UMCC 2015.126: Phase II Treatment Stratification Trial Using Neck Dissection-Driven Selection to Improve Quality of Life for Low Risk Patients with HPV+ Oropharyngeal Squamous Cell Cancer

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1.0 Introduction

Over the past three decades, there has been an increase in the incidence of oropharyngeal squamous cell carcinoma (OPSCC)[2,3]. More recently, it has been shown that high-risk human papillomavirus (HPV) is associated with and is a causative factor leading to OPSCC[4]. Patients who have HPV-positive cancers have a better prognosis than patients who are HPV-negative, and distinct oncologic mechanisms have been elucidated in this biologically favorable disease[5-8]. Given the significance of HPV with prognosis, p16 staining (a well-documented biomarker for tumor HPV status[9]) is standard of care for all oropharyngeal tumors at the University of Michigan.

Despite the favorable prognosis associated with HPV-positive OPSCC, this biologic marker has not yet been used to determine optimal therapeutic management. Both surgical and non-surgical management in patients with OPSCC have shown excellent locoregional control rates[10-12]. Patients with HPV-positive OPSCC tend to be younger and healthier[4], and with such high survival rates for this disease, there is an important shift of focus to long term treatment complications that impact quality of life (QOL)[13].

Our group has undertaken two single arm phase II trials looking at the optimal management of and toxicity associated with treatment in OPSCC (UMCC 9921 and UMCC 0221)[14-17]. UMCC 9921 used chemoselection followed concurrent high dose cisplatin or carboplatin with radiation for responders in patients with OPSCC[14]. The majority of patients showed good response to induction and subsequently high survival rates, especially HPV-positive patients. One limitation was the treatment related toxicity with this paradigm, with grade 3,4 toxicities of up to 75% and 25% of patients requiring a G-tube longer than 6 months. UMCC 0221 was designed to improve the toxicities of treatment and focused on IMRT planning objectives included sparing of the swallowing structures (ie, pharyngealconstrictor muscles, esophagus, glottic and supraglottic larynx, major salivary glands, and oral cavity)[18]. Concurrent chemotherapy included weekly carboplatin (AUC 1) and paclitaxel (30 mg/m2). Survival rates were higher in UMCC 0221 when compared to a matched cohort in UMCC 9921. Toxicities with this treatment paradigm were also greatly improved including the grade 3,4 toxicity profile as well as G-tube rates[19]. QOL data was also collected in this cohort, with relatively good scores in dysphagia, xerostomia and overall QOL measures[20].

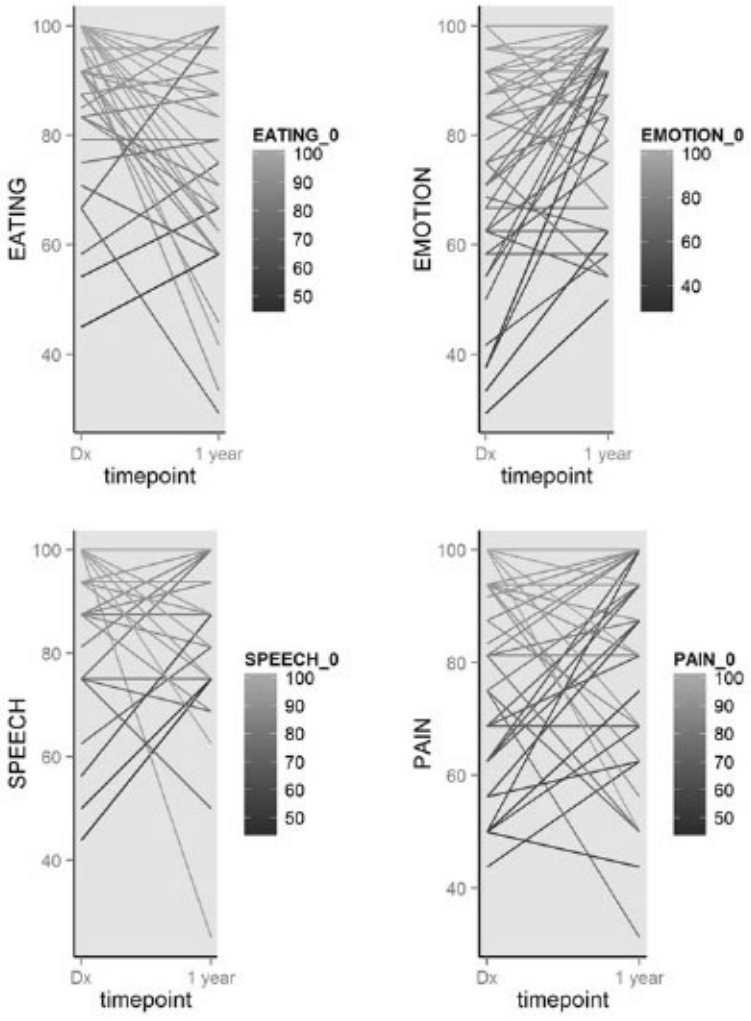
The Head and Neck Quality of Life (HNQOL) Instrument is a multiple domain instrument for the assessment of disease specific quality of life in head and neck cancer patients. The instrument consists of four domains: communication, head and neck pain, eating and swallowing, and emotional score and transformed to a 0 (worst) to 100 (best) score.

