with cisplatin and 5000 cGy
- Monthly clinical evaluation first year,

PET or CT at 4 months, 12 months, 24 months. 36 months 48 54, and 60 months unless clinically indicated.

Group IIIB

- Incomplete surgical resection with +surgical margins
- ≥1mm ECS or matted nodes
- > 6 + nodes

Group IIIB Protocol

- CCRT with cisplatin and 5600 cGy
- Monthly clinical evaluation first year,

PET or CT at 4 months, 12 months, 24 months. 36 months 48 54, and 60 months unless clinically indicated

PATHOLOGY REVIEW CHECKLIST

1. Primary OPSCC, location
2. Histologic differentiation (H/E)
3. HPV + PCR
4. p16+
5. Margin status in mm
6. PNI
7. LVI
8. ECS < = > 1mm
9. Number of cervical metastatic nodes
10. Location of involved nodes (i.e., supraclavicular, ipsilateral vs. contralateral)
11. pAJCC staging

DELIVERY OF RADIATION (XRT)

All patients will receive daily radiation treatment with intensity-modulated radiotherapy (IMRT). Treatment will be given 5 days per week and, as per standard practice, will not be delivered on Saturday, Sunday or major holidays. Radiotherapy will be administered according to the guidelines below:

Technical Factors

Photon beams of ≥4 MV are required. Intensity Modulated Radiotherapy (IMRT) is required for all cases. IMRT via dynamically moving leaves, step-and-shoot with a multileaf collimator, Rapid Arc, binary multileaf collimator and tomotherapy are allowed. Three-dimensional conformal radiotherapy (3D-CRT) and proton therapy are not allowed.

Immobilization, Simulation, and Localization
A thermoplastic head mask (or similar immobilization device) is required for IMRT. Bite blocks, dental rolls and other set-up techniques may be used at the discretion of the treating radiation oncologist. A treatment planning CT scan is mandatory for defining target volumes. IV contrast is not required for the treatment planning CT. CT scan thickness should be ≤0.3 cm. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. Volumes for all structures must be contoured on each relevant CT slice.

Treatment Planning/Target Volumes

Gross Tumor Volume (GTV)
Since radiotherapy will be given postoperatively there should not be any gross disease and therefore no GTV.

Clinical Target Volume (CTV) – Group II and IIIA

The clinical target volume (CTV) is generated to account for microscopic disease. CTV50 may include the primary tumor bed and/or lymph node regions in the neck at risk for harboring microscopic disease. CTV50 should not include bone or air. There will be only one CTV (CTV50) for patients in Group II and IIIA.

Clinical Target Volume (CTV) – Group IIIB
CTV56 is generated to account for areas at highest risk of harboring microscopic disease (positive margin or positive ECS >1mm). If there is a positive margin, CTV56 should encompass the primary tumor bed. If there is extracapsular spread >1mm, CTV56 should encompass the operative bed of the lymph node that was found to have ECS. Group IIIB will have a second CTV, called CTV50.4. CTV50.4 is generated to account for areas at lower risk for harboring microscopic disease than CTV56. CTV50.4 may include the primary tumor bed (if negative margin) and/or lymph node regions (if no ECS) in the neck. CTV56 and CTV50.4 should not include bone or air. There are 2 CTVs for the Group IIIB(CTV56 and CTV50) which will be treated with a simultaneous integrated boost (SIB) technique.

Planning Target Volume (PTV)
PTV incorporates a margin that accounts for daily set up variation. The PTV should be a 0.5 cm expansion of all CTVs. Modification of PTV is allowed at the discretion of the treating radiation oncologist for sparing of normal tissues, or if it is needed to facilitate the planning process, e.g. if the PTV overlaps a critical structure that must be spared. Each CTV will have an individual PTV designed for set-up uncertainty.

Avoidance Structures
The following normal tissue structures will be defined. The dose constraints are listed for each structure.

A. Spinal cord: Maximum dose <45 Gy
B. Expanded spinal cord (5 mm expansion around spinal cord): Maximum dose <50 Gy
C. Brainstem: Maximum dose <54 Gy
D. Parotid glands: Mean dose <26 Gy. If this is not possible due to adjacent disease, then the volume of one parotid gland receiving 30 Gy or more (V30) should be <50%.
E. Larynx: Mean dose <45 Gy

F. Mandible: Maximum dose <70 Gy
G. Oral cavity: Mean dose <45 Gy

For cases in which treatment volumes approach the base of skull, the following avoidance structures will be added:

A. Inner ear: Mean dose <50 Gy
B. Optic nerves: Maximum dose <50 Gy
C. Optic chiasm: Maximum dose <50 Gy
D. Expanded optic nerve and chiasm (2 mm expansion around these structures): Maximum dose <54 Gy
E. Retina: Maximum dose <45 Gy
F. Brain: Maximum dose <60 Gy

Target Dose Prescriptions
To accommodate for tissue heterogeneity, density corrections are required, and will be applied to all plans, unless contraindicated, for example, by significant amounts of scatter on the planning CT scan.

Group II and Group IIIA

- **PTV50 will be treated to a total dose of 50 Gy in 2.0 Gy/fraction.**

Group IIIB

- **PTV56 will be treated to a total dose of 56 Gy in 2.0 Gy/fraction.**
- **PTV50.4 will be treated to a total dose of 50.4 in 1.8 Gy/fraction.**
- **PTV56 and PTV50.4 will be treated via simultaneous integrated boost (SIB) technique.**

PTV Coverage
All plans must be normalized such that 95% of the PTV is covered with the prescription dose. No more than 20% of the PTV may receive > 110 % of the prescription dose. No more than 1% of the PTV may receive < 93% of the prescription dose. No more than 1cc of tissue outside the PTV may receive > 110% of the prescription dose.

Note: in any case with a conflict/overlap between target and normal tissue, target dose considerations will take priority, with the exception of the spinal cord limits.

Treatment Breaks
There are no planned treatment breaks on this study; any breaks in planned radiotherapy are strongly discouraged. Radiotherapy interruptions will be permitted for unavoidable mechanical malfunction or serious illness requiring hospitalization, such as sepsis, delirium, severe respiratory compromise or hemodynamic instability, at the discretion of the Principal Investigator. Treatment breaks should be as short as possible. The reason for any interruption in treatment must be documented in the treatment chart.

Quality Assurance

Initial: Prior to the first radiation treatment, the standard quality assurance procedures will be followed. The monitor units required to deliver the prescribed dose shall be calculated. The monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in

a quality assurance phantom will be done for each patient that will be treated. An ion chamber measurement, to assess absolute dose, in addition to a film or matrix measurement will be taken during the QA period.

On the first day of treatment each patient will have electronic portal images taken that localize the isocenter placement, which will be approved by a radiation oncologist prior to delivery of the first treatment, per standard practice.

Weekly: Verification portal images will be taken at least once per week and approved by a radiation oncologist prior to continuation of treatment per standard practice.

Isodose Distribution
All plans will have complete documentation in the patient's chart, including representative CT slices with treatment isodoses. A DVH with all PTV and CTV structures and all normal tissue structures will be generated for each patient and documented in the patient's radiotherapy chart.

Quality Assurance:
Each treatment plan will be reviewed by at least one non-treating radiation oncologist prior to therapy to assure that the appropriate fields and doses will be delivered.

Chemoradiotherapy Treatment Plan

5.1 Chemoradiotherapy

Chemoradiotherapy Agent Administration

Cisplatin

Dose: 40mg/m2/week

Route: IV over approximately 30 minutes, mixed in 250ml normal saline

Schedule: Weekly on Monday or Tuesday any time, or Wednesday prior to radiation

Prehydration: Prehydration IV fluids are required, KCl and Magnesium sulfate will be administered as well as antiemetic regimen to include a 5HT3 antagonist prior to cisplatin administration.

All patients assigned to Group IIIA and Group IIIB will receive daily radiation treatment with intensity-modulated radiotherapy (IMRT). Treatment will be given 5 days per week and, as per standard practice, will not be delivered on Saturday, Sunday or major holidays. Radiotherapy will be administered according to the guidelines above.

5.2 Salvage Protocol

In the event of suspected disease recurrence in the surveillance group (Group I), appropriate imaging including PET/CT scan and biopsies will be performed. Biopsies will be evaluated for HPV16 and p16 expression and

stored for further analysis. If there is solely a local regional recurrence, Surgical salvage will be offered to patients who have resectable limited disease defined as recurrent disease at the primary site or level 2 or 3 lymph nodes and <3 positive nodes on scan, followed by post-operative CRT as above for group 3 patients. For patients with limited recurrence deemed unresectable for reasons of organ preservation or ability to reasonably expect a complete surgical resection, definitive CRT with a total dose of 6600-7200 cgy and cisplatin as above will be performed.

For patients with extensive local regional disease defined as infiltrative, >2 positive nodes, nodal involvement of levels 4, 5 or N2c disease or those with metastatic disease, TPF chemotherapy will be given After completion of 3 cycles of TPF, sites of initial disease will be treated with carboplatin to 5600 cGy as defined in the Quarterback trial. TPF will be given even if the metastases have been completely resected post TPF. CRT will be delivered to sites and watershed areas of metastatic disease that has been resected or is unresectable and there was no LR recurrence. For multiple metastases TPF and CRT may be withheld if in the opinion of the clinician the DM are too numerous and desiminated to be safely or effectively treated.

Patients in Group II or Group III who fail with LR disease will be treated with best available therapy.

If a specific and highly effective therapy is identified during the conduct of the study that is an improvement over treatment with TPF and CRT as salvage, that therapy may be offered to the patients as a standard treatment, and will be added as an amendment in due course.

6.0 STUDY PARTICIPATION

6.1 Duration of Follow Up

Participants will be followed for 5 years after completion of study treatment or until death, whichever occurs first through standard of care treatment after therapy as prescribed by the Investigator which can include clinic visits or other follow-up by other means. Participants removed from study for unacceptable adverse events will also be followed until resolution or stabilization of the adverse event.

6.2 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed below applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator,Raymond Cahi, MD at 212-844-8560

- Patient is removed early from protocol therapy at PI's discretion
- Patient is found ineligible
- Patient completion of protocol requirements
- Unacceptable toxicity
- Pregnancy
- Adverse Event
- Progressive disease/ relapse
- Lost to follow-up (documented 3 attempts via telephone or signature confirmation letter)

 Non-Compliance with therapy and protocol procedures

 Death

 Other

7.0 EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

7.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting in addition to routine reporting.

7.1.1 Adverse Event List(s) for Cisplatin

The major dose limiting toxicities observed with Cisplatin single agent are nausea and vomiting, peripheral neuropathy, nephrotoxicity and ototoxicity.

7.1.2 Adverse Event List(s) for Carboplatin

The major dose limiting toxicities observed with Carboplatin single agent are myelosuppression and renal toxicity.

7.2 Dose Modifications/Delays

7.2.1 Cisplatin

Peripheral Neuropathy

- A neurological examination must be performed at least before entry into the study and then **Should be done at the end or CRT for chemoRT groups amnd then at 3 month follow up**. In case of symptoms or signs experienced by the patient, more frequent examinations should be performed and dose modification will be as follows:
  - Grade 0, 1: No change
  - Grade $\geq$ 2: Carboplatin at an AUC of 2 may be substituted for Cisplatin

Ototoxicity

- Cisplatin is known to cause high frequency hearing loss. If grade 1 or 2 hearing loss occurs, the risk of additional hearing loss versus the potential benefit of continuing Cisplatin chemotherapy should be made. Grade 3 and 4 hearing loss is an indication to discontinue the drug however this decision can be made with the patient and after formal hearing tests.
- Audiomeric testing will be performed at baseline and prior to each dose

- In case of grade 3 or 4 toxicity, Carboplatin (at dosage of AUC 2) may be used to replace Cisplatin in the remaining chemo cycles. The dose of Carboplatin AUC 2 will be calculated based on the Calvert formula.

Thrombocytopenia

- Pre-treatment hematologic parameters prior to administration of chemotherapy will include an ANC greater than or equal to 1.5 x 10^9/L, platelet greater than or equal to 100,000mm3

Dose Modification for Thrombocytopenia

Nadir of last course ≤ 100,000	**Dose of Cisplatin Platelets (day 1 of each cycle)**	
	<100,000	**≥100,000**
≥ 50,000	Hold	Cisplatin = 100%
< 50,000 (1st occurrence)	Hold	Cisplatin = 80%
<50,000 (2nd occurrence)	Hold	Cisplatin = 60%

** Please note that dose reduction percentage is calculated by taking off from the original dose and not the previous dose.

Dose Modification of Cisplatin in Kidney Impairment

Calculated Creatinine Clearance (mL/min)	Percent Dose to Give	
≥ 60	100%	
< 60	0% (withhold treatment for a maximum of 2 weeks and repeat serum creatinine weekly after additional hydration), then	
	If CCl was < 60 mL/min and is now:	** The percent dose to give is:
	> 50 but < 60	80%
	≥ 40 but ≤ 50	50%
	< 40	0%

**Please note that dose reduction percentage is calculated by taking off from the original dose and not the previous dose.

If creatinine clearance recovers, the dose of Cisplatin for the following cycle should be re-escalated to the previous dose level.

Formula to calculate Creatinine Clearance:

CrCl (mL/min) = (140-age) (weight kg)_____

72 x serum creatinine (mg/dL)

N.B. For females, use 85% of calculated CrCl value.

Ototoxicity, Nausea and Vomiting

Cisplatin is the preferred therapy for TPF and chemoradiotherapy, Carboplatin may be substituted for Cisplatin if a patient develops grade 3 ototoxicity, or an unacceptable Cisplatin associated nausea and vomiting, after receiving 1 or 2 doses of Cisplatin.

Dose alteration for toxicity is to be based on single worst toxicity. Once Carboplatin dose is reduced, there will be no re-escalation.

Neurotoxicity

- In the event of neurotoxicity (≥ grade 3), Carboplatin therapy is discontinued.

Nephrotoxicity

If, despite adequate rehydration, serum creatinine increases to Formula to calculate Creatinine Clearance:

$$\text{CrCl (mL/min)} = \frac{(140\text{-age}) \text{ (weight kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

N.B. for females, use 85% of calculated CrCl value.