In unadjusted analysis, quality of life at one year in our historical control population was significantly better in the emotional domain, but significantly worse in the eating domain. No significant changes in means were observed for the speech and pain domains. Means (std) for each domain pretreatment and at 1 year are summarized in the table below.

	Pretreatment			**1 year Post**			**Δ at 1 year**		
Domain	n	Mean	Std Dev	n	Mean	Std Dev	n	Mean	Std Dev
Eating	64	92.4	12.4	57	78.7	17.5	57	-13.0	18.4

Speech	64	93.2	12.7	57	90.2	14.7	57	-2.1	16.1
Emotion	64	76.3	18.4	57	87.6	14.8	57	11.1	16.3
Pain	64	81.8	15.8	57	83.8	18.0	57	2.9	21.2

Although a higher score is desirable in every domain, reasonable expectations for 1 year quality of life score are domain specific. The score profiles for individual patients pretreatment to 1 year post treatment from our historical cohort are presented in Figure 2. Each individual line represents a single patient and is shaded by their reported pretreatment domain score (lighter color indicates BETTER pretreatment QOL). Patients' pretreatment scores were a significant predictor of one year score in every domain, though the associations were not necessarily monotonic. For example, patients who experienced decreases in their eating scores at one year tended to be those who had the best eating quality of life pretreatment. In the pain domain, patients with high levels of pain pretreatment (low pain domain scores) tended to see improvement at one year although, on average, the mean change in pain domain score was not significant and displayed high variability.



While there is no randomized data comparing surgery followed by adjuvant therapy to primary chemoradiation in OPSCC, there is an increased interest in surgery as a treatment modality, especially in the HPV positive era. Surgery allows for more accurate patient staging (pathologic stage) to determine their optimal treatment, including the need for adjuvant therapy[13]. Our previous trials used clinical and radiologic staging, and the accuracy of a radiologic compared to pathologic staging has been shown to differ in other studies where pathologic staging was available in up to 40% of patients[21]. In fact, Walvekar et al found that 24% of patients who were downstaged after surgery for OPSCC, meaning a avoidance of chemotherapy or radiation could have been possible in up to a quarter of their cohort. Thus surgery may be used to de-escalate therapy in a proportion of patients, which would allow less treatment modalities and could improve quality of life.

Most surgical treatment paradigms involve a surgical approach to both the primary tumor site and cervical lymph nodes[11-13]. With these treatment paradigms, adjuvant radiation is required in up to 90% of patients and the addition of chemotherapy in up to 50% of patients[11]. Another interpretation of this data is that three modalities of treatment (surgery, radiation, chemotherapy) are required in up to 50% of patients. While survival rates are high even for the patients with triple modality therapy, quality of life metrics including dysphagia and performance scores in diet for patients who receive three modalities is lower than patients who receive one or two modality therapy[22]. Thus any trial focusing on quality of life should minimize the number of treatment modalities when possible.