- Grade 0, 1: No change
- Grade ≥ 2: Carboplatin at an AUC of 2.0 may be substituted for Cisplatin

7.2.2 Carboplatin (AUC 2.0)

The carboplatin dose for weekly concurrent chemoradiotherapy is an AUC of 2.0. Thereafter, the AUC will be changed only in case of hematological toxicity.

See the tables below for approach to myelosuppression.

Table: Carboplatin dose modification based on ANC

ANC ($x10^9$/L) within 24 hrs. of therapy	**Action to be taken**
≥ 1.5	Treat at current dose
≥ 1.0, < 1.5 < 1.0	Treat at AUC of 1.5 Hold treatment, and resume therapy at AUC of 1.5 at the next weekly therapy planned when ANC ≥ 1.0. If neutropenia requiring further

	chemotherapy break occurs, carboplatin will be discontinued for the remainder of the therapy.

**For febrile neutropenia, instructions for ANC <1.0 will be followed. In addition, prophylactic antibiotics and growth factor support may be administered as clinically indicated.

Table: Carboplatin dose modification based on platelet count	
Platelet count within 24 hrs. of therapy	Action to be taken
≥ 100,000	Treat at current dose
< 100,000	Hold treatment, and resume therapy at AUC of 1.0 at the next weekly therapy planned when platelets ≥ 100,000. If thrombocytopenia requiring further chemotherapy break occurs, carboplatin will be discontinued for the remainder of the therapy.

- Renal toxicity: Serum creatinine will be measured weekly within 24 hours of carboplatin dosing. If the serum creatinine has not changed more than 25% relative to the serum creatinine at baseline, the creatinine clearance and carboplatin dose need not to be recalculated. If there is a rise or fall greater than 25% relative to baseline serum creatinine values, then the creatinine clearance and carboplatin dose must be recalculated.

8.0 DRUG FORMULATION AND ADMINISTRATION

Drug formulation and administration are in accordance with commercially available product guidelines for all agents listed in Section 5.0.

9.0 CORRELATIVE/SPECIAL STUDIES

9.1 Probable Laboratory Correlative Studies

This clinical trial aims to investigate a reduction in radiation intensity in patients with HPVOC. The goals of these exploratory translational studies are to understand the tumor biology, immunology, and epidemiology; and to develop predictive biomarkers to be examined in a larger prospectively randomized trial.

The following projects will be carried out with specimens from study participants:

1. Tumor tissue will be evaluated for the following markers (this is a preliminary list which may change and expand as new technology and biomarkers become available: HPV copy number, c-Met expression, BCL-x, EGFr copy number, EGFr expression and EGFr phosphorylation.
2. CTC assessment: The number of circulating tumor cells will be evaluated as a possible prognostic indicator.
3. Cytokine profiling of the patients plasma will be assessed with baseline samples obtained prior to therapy.
4. Circulating immune cells will be assessed including MDSC, T regulatory and T cell subsets.

5. The immunologic function and specificity of patient's T lymphocyte responses to HPV epitopes will be studied and targeted epitopes identified.
6. Serologic responses to HPV proteins will be investigated in patients over time in response to therapy.
7. Tissue microarrays and IHC will be used to establish differences between primary tumors with and without distant spread.

9.2 Specific Study Plans

The following studies are given a brief description as technology will change and samples will not be accessed until the study is complete.

1) T Cell specificity and Function in HPV Oropharynx Cancer

It is possible that preserved or improved immune responses in HPVOC patients may protect against distant metastases, second primaries or recurrence or may mediate some portion of the responsiveness. We have identified immunogenic HLA-A2-restricted peptides derived from HPV16E6 and E7 (Reimer, Anderson, and Reinherz, unpublished data). Here, we will evaluate pre and post therapy T cell function towards HPV peptides by ELISPOT in vitro and correlate responses with stage, clinical response and tumor control. We hypothesize that cured patients will have a more robust response after therapy has completed and we may identify preferred peptide epitopes associated with improved survival and/or response.

2) Serologic assessments

We have developed a novel multiplex antibody assay using the Luminex system that allows us to establish the titers of complex and seemingly heterogeneous antibody responses to the full genome of HPV16. Using this system we will monitor the antibody response of the HPVOC prior to, and 6 months after therapy has completed and then at 12 months and then at 24 Months and 36 months to determine if response can predict tumor control, and can establish patterns that might be useful in predicting the development of cancers.

3) Tissue microarrays

There will be distinct differences between primary tumors and metastatic, nodal and persistent disease in patients. We will use TMA to evaluate biomarkers and tumor differences that can be used to predict metastatic behavior and response. While tumor control is frequently a process related to tumor volume, those cells that can metastasize may have a distinct signature that can point to a pathway that can be exploited for better anti-tumor therapy, could be identified in small numbers of tumor cells, might be present in CTC, etc. This is exploratory study data set.

9.3 Blood and Tissue Collection and Preparation

Blood will be collected to measure plasma and serum factors such as antibodies, cytokines, DNA, etc. and cells for immune studies and germ line DNA. The target amount to be collected from each subject will be less than 200 mls of whole blood (46ml at baseline, 3 month (or pre-XRT) and 24 months; 16 ml at 6, 12, and 36 months). Blood will be collected in 1x 6ml red top tube and 4 x 10ml green top tubes at baseline, 3 month (or pre-XRT) and at the 24 month visit. Only 1 red top tube and one green top tube will be collected at the 6 month, 12 month, and 36 month visits. Processing and labeling of

the blood will be done according to the "Blood Handling" section outlined below. Lag time between collection and the start of processing will be within 5 hours and this time will be recorded for each sample. Components will be stored from these tubes including serum, plasma and buffy coat. If collected and handled properly, each of the tubes should yield approximately 3mls of serum. Serum will be maintained as 1ml aliquots and frozen and stored at –80°C and buffy coat will be stored from green tubes, at local institutional temperature guidelines. A portion of each of these samples will be stored at the biospecimen repository, and a portion maintained at this facility, until exhausted. Samples will be labeled a code linked to the patient case report form. All patients will have tumor testing for HPV and p16 in a central laboratory as part of their screening. Slides and microarrays from tumor tissues will be labeled similarly as blood samples above.

Blood Handling

Blood collection will be performed before surgery (if necessary) and in the absence of any systemic anesthesia.

Samples (6 ml of blood/tube) will be obtained at each visit as noted, according to the table below for Group 1.Times refer to post-surgery collection. For Group 2 and 3 there will be a pre-radiation sample in place of the 3 month post-surgery collection.

	Pre-Surgery	Post-Surgery				
	Baseline	3 ± 1Month Or preXRT[1]	6 ±1 Month	12 ±1 Month	24 ± 2 Month	36 ± 2 Month
	V1	V2	V3	V4	V5	V6
Serum (red tops)	X	X	X	X	X	X
WBC (green tops)	xxxx	xxxx	X	X	xxxx	X

1 pre-XRT for Groups 2 and 3

Viable lymphocytes will be processed from green top tubes using standard ficoll-hypaque density gradient separation. Buffy coat layers will be stored as viable cells in DMSO-containing media at -80C to -170C.

Blood for serum will be spun within 5 hours of collection. Blood tubes will be spun at 3000 x g for 10' at 4°C and the serum removed by pipetting. Serum will be stored in 1ml aliquots. All samples will be stored at -80°C. White blood cell fraction will be stored in a single tube at local institutional temperature guidelines and kept locally.

Tissue Collection

All patients will have their tumors tested for HPV and p16 in the central laboratory at at Icahn School of Medicine at Mount Sinai per current standard protocol. Paraffin embedded and formalin fixed blocks from the original and subsequent biopsy specimens will be sent to the laboratory and will be cut in his laboratory for PCR testing and IHC. The primary untreated tumor will be tested for HPV and p16 prior to the start of radiotherapy or concurrent chemoradiotherapy.

Additional slides, from 5-20, and tissue microarrays will be cut from the blocks and stored in the Mount Sinai Biorepository before they are returned to the site. Any additional biopsies from the primary tumor or a recurrence will be obtained and handled in the same fashion.

Specimen Management Committee

A Specimen Management team will decide priority and allocation of samples not included in the original plan. The team will consist of the Overall study PI, and the Site PIs and Chairmen of the Pathology, Radiation Oncology, ENT, and Medical Oncology for the study and for the teams at each site.. Proposals will be reviewed and upon a majority agreement, samples will be allocated for each study. A quorum for decisions would include at least one member from each site and one of the study chairmen of Radiation Oncology, Otolaryngology, Pathology, and Medical Oncology.

10.0 STUDY CALENDAR (History, Exam and Lab)

	Pre-Study[5]	**Post Surgery Surveillance** **Follow up**	**During Chemo/RT, groups 2,3**	**Post CRT Follow up** (± 1 month)
Informed Consent	To be obtained before enrollment			
Medical History	Within 10 days before registration	Every Visit	Per SOC at all clinical visits	Every Visit
Smoking History	Within 10 days before registration			
Concurrent meds[4]	At Screening	Every Visit	Weekly	
Physical Exam[1]	Within 10 days before registration	Every Visit	Per SOC at all clinical visits	
CBC/BMP	Within 10 days before registration	Preop and post-op and then no requirement for Groups I and II and per SOC for Group IIIA and IIIB	Preop and post-op and then no requirement for Groups I and II and per SOC for Group IIIA and IIIB	
Dysphagia Assessment Questionnaire	Within 10 days before registration	12, 24, 36 months (± 1 month)	Weekly	12, 24, 36 months
Adverse Event evaluation[4]			Weekly	Each visit
B-HC (for WOCP)	Within 7 days before registration			

[1] Ht, Wt, Performance status, neurologic examination, vital signs (heart/blood pressure/temperature). Height is only collected at baseline/pre-study.

	Tumor Assessment					
	Pre-Study	**Surgery**	**Pathological Evaluation**	**ChemoRT (if reassigned)**	**Reassessment (Week 8-10)**	**Surveillance (± 1 month)**
Physical tumor Examination	Patients get an exam as part of their routine visits, same for TNM and will be done when the patient is seen and before they are consented	Intraoperative	Path Check List		X	
TNM Staging	patients get an exam as part of their routine visits, same for TNM and will be done when the patient is seen and before they are consented		Path Check List			
Nasopharyngoscopy					X	
Examination under anesthesia (EUA)	Within 8 weeks before registration if possible. (Does not need to be repeated if time period exceeds 8 weeks)	May be done if investigator deems it necessary				
PET/CT and/or high resolution CT or MRI of the neck (base of skull clavicles)	Within 28 days before registration				PET/CT or CT with contrast and examination At 12-16 weeks	PET/CT or CT with contrast and examination Refer to Section 5.0 "Treatment Plan" for the frequency in each group

CORRELATIVE STUDIES CALENDAR (See Section 16.0 for QOL)					
	Pre-Study				**Post-Study Follow-up** **(± 1 month)**
Tissue Microarray	X				
CTC's (cell Save tube)	X				
T Cell Specificity and Function	X				12,and 24 months
Serologic Assessments	X				6, 12, 24 and 36 months

11.0 MEASUREMENT OF EFFECT

11.1.1 Definitions

Evaluable for toxicity. All participants who go on to surgery will be evaluable for toxicity from the time of their first treatment. Patients who are screened will be evaluated and the reason for screen failure will be recorded

Evaluable for Primary Outcome: Only patients who are entered and have surgery will be eligible for assessment of the primary outcomes (LRC, PFS). All patients who have had surgery will be analyzed on an ITT for LRC, PFS, and survival.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression or death.

Local Regional Control (LRC) will be defined as local and regional control of disease, censored for death.

Overall Survival (OAS) will be defined as alive at the time of analysis, this will be analyzed as for the entire trial, for all randomized patients and only for those patients randomized who received one dose of radiotherapy.

Post Recurrence LRC: Surveillance Patients who recur will be assessed for LRC post treatment for their initial recurrence

Post Recurrence PFS Surveillance Patients who recur will be assessed for PFS post treatment for their initial recurrence

Ultimate Disease Control will be defined as those patients who are alive and disease free at the time of analysis

12.0 ASSESSMENT OF QUALITY OF LIFE AND PATIENT REPORTED SYMPTOMS

Head and neck cancer often arises in cosmetically or functionally important areas. Thus, the ability to eat, speak, breathe easily, as well as the patient's overall sense of comfort is frequently affected by therapy. In addition to these disease-specific symptoms, patients with head and neck cancer may also experience symptoms related to surgery (e.g. disfigurement) or to radiation therapy (e.g., dysphagia, xerostomia, and mucositis). These may lead to feeling of general overall sickness and can potentially result in social isolation. Patient-reported symptoms tend to be more severe than those recorded by physicians, patient reported outcome instruments are increasingly being used to measure symptom burden, functionality and quality of life. It can provide more comprehensive and improved toxicity data. Quality of life (QOL) assessment is a multi-dimensional construct that involves an individual's subjective assessment of the impact of an illness or treatment on his/her physical, psychological, social, and somatic functioning and general well-being. The European Organization for Research and Treatment of Cancer Core measure (EORTC QLQ-C30) is a well validated cancer-specific QOL scale that is used as a generic measurement for patients with cancer that in head and neck patients is used in conjunction with the site specific measurement tool EORTC QLQ H&N35. The M.D. Anderson Symptom Inventory-Head and Neck (MDASI-HN) module is a validated instrument that provides a brief measure of the symptom distress experienced by the head and neck cancer patients as a result of their disease and/or treatment. This symptom burden instrument was closely associated with the severity of radiation-induced mucositis. The MDA Xerostomia and Dysphagia questionnaires are radiotherapy/head and neck cancer directed questions which have a robust, validated assessment the specific concerns of swallowing and salivary function in head and neck cancer treated patients.

In this study, patients will complete the EORTC QLQ-C30, EORTC QLQ H&N35, MDASI-HN, the MDADI-HN (dysphagia) and xerostomia questionnaires prior to therapy and then at 3, 6, 12 and every 12 months after therapy for 5 years for all patients. During the concomitant chemo-radiation phase of treatment, in order to avoid patient fatigue, the EORTC QLQ-C30, EORTC QLQ H&N35, MDASI-HN module, MDADI-HN (dysphagia) and xerostomia questionnaires will be completed on pre and weeks 5, 7 and post rx 3 months; and the . The adverse events assessments, the (see table). As shown in the statistical plan we will use these assessments in conjunction with adverse events assessments to compare the experiment and control arms of this study.