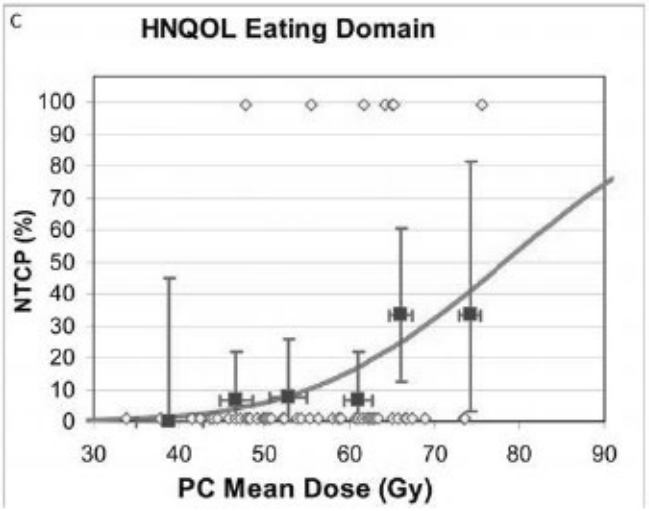
Currently the addition of chemotherapy to radiation is recommended in patients with oropharyngeal cancer staged T2 N1 M0, any T N2-3 M0, or those with extracapsular extension post-operatively. However, it is important to recognize the relative benefit and associated toxicity as to appreciate the interest in de-intensification. The MACH-NC meta-analysis is the largest analysis to examine the role of adding chemotherapy to radiation and combined 93 randomized trials and more than 17,000 patients with head and neck cancer of any site (oral cavity, oropharynx, larynx, etc) but did not stratify by prognostic factors (including stage, HPV, smoking, or age). In this study concomitant chemotherapy and radiation was found to offer a significant improvement in 5-year overall survival compared to radiation therapy (absolute difference of 6.5%)[23]. Although several prospective studies are aiming to identify the effects of therapy de-intensification, only one retrospective study has elucidated the pattern of recurrence in low risk patients (HPV+, <10 pack-year smoking, and T1-3 disease) based on treatment with radiation alone versus concomitant chemoradiation. It was shown that low risk patients, those with N0-N2 nodal involvement, had no difference in disease control rates with the introduction of chemosensitization as compared to those receiving only radiotherapy[24]. Considering the relative benefit of the addition of chemotherapy, there are significantly increased rates of severe toxicities with the addition of chemotherapy to radiation. Rates of serious grade 3-4 toxicities range between 19-25%[25-27] with radiation alone versus 40-70% with chemoradiation[19,28]. Hence, de-intensification in low risk populations, including limiting the use of chemotherapy, is a crucial research question in OPSCC research.

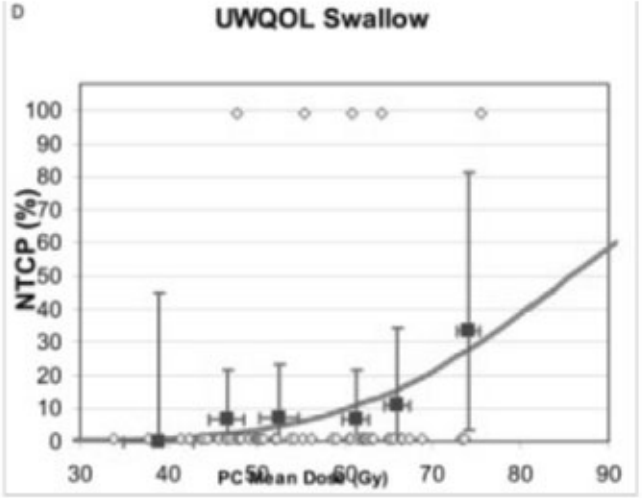
The largest ongoing prospective trial to decrease toxicities in patients with HPV positive OPSCC given the high cure rates is ECOG E3311. This prospective trial treats all patients with surgery including TORS and neck dissection, and the randomization occurs after pathologic staging. Low risk patients (T1T2N0-1) are observed after surgery and high risk patients (more than 5 nodes, positive margins, gross extracapsular extension) receive adjuvant weekly cisplatin and radiation. This study randomizes patients between low dose and standard radiation that are at intermediate risk (between 2-5 metastatic

nodes, close margins, micro extracapsular spread) with the primary endpoint of 2 year progression free survival.