	Pre-Study	**CRT**	**Post-Study Follow-up**
Informed Consent	To be obtained before enrollment		
EORTC QLQ-C30, EORTC QLQ H&N35	Within 10 days before registration	pre and weeks 5 7 and post rx 3 months	3, 6, 12, and every 12 months for 5 years
MDASI-HN	Within 10 days before registration	pre and weeks 5 7 and post rx 3 months	3, 6, 12, and every 12 months for 5 years
MDADI-HN (Dysphagia Assessment Questionnaire)	Within 10 days before registration	pre and weeks 5 7 and post rx 3 months	3, 6, 12, and every 12 months for 5 years
Xerostomia		pre and weeks 5 7 and post rx 3 months	3, 6, 12, and every 12 months for 5 years

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

13.1 Definitions

13.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

13.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death.

- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.
- Respite care.

13.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

13.1.3.1Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

13.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

13.1.4.Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

13.2 Procedures for AE and SAE Recording and Reporting

Reporting: Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

13.3 Reporting Requirements

Each participating investigator is required to abide by the reporting requirements set by the MSSM. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigator will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

13.4 Reporting to the Study Center

13.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the MSSM Overall Principal Investigator on the local institutional SAE form for the local IRB and electronically on the eRAP CRF. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

  Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the MSSM Overall Principal Investigator within 24 hours of learning of the occurrence by Fax and email. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:
Raymond Chai at Ph- 212-844-8560 Raymond.Chai@mountsinai.org

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

13.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the MSSM Overall Principal Investigator on the toxicity Case Report Forms.

13.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within MSSM will report all serious adverse events directly to the MSSM Office for Human Research Studies

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Raymond Chai at Ph- 212-844-8560 Raymond.Chai@mountsinai.org
The MSSM Principal Investigator will submit SAE reports from outside institutions to the MSSM Office for Human Research Studies according to MSSM IRB policies and procedures in reporting adverse events.

13.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

13.7 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the MSSM Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

14 DATA AND SAFETY MONITORING

14.1 Data Reporting

Method

The Study team and the CCTO will collect, manage, and monitor data for this study.

Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form/eCRF	Estimated Submission Timeline
Eligibility Checklist	Complete prior to registration with MSSM
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

14.2 Safety Meetings

Because this is a Phase II trial an internal Data Safety Monitoring Board will be required to review and monitor toxicity, accrual data from this trial and interim results on this trial. The committee will be composed of Dr. Raymond Chai (Chair), Dr. Marshall Posner, Dr. Richard Bakst, Dr. Vishal Gupta and the statistician. The

Review group will meet quarterly to review survival and recurrence data from the trial. An independent MSSM statistician shall be a member. The chairman of the DSMB will prepare minutes and report to the DSMC. The study report will remain blinded for efficacy results unless there is sufficient reason for the DSMB to consider halting the trial.

The DSMB will meet semi-annually and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; all unexpected adverse events that have been reported; summary of all surgical complications or deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

Adverse Events. safety data, including all protocol-defined and serious unanticipated adverse events, will be collected throughout the entire course of the study. Expedited reporting to the IRB and study sponsor will be required for any unexpected serious adverse event.

Reporting of Serious Adverse Events

All investigators NHLBI must report both expected (protocol defined) and unexpected serious adverse events. All serious adverse events must be reported directly to the clinical center's IRB within 10 working days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All deaths and unexpected serious adverse events must be reported to the IRB within 24 hours of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. The investigators will notify the study sponsor of any deaths and unexpected serious adverse events via e-mail within 24 hours of receipt of the event. These events will also be reported to the DSMB chair within 72 hours of notification. All serious adverse events will be reported to the DSMB at least semi-annually, at the discretion of the DSMB. In addition, the investigators are expected to comply with their institutional policies and reporting requirements.

After recruitment of half of the study subjects (100) a full dataset analysis will be performed by the investigators and the statistical support group to ensure that outcomes are comparable to current standards. This will include statistical analysis of adverse events, recurrence rates after surgical therapy, outcomes of adjuvant therapy arms, and disease specific survival. Deviation from the proposed recurrence rates or overall disease specific survival will result in halting the trial. The primary endpoints are DFS and LRC at 3 and 5 years. Kaplan-Meier curves will be estimated for the standard therapy and the experimental therapy groups. Ninety-percent one-sided confidence intervals will be calculated for DFS at 3 and 5 years in the surgical and surgical/adjuvant therapy groups. The secondary endpoint of overall survival will be analyzed using Kaplan-Meier curves and a log-rank test for the difference between the two therapy groups. Five year OAS, DFS and LRC will be calculated using a log-rank test will be used to test for differences between the two treatment groups. Toxicity is another secondary endpoint. We will compute for each arm the toxicity rate and provide the corresponding 90% confidence intervals based on the exact binomial distribution.

Stopping Boundaries: Based on stopping if the probability that recurrence exceeds 50% is ≥ 0.80

The following are greater-than-or-equal boundaries:
a pair (n, m) means to stop if the number of adverse events after treating m patients is greater than or equal to n.

n (# events)	m (# patients)	n (# events)	m (# patients
7	10	35	62
8	12	36	64
9	14	37	66

10	16	39	69
11	18	40	71
13	21	41	73
14	23	42	75
15	25	43	77
16	27	44	79
17	29	46	82
19	32	47	84
20	34	48	86
21	36	49	88
22	38	50	90
23	40	51	92
25	43	52	94
26	45	54	97
27	47	55	99
28	49	55	100
29	51		
30	53		
32	56		
33	58		
34	60		
35	62		

15 REGULATORY CONSIDERATIONS

15.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The MSSM Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

15.2 Informed Consent

15.3 All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the

consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file15.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

  - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- MSSM research policies and procedures

  It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

15.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

15.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

15.6 Multi-center Guidelines

Protocol Chair – Raymond Chai, MD

The Protocol Chair is responsible for performing the following tasks:

1. Coordinating, developing, submitting, and obtaining approval for the protocol
2. as well as its subsequent amendments
3. Assuring that all participating institutions are using the correct version of the
4. protocol.
5. Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
6. Reviewing and ensuring reporting of Serious Adverse Events (SAE)
7. Reviewing data from all sites, and performing interim analysis as indicated.
8. Initiation of stopping rules at all participating sites if necessary

Coordinating Center- Mount Sinai Health System

The Coordinating Center is responsible for performing the following tasks:

1. Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
2. Managing central patient registration
3. Collecting and compiling data from each site.
4. Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
5. Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.
6. Providing a protocol appendix for each Participating Site describing the participating site patient population, expertise, and available resources.
7. Coordinating Center personnel and the PI will collect information from the Participating Site and report appropriately to the IRB. Information reported may include but is not limited to adverse events, stopping rule triggers, interim analysis results, study results, unanticipated events related to the study, etc.

Participating Sites

1. Participating sites are responsible for performing the following tasks:
2. Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
3. Submitting data to the Coordinating Center through ERAP.
4. Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
5. Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
6. Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.

Meetings

Teleconferences of all investigators, research nurses and other study staff involved in the study will take place, starting once both sites have enrolled a subject. The following study team members involved with the conduct of the trial will be included as appropriate: study coordinators, data managers, research nurses, sub-investigators, collaborators (if applicable), and the statistician. The timing of these meetings will be at minimal quarterly, but more frequent during initial accrual, adverse event reporting, or at any time at the discretion of the Participating Site or Coordinating site.

During these meetings, matters related to the following will be discussed: enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), validity and integrity of the data, toxicities, surgical complications, unanticipated barriers, acquisition of serum samples and transfer to lab, and progress of data for objectives. Any other issue related to the trial may be discussed with the Participating Site and the Coordinating Center. Formal minutes of these discussions will be provided to the appropriate personel, and if applicable, formal action plans.

16.0 **STATISTICAL CONSIDERATIONS**

16.1 Study Design/Endpoints

This is a prospective clinical trial evaluating surgery alone for early stage HPV related oropharyngeal squamous cell carcinoma. The primary endpoints are the rate of local-regional control OAS, and PFS at 3 years in patients with HPV 16 and p16+ related head and neck cancer, treated with surgery alone. The secondary objectives include 5 year PFS, LRC, Overall Survival, Ultimate Disease Control, QOL, site of failure and rate of salvage, as well as establishing biomarkers predictive of treatment outcomes and collection of tumor tissue, germline DNA and a plasma bank for future studies. The main study hypotheses is that OAS and UDC at 5 years for surgery alone for early stage HPV related oropharyngeal squamous cell carcinoma is equivalent to current regimens involving standardized post-operative radiotherapy (>85%) and that LRC without radiotherapy will be > 50%. Additional Hypotheses relate to Group 2 and 3 - OAS and PFS at 5 years for reduced dose XRT and CRT intermediate stage HPV related oropharyngeal squamous cell carcinoma is equivalent to current regimens involving standardized post-operative radiotherapy (>85%) and that LRC will be > 85%.

16.2 Sample Size/Accrual Rate

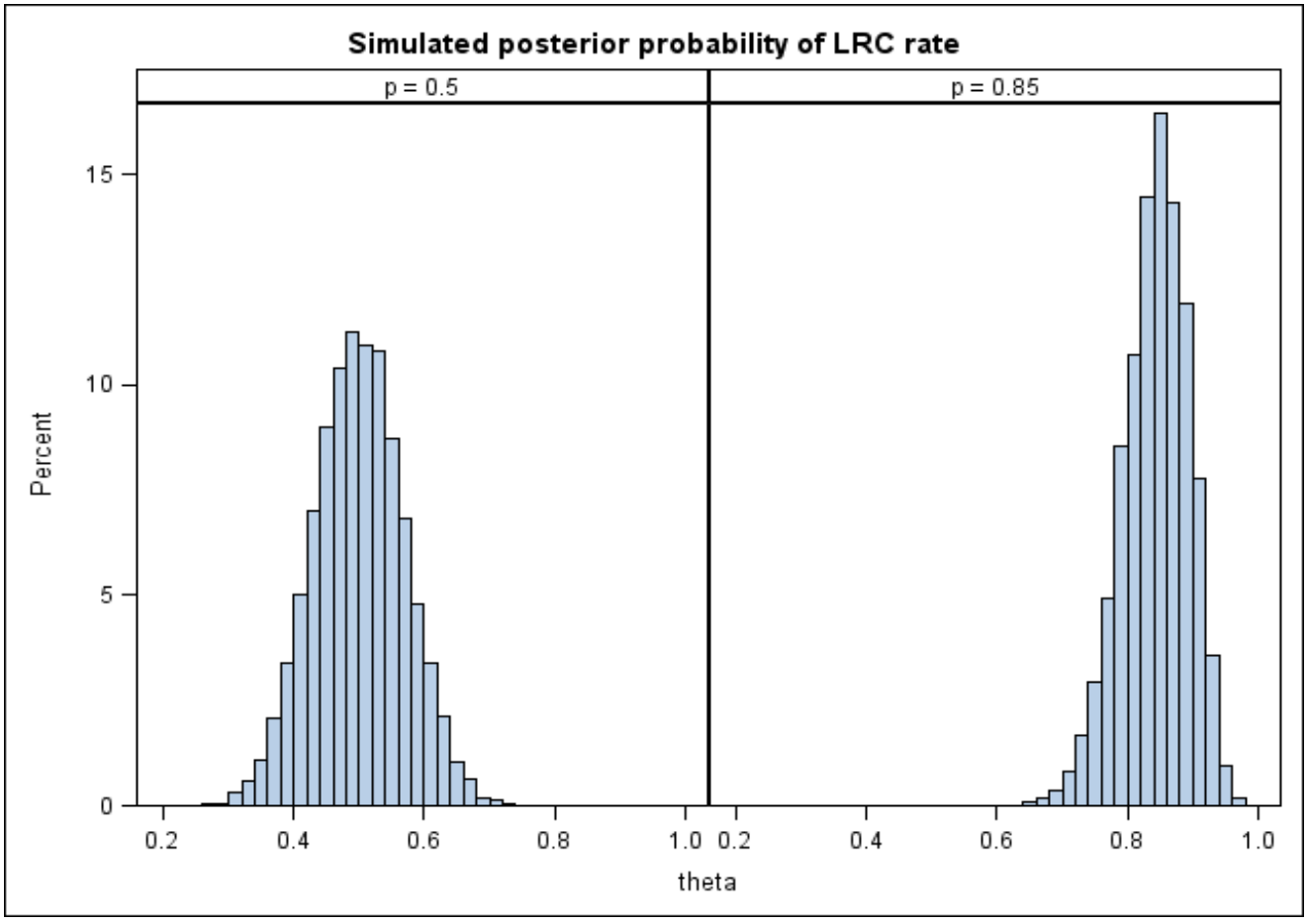
Sample size justification:
The proposed sample size of 100 for Group 1 has been determined to ensure that an upper bound for recurrence may be estimated with adequate precision, defined as within 8-12% of the true recurrence rate. The upper bound is estimated by the posterior probability of recurrence given the observed data, assuming a non-informative beta(1,1) prior distribution. The table below provides the upper 95% bound (from the Bayesian credible interval) assuming the true rate of recurrence is .1,.2,.3,.4, or .5 and 100 patients are studied.

True recurrence	Upper 95% bound
.1	.184
.2	.301
.3	.413
.4	.516

.5	.614

The various specific aims outlined in Aim 1 share a common objective: determining rates of important measures of treatment response (progression-free survival, overall survival, local regional control and ultimate disease control) for patients treated with surgery alone and compare them to those expected in patients with similar diagnostic criteria. We will assess this overall objective by using a Bayesian approach to estimate the posterior probability distributions for each respective sub-aim based on observed outcomes. This approach permits estimating probabilities with which a specified rate of interest exceeds a threshold value (e.g.; 50% local regional control, 85% overall survival, etc.)

Our approach begins with the premise that surgery alone offers no improvement in expected outcomes. This is an exact correspondence to a "null hypothesis". We incorporate this assumption through a prior distribution for each suspected rate; for example, for Group I patients we would assume that the rate of local regional control (LRC) at three years is 50%. After the studies are conducted, each respective rate is combined with the "null" prior distribution through Bayes' Theorem to yield the posterior distribution for the rate. The table below depicts simulated results for the posterior LRC (theta) using 100 patients based on two differing assumptions: that LRC at three years is 50% (p=0.5 shown on the left) and 85% (p=0.85 shown on the right).