This study design has two major drawbacks. First, all patients are receiving surgical treatment to the primary site, even in advanced stage neck disease. This means that the majority of patients will either receive adjuvant radiation or chemoradiation (over 90% based on historical data) to the primary site after surgery. TORS, therefore, adds a risk of surgery to the primary site and adds morbidity to the swallowing organs when these patients could undergo radiation to the primary site with the same cure rates. With multimodality treatment known to predictor lower quality of life scores[22], we sought to design a trial that does not subject all patients to TORS rather only candidates who would undergo surgery alone without the need for adjuvant treatment.

Secondly, the primary endpoint of E3311 is really to determine the effect of decreasing the radiation dose from 60Gy/30 fractions to 55Gy/25 fractions in the intermediate risk group. All of these patients would have undergone resection of the primary site in this trial. Our group is not sure the significance of the decrease from 60Gy to 50Gy in terms of quality of life. While we have no direct comparisons using radiation alone, our group did publish examining swallowing organ late complication probabilities and dosimetric correlates in a cohort that underwent chemoradiation for oropharynx cancer. When examining the mean dose to the pharyngeal constrictor and its relationship to patient reported quality of life, the differences in the normal tissue complication probability between patients who received 50Gy and 60Gy is minimal[29]. In the figure below, the blue boxes represent groups of 10 Gy, and while the overall model shows increasing NTCP with increasing doses to the pharyngeal constrictor, the blue boxes show minimal increases when looking at the reported quality of life between 50Gy and 60Gy. So while this trial may indeed show lower dose radiation is as effective to cure patients with OPSCC with intermediate risk disease, the quality of life scores may not show improvement.





The driver of adjuvant therapy in surgical trials is typically the adverse features found during the neck dissection. Groups that perform surgery on the primary site up front or concurrent with neck dissection[11,12] have shown less than 5% have adverse features of the primary site (perineural invasion, positive margins) that require the addition of adjuvant therapy. In fact, patients with OPSCC, particularly that are HPV positive, tend to present with earlier T classification disease[30]. Thus treatment

of the primary site is not the driving factor in determining adjuvant therapy, rather the N classification of disease during neck dissection is most important part of determining adjuvant treatment.

This trial seeks to minimize the number of treatment modalities in patients with HPV positive OPSCC in order in improve quality of life. We plan to perform neck dissection up front to more accurately pathologically stage patients, and then stratify treatment based on adverse features found on pathologic examination. This paradigm will minimize treatment modalities to the primary site, because patients with adverse features in the neck that would require adjuvant radiation or chemoradiation will not undergo surgery to the primary and thus will only receive one (radiation alone) or two chemoradiation) modalities to critical swallowing structures. Alternatively, patients who undergo neck dissection who have no adverse features have the potential to undergo single surgical modality to the primary site. Our hypothesis is that patients treated with this paradigm will have superior QOL compared to our historical cohort treated under UMCC 0221.

2.0 Objectives

2.1 Primary Objectives

2.1.1 To determine whether neck dissection-driven treatment stratification can improve eating and swallowing quality of life.

2.2 Secondary Objectives

2.2.1 To determine whether neck dissection-driven treatment stratification to minimize the number of treatment modalities in patients with low risk oropharyngeal squamous cell carcinoma will change quality of life in other domains (speech, emotion, pain) and methods of assessment (videofluoroscopy, UWQOL).