Our expected sample size of 100 for Group I patients ensures that the inter-quartile range for the estimated probability distributions will extend from approximately 10-12 percentage points. This range is wider for smaller sample sizes (e.g. 30 or 50) but still less than 20 percentage points.

16.3 Stratification Factors

Study subjects will be stratified based on final pathological data for statistical analysis and outcomes reporting.

16.4 Analysis of Primary Endpoints

The primary endpoints are DFS and LRC at 3 and 5 years. Kaplan-Meier curves will be estimated for the standard therapy and the experimental therapy groups. Ninety-percent one-sided confidence intervals will be calculated for DFS at 3 and 5 years in the surgical and surgical/adjuvant therapy groups.

16.5 Analysis of Secondary Endpoints

The secondary endpoint of overall survival will be analyzed using Kaplan-Meier curves and a log-rank test for the difference between the two therapy groups. Five year OAS, DFS and LRC will be calculated using a log-rank test will be used to test for differences between the two treatment groups.

Toxicity is another secondary endpoint. We will compute for each arm the toxicity rate and provide the corresponding 90% confidence intervals based on the exact binomial distribution.

Reporting and Exclusions

Not Applicable.

17.0 PUBLICATION PLAN

The results should be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of data collection.

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19.0 APPENDICES

Appendix 1: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

<u>Appendix 2</u>: Video Swallowing

The video swallow study report will include the following information:

Impressions:

1. Oropharyngeal findings
    a. Penetration-Aspiration-Scale
    b. Severity rating of OP function
        i. Within Normal Limits
        ii. Mild
        iii. Mild-Moderate
        iv. Moderate
        v. Moderate-Severe
        vi. Severe

2. Cervical Esophageal findings
    a. No stenosis
    b. Partial stenosis
    c. Complete stenosis

Recommendations:

1. Diet
    a. Regular diet
    b. Soft diet
    c. Puree diet
    d. Liquid diet
    e. G-tube w/trials
    f. G-tube, NPO

2. Liquids
    a. Regular
    b. Thickened

3. Therapeutic precautions/interventions
    a. Implement postures/strategies to decrease penetration/aspiration or residue

Consider esophageal dilation Yes or No

Appendix 3: QOL Questionnaires

Name_____ Date_____ Hospital Number_____

The M. D. Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you.

Please read each statement and circle the response which best reflects your experience in the past week.

My swallowing ability limits my day-to-day activities.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E2. I am embarrassed by my eating habits.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

F1. People have difficulty cooking for me.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P2. Swallowing is more difficult at the end of the day.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E7. I do not feel self-conscious when I eat.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E4. I am upset by my swallowing problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P6. Swallowing takes great effort.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E5. I do not go out because of my swallowing problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

F5. My swallowing difficulty has caused me to lose income.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P7. It takes me longer to eat because of my swallowing problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P3. People ask me, “Why can’t you eat that?”

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E3. Other people are irritated by my eating problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P8. I cough when I try to drink liquids.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

F3. My swallowing problems limit my social and personal life.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

F2. I feel free to go out to eat with my friends, neighbors, and relatives.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P5. I limit my food intake because of my swallowing difficulty.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P1. I cannot maintain my weight because of my swallowing problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E6. I have low self-esteem because of my swallowing problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P4. I feel that I am swallowing a huge amount of food.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

F4. I feel excluded because of my eating habits.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

Thank you for completing this questionnaire!

Name_____ Date_____ Hospital Number_____

Xerostomia Questionnaire (XQ)

This questionnaire asks your view about your dry mouth issue. This information will help us understand how you feel about dry mouth. Please rate your response which best reflects your experience in the past week. The higher the score, the worse your dry mouth.

1. Rate your difficulty in talking due to dryness

0___1___2___3___4___5___6___7___8___9___10

2. Rate your difficulty in chewing due to dryness

0___1___2___3___4___5___6___7___8___9___10

3. Rate your difficulty in swallowing solid food due to dryness

0___1___2___3___4___5___6___7___8___9___10

4. Rate the frequency of your sleeping problems due to dryness

0___1___2___3___4___5___6___7___8___9___10

5. Rate your mouth or throat dryness when eating food

0___1___2___3___4___5___6___7___8___9___10

6. Rate your mouth or throat dryness while not eating

0___1___2___3___4___5___6___7___8___9___10

7. Rate the frequency of sipping liquids to aid swallowing food

0___1___2___3___4___5___6___7___8___9___10

8. Rate the frequency of sipping liquids for oral comfort when not eating

0___1___2___3___4___5___6___7___8___9___10

Thank you for completing this survey.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ | | | ⌋

Your birthdate (Day, Month, Year): ⌊ | | | | | | | | ⌋

Today's date (Day, Month, Year): 31 ⌊ | | | | | | | | ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

M. D. Anderson Symptom Inventory - Head & Neck (MDASI-HN)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
1. Your **pain** at its WORST?											
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?											
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?											
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?											
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?											
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?											
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?											
14. Your problem with **mucus** in your mouth and throat at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **swallowing/chewing** at its WORST?											

Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject's Initials: _____

Study Subject # ☐☐☐☐

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

PLEASE USE BLACK INK PEN

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
16. Your choking/coughing (food/ liquids going down the wrong pipe) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your difficulty with voice/speech at its WORST?											
18. Your skin pain/burning/rash at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your constipation at its WORST?											
20. Your problem with tasting food at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your mouth/throat sores at their WORST?											
22. Your problem with your teeth or gums at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. General activity?											
24. Mood?	○	○	○	○	○	○	○	○	○	○	○
25. Work (including work around the house)?											
26. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
27. Walking?											
28. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

Appendix 4

Additional Participating Site:

Valley Health System
223 N. Van Dien Avenue
Ridgewood, NJ 07450
201-447-8000

Setting of Human Research

Valley Hospital/Valley Health System/Blumenthal Cancer Center

The Valley Health System (VHS) is comprised of three entities: The Valley Hospital (TVH), Valley Home Care, and Valley Physician Services. TVH is a private, not-for-profit hospital located in northern New Jersey. It is a fully accredited, 450 bed, acute care institution serving more than 440,000 people in Bergen county and the surrounding communities and is affiliated with the New York - Presbyterian Healthcare System and the Mount Sinai Health System. TVH earned the Gold Seal of Approval from the Joint Commission on Accreditation of Healthcare Organizations and is a nine-time winner of the JD Power and Associates Distinguished Hospital Award for Service Excellence.

TVH has developed and established a robust research infrastructure. In 2013, research administration and clinical trials were centralized to form The Valley Hospital Okonite Research Center (TORC). This support translates into over 25 dedicated research FTEs and a total operating budget of over $3M annually. TORC's programs include, the Human Subjects Protection Program (HSPP), Research Administration and Sponsored Programs (RASP), Clinical Trials & Research Program (CTRP), and the Translational Research Program (TRP) which houses the institutions core facilities and robust biorespositories, including the Oncology Biorepository and the Cardiac Bio-registry for Translational Research (CBTR).