2.2.2 To determine progression free survival, disease specific survival and overall survival outcomes

2.2.3 To determine the impact of neck dissection on shoulder function using the Neck Dissection Impairment Index within each treatment strata

2.2.4 To assess acute and late toxicities of each treatment modality (surgery, chemotherapy, radiation)

2.2.5 To evaluate serum and tissue biomarkers to predict treatment outcome

3.0 Eligibility Requirements

3.1 Patients must have pathologically-confirmed, previously untreated, p16-positive oropharyngeal squamous cell carcinoma

3.2 Patients must have pretreatment neck and chest imaging

3.3 Tumors must be potentially surgically resectable via a transoral approach, at the discretion of the treating surgeon

3.4 Patients with T stage T1-3

3.5 Patients with N stage N0-N2c

3.6 ECOG Performance status 0-2 (See **Appendix A**)

3.7 Patients are adults (Age ≥18)

3.8 Patients must agree to biospecimen submission for tissue and serum processing and storage for secondary biomarker studies

3.9 Patients must give documented informed consent to participate in this study.

3.10 Patients must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry, for the duration of chemoradiation (treatment) and for 3 months after discontinuing treatment. Women of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to starting treatment.

3.11 Women of child-bearing potential, unless they are using highly effective methods of contraception during dosing and for 30 days after study treatment. Women not of child-bearing potential will be defined as all women older than age 50 and anovulatory for 12 months.

3.12 Sexually active males must use a condom during intercourse while receiving chemoradiation and for 90 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. Likewise, male subjects should not donate sperm during the time they are receiving chemoradiation and for 90 days after stopping treatment..

4.0 Exclusion Criteria

4.1 Prior head and neck radiation or prior chemotherapy for HNSCC.

4.2 Patients with T4 disease.

4.3 Patients with N3 disease.

4.4 FNA evidence of squamous cell carcinoma involving 3 or more lymph nodes

4.5 Patients with matted lymph nodes, defined as three nodes abutting one another with loss of intervening fat plane that is a replaced with radiologic evidence of extracapsular spread.

4.6 Patients with an outside primary site biopsy showing perineural or perivascular invasion

4.7 Documented evidence of distant metastases.

4.8 Active infection.

4.9 Patients residing in prison.

4.10 Age < 18 years.

4.11 Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (Appendix B).

4.12 Unstable angina or a history of myocardial ischemia within prior 6 months

4.13 Patients with any of the following laboratory values at baseline:
4.13.1 Absolute neutrophil count (ANC) < 1,000/mm3 [SI units 109/L]
4.13.2 Platelets < 75,000/mm3 [SI units 109/L]
4.13.3 Hemoglobin < 9.0 gm/dL [SI units gm/L]
4.13.4 Calculated or measured creatinine clearance (method determined by the prescribing physicians) < 50 ml/min
4.13.5 Bilirubin > 1.5 x ULN, except for patients with known Gilbert syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
4.13.6 Aspartate transaminase (AST) > 3.0 x ULN
4.13.7 Alanine transaminase (ALT) > 3.0 x ULN

4.14 Pregnancy or breastfeeding female.

4.15 Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for the study

5.0 Initial Screening

Note: Day 1 is defined as day of neck dissection. All Initial Clinical Evaluations must occur prior to Day 1 unless otherwise specified.

5.1 Complete history and physical examination, multidisciplinary examination by Otolaryngology and Medical Oncology, with descriptive documentation of extent of primary tumor and regional disease.

5.2 PET/CT of the head though thighs within 42 days. Imaging studies obtained at outside institutions prior to consultation and available for digital review are acceptable. Comment regarding review of imaging for the presence/absence of matted nodes will be required in initial screening visit documentation. Decision to obtain additional imaging (i.e. bone scan) is to the discretion of the prescribing physician

5.2.1 Diagnostic CT of the Neck and Chest will be required only if the PET/CT does not have diagnostic quality CT imaging or if PET is not within 42 day window.

5.3 Completion of laboratory studies: Comprehensive panel, CBC with differential and platelets, magnesium and creatinine clearance (calculated or measured).

5.4 Quality of life assessments (UWQOL, FACT-HN: version 4, HN-QOL, AND V-RQOL, Neck impairment index) (See Section 23, Appendix D)

5.5 Financial and Work Survey (See Section 23, Appendix D)

5.6 Videofluoroscopy of swallowing within 28 days

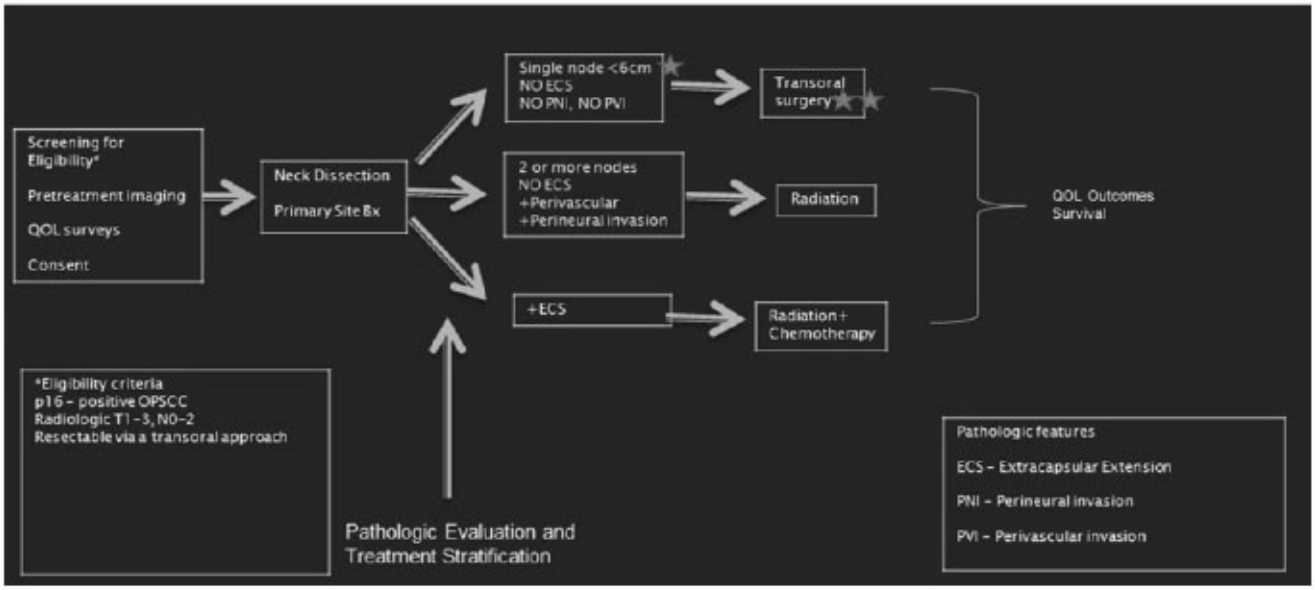
5.7 Representative tumor if available and blood specimen sent to Head and Neck Cancer Research laboratory (samples as determined by the prescribing physicians)

5.8 Pregnancy test for women of child bearing potential.

5.9 Audiograms for patients with hearing complaints or hearing loss at the discretion of the prescribing physician.

6.0 **Schema**

Figure 1: Study Schema



★ Patients with a single node ≥ 6 cm will be taken off study

★★ Patients who undergo transoral surgery and have a positive margin will undergo a further resection to obtain negative margins if possible. If negative margins cannot be obtained, the patients will be referred for adjuvant chemoradiation

After enrollment, all patients will undergo neck dissection (see section 14.1) and primary site biopsy. Pathology will be reviewed and patients will be stratified into one of three treatment groups. This trial utilizes Version 7 (2010) of the AJCC Pathologic Staging Criteria. 1) Patients with a single lymph node that measures less than six centimeters, have no extracapsular extension in the lymph node, and have no perineural or perivascular invasion of the primary biopsy will undergo transoral surgery of the primary site. Patients with a single lymph node greater than or equal to six centimeters will be taken off trial. 2) Patients who have 2 positive nodes with no extracapsular extension, or have perineural or perivascular invasion of the primary biopsy will undergo radiation. 3) Patients who have extracapsular extension in any number of lymph nodes or in those patients in whom negative margins are unable to be obtained after the completion of transoral surgery will undergo chemoradiation.