HSPP provides the institution with regulatory policies and procedures, the IRB, regulatory education and training and the continual improvement processes. Valley received AAHRPP accreditation of its HSPP in June of 2016. RASP regulates all pre and post award activities, contract negotiation, coverage anaylsis, budget development and implements the cost accounting principles for federal awards and oversees the clinical trials management systems for the institution. The CTRP includes dedicated outpatient clinical research facilities and research coordination staff. The TRP is located in a dedicated building that houses state-of-the-art laboratories, a freezer farm with dedicated back-up generated and fully alarmed systems, dark room, shared equipment and core facilities that include biostatistics and bioinformatics.

Oncology Clinical Research Center

The oncology clinical research unit is comprised of dedicated research space imbedded in the Blumenthal Cancer Center. There is a dedicated Supervisor of Oncology Clinical Research and 5.0 FTEs of dedicated clinical trials research nurse and study coordinators in addition to a dedicated regulatory specialist. The physical location of the clinical trials staff adjacent to the

oncology medical practices and surgeons allows for streamlined, efficient and effective facilitation of investigators and patients enrolled in clinical research. On average the unit oversees 40 active clinical trials in the areas of lung, breast, gastrointestinal, brain, hematological, gyn and genitourinary cancers. In 2017, there were 16,163 oncology infusion visits, and 24 head and neck cancers treated at the Blumenthal Cancer Center.

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201-389-0193

Setting of the Human Research

All patients will be evaluated and consented in the multidisciplinary head and neck cancer clinic where eligibility criteria, entry and disease parameters will be evaluated and documented. Subjects who enroll on this study must be diagnosed with HPV related squamous cell carcinoma in the oropharynx, and must not have received any prior chemotherapy, radiotherapy or surgery for their cancer. Potential participants will be screened based on their past medical history, the results of their radiological scans, blood work, as well as a number of other required studies that will determine their eligibility. To be screened and consented on this study subjects must have had a biopsy and must display clinical features that are consistent with p16 positivity (i.e., no history of smoking/alcohol, age range, etc.). To be assigned to a group and participate in the experimental portion of the trial, surgery must be performed at MSSM, tumor tissue must be available, and both p16 and HPV status must be assessed and proven to be positive for HPV 16 or any high risk HPV subtype (i.e., 18, 33, 35, etc.) by PCR and p16 positive by IHC.

8.0 REGISTRATION PROCEDURES

After the patient signs the informed consent the patient will be registered for screening and once the investigator has verified that the patient meets all inclusion/exclusion criteria, the patient will be registered for and started on the protocol. Patients who lack p16 and HPV PCR may proceed to surgery however they will not be assigned to an experimental group and registered on the protocol until p16 IHC and HPV PCR are completed and positive. The verification of patient's eligibility and screening completion will be performed centrally after the receipt of the patient primary post-surgical registration form. It is mandatory not to exceed 21 days between the date of registration for screening and the start of the study treatment (surgery). In any case, all events occurring after the registration for therapy must be recorded in the case report form and will be taken into account in the analysis, whether the patient received the study treatment or not. Patient must receive surgery and be p16 IHC and HPV PCR positive to be included in the intent to treat analysis. Patients found to not meet entry criteria will be offered best therapy. Of note Drs Genden and Teng will be seeing patients at the Participating Site (VHS) to facilitate evaluation and recruitment procedures.

Procedures Involved in Human Research – Participating Site

Surgical Intervention
Transoral Robotic Resections or TORS will be peformed by the investigators listed above at Mount Sinai Health System (Mount Sinai Hospital and Mount Sinai West). Surgical guidelines will be performed as outlined in the protocol above.

Delivery of Radiation
Radiotherapy will be delivered by VSH department of Radiation Oncology by the VSH investigators noted above. The delivery, dosage, and technical factors will be uniform across all study sites, in keeping with the primary protocol document. In addition, formal volume reviews will be performed by Mount Sinai prior to treatment initiation . This will ensure consistency in radiation treatment planning, volumes, and delivery. VSH department of Radiation Oncology will adhere to the protocol quality assurance measures and isodose distribution as noted in the protocol. Protocol deviations will be reported to the Coordinating Site PI, and the radiation oncology co-investigators.

Delivery of Chemotherapy
Delivery of Chemoradiotherpy will mirror the protocol noted above for all patients accrued at the VHS Participating Site. Protocol deviations will be reported to the Coordinating Site PI, and medical oncology co-investigators.

Salvage Protocol
The salvage protocol for patients accrued at VHS will mirror the primary protocol salvage protocol. Referral to the Mount Sinai Health system surgeons who are investigators in the study will be performed in cases requiring surgical salvage. All salvage treatment plans will be reviewed by the Coordinating Site and Partipating Site investigators prior to initiation of therapy.

Number of subjects
The total number of subjects for trial completion remains unchanged. The addition of the VHS study subsite is for accrual support only. We expect approximately 5-10 patients per year to accrue from the VHS.

Blood Collection

Blood collection will adhere to the protocol for all patients accrued from the participating site. Samples (6 ml of blood/tube) will be obtained at each visit as noted in the protocol by VHS research personel. The exception to this will be if the intital blood sample is obtained immediately prior to surgery, which will be occurring at Mount Sinai Hospital and Mount Sinai West. All other blood samples will be stored in the VHS. Viable lymphocytes will be processed from green top tubes using standard ficoll-hypaque density gradient separation. Buffy coat layers will be stored as viable cells in DMSO-containing media at -80C to -170C.

Blood for serum will be spun within 5 hours of collection. Blood tubes will be spun at 3000 x g for 10' at 4°C and the serum removed by pipetting. Serum will be stored in 1ml aliquots. All samples will be stored at -80°C. White blood cell fraction will be stored in a single tube at local institutional temperature guidelines and kept locally. Blood samples will then be batched shipped to the Mount Sinai Health System Immune Core (as outlined above) at frequencies appropriate for the number of samples.

Specimen Banking

As no surgical intervention/transoral robotic surgery will be performed at the VHS Participating Site, all specimens obtained from subjects accrued at VHS will be managed per the protocol, as surgical interventions will only occur at Mount Sinai Hospital and Mount Sinai West, and therefore from the standpoint of specimen management, the management is identical and will be handled the same for all SIRS study sujects. Any additional biopsies from the primary tumor or a recurrence obtained at VHS will be processed at the VHS laboratory, reviewed by VHS Department of Pathology, and then shipped to the main biorepository at Mount Sinai for storage for correlative studies.

Data Management

Data Transfers

Vulnerable Populations

Multi-Site Human Research (Coordinating Center). Discuss how management and oversight of the project will occur. Describe the process by which the lead PI will collect information from each site and report appropriately to the IRB.

A. Recruitment materials for each site
B. Consent Template with local site PI name and address, for each site
C.

Participating Site Responsibilities:

Track Human Subjects Research education/Conflicts of Interest/administrative training

Ensure all personnel have completed the education requirements to be allowed to conduct research at their sites through CITIprogram.org

Ensure that all financial conflict of interest (FCOI) disclosures have been made through Sinai Central

Ensure that any required submission to a grants and/or contracts office to open a new study at a site are made

Comply with Mount Sinai Health system research committee review and recommentations: Peer Reviewed Monitoring Committee, Radiation Safety Committee,

Storage and Handling of Research Data

Transfer of Specimens