7.0 Study Design

7.1 All treatment after enrollment (including neck dissection, biopsies, radiation therapy, and chemotherapy) will be administered at the University of Michigan (Ann Arbor, MI)

7.2 Patients with p16+ oropharyngeal cancer will be enrolled. Diagnosis of oropharyngeal cancer will be based on multi-disciplinary clinical decision making including review of pre-enrollment imaging and biopsies.

7.2.1 Prior to enrollment, biopsy of either the primary lesion or a non-primary lesion with p16 testing are acceptable.

7.2.2 Biopsies performed at an outside institution will be acceptable for enrollment

7.3 Patients will undergo baseline evaluation prior to surgery including QoL surveys, imaging, and oral rinses, plasma/blood draws for correlative analysis

7.4 All patients will undergo a neck dissection (see section 14.1) with tissue biopsy as well as biopsy of the primary site when possible. Pathology of the primary and nodal specimens will then be reviewed as to determine the next intervention per protocol (See 6.0 Schema).

7.4.1 Tissue biopsies (both primary tumor and adjacent normal) will be obtained at time of neck dissection per operating surgeon's discretion and patient safety. If feasible, fresh tissue will be obtained for correlative analyses.

7.4.2 Every effort will be taken to obtain a biopsy of the primary site however, if it is unable to be obtained (i.e. due to a small primary lesion previously extensively biopsied), these patients will not be excluded from the study assuming adequate outside institution biopsy specimen is available and submitted for histopathologic review.

7.5 Based on operative findings including degree of nodal involvement, extracapsular spread, and lymphovascular involvement, patients will be designated to be treatment arms consisting of surgery, definitive radiation, or definitive chemoradiation. After completion of therapy (surgical, radiation, or combined modality) patients will be followed closely on an outpatient basis including regular exams, quality of life questionnaires, and interval surveillance imaging as clinically indicated. Swallowing function will also be addressed by videofluoroscopy one year after completion of therapy. Blood/plasma and oral rinses for correlative studies will be collected at 3-month intervals during 3 years of follow up.

7.5.1 Biopsies obtained (prior to study, of the primary site, and of involved lymph nodes) will be divided and stored at both the laboratory of Dr. Brenner as well as the UMCC Head and Neck SPORE Tissue Repository per standard procedures

7.6 Patients will be taken off trial for disease progression (detected clinically or radiologically), significant side effects, per patient preference, or for noncompliance with treatment plan. Off trial patients will continue to be followed for survival, disease specific survival, and disease status through 3 years. There will be a hard stopping rule based on worse than expected 3 year disease specific survival and/or worse than expected impairment neck function to ensure patient safety (See Statistical section).

7.7 Study Schedule

7.7.1 All Enrolled Patients Prior to Neck Dissection

7.7.1.1 Prior to undergoing neck dissection, patients will undergo baseline staging imaging (PET/CT). Imaging studies obtained at outside institutions prior to consultation and available for digital review are acceptable.

7.7.1.2 All trial patients will be seen and followed in the Medical Oncology clinic for enrollment and data collection purposes as to standardize data and specimen collection processes.

7.7.1.3 Baseline labs as well as correlative studies (plasma, oral rinses) will be obtained prior to neck dissection and primary site biopsy.

7.7.1.4 To assess swallowing function on a longitudinal basis and analyze the effect of therapy, a baseline videofluoroscopy study will be obtained prior to primary site biopsy/neck dissection.

7.7.2 All Patients Undergoing Neck Dissection and Tumor Biopsy

7.7.2.1 A biopsy of the primary site will be performed whenever possible. However, given that in some patients with early disease the primary tumor volume is very low there may not be a possibility to obtain a biopsy of the primary site.

7.7.2.1.1 In such patients where a biopsy of the primary site is not possible due to prior biopsy, tissue obtained prior to enrollment will be used to determine eligibility and for correlative studies

7.7.2.2 Patients will undergo neck dissection as described in section 14.1

7.7.3 Transoral Surgery Arm

7.7.3.1 Patients will undergo transoral surgery as described in section 14.2 with no additional pre-therapy evaluation from that described above.

7.7.3.2 Transoral surgery will be performed following neck dissection when deemed medically appropriate by treating head and neck surgeon (within 28 days).

7.1.1.1 Patients with negative margins and no adverse features will be followed by observation

7.1.1.2 Patients with positive margins will undergo a further resection to obtain negative margins if possible, at the discretion of the treating physician. If negative margins cannot be obtained, the patients will be referred for adjuvant chemoradiation

7.1.1.3 Patients with adverse features in the primary site (perineural invasion, perivascular invasion) will be referred for adjuvant radiation.

7.1.2 Post-dissection Radiation only Arm

7.4.4.1 After allocation into the adjuvant radiation arm post-neck dissection, patients will undergo radiation therapy

7.4.4.2 Radiation will be started following neck dissection when deemed medically appropriate by the treating ENT surgeon (within 28 days).

7.4.4.3 During radiation therapy, patients will be followed on a weekly basis for symptom management and supportive cares

7.4.5 Post-dissection Chemotherapy + Radiation Arm

7.4.5.1 After allocation into chemoradiation arm post-neck dissection, patients will undergo radiation therapy in combination with weekly Carboplatin (AUC=1) and Paclitaxel (30 mg/m2)

7.4.5.2 Chemoradiation will be started following neck dissection when deemed medically appropriate by treating ENT surgeon (within 28 days).

7.4.5.3 During chemoradiation, patients will be followed on a weekly basis in the medical oncology clinic for symptom management, supportive cares, and toxicity management.

7.5 Evaluation of Response to Treatment

7.5.1 Outpatient research examinations will be performed 1 month (+/- 2 weeks) after the completion of definitive therapy at 3-month intervals (+/- 3 weeks) during year 1 of follow-up and at 3-month intervals during years 2 and 3 of follow-up (+/- 4 weeks). All patients will be seen in Medical Oncology for research visits for the duration of research follow up as to standardize enrollment and data collection (including survey collection). (See Section 9.0, Study Calendar)

7.5.2 Patients will be seen by Radiation Oncology or Otolaryngology 1 month (+/- 2 weeks) after the completion of definitive therapy then at 3-month intervals (+/- 3 weeks) during year 1 of follow-up and at 3-month intervals during years 2 and 3 of follow-up (+/- 4 weeks). At these visits surveillance exams will be performed including flexible laryngoscopy. (See Section 9.0, Study Calendar)

7.5.3 Toxicities related to treatment will be evaluated using the Common Toxicity Criteria Adverse Events (CTCAE, version 4.03) weekly during treatment and at every follow-up visit for 3 years.

7.5.4 Quality of Life Questionnaires (UWQOL, FACT-HN: version 4, HN-QOL, and V-RQOL, Neck Impairment Index) will be given to patients at each follow-up research visit after completion of definitive therapy through 3 years.

7.5.5 A Financial and Work Survey will be given to patents at 3, 12 , and 24 month follow-up research visits

7.5.6 PET/CT will be obtained at 3 months (+/- 2 weeks) post definitive therapy

7.5.7 Chest imaging (CT Chest or Chest X Ray per discretion of treating physician) will be obtained at 1-year increments (+/- 2 weeks) following completion of definitive therapy.

7.5.8 Repeat videofluoroscopy will be performed at 12 months (+/- 1 month) after completion of radiotherapy.

7.5.9 Blood/plasma draws and oral rinses for correlative studies including HPV analyses will be collected at each follow up visit through 3 years.

8.0 Dose Delays and Modifications

Toxicity	Action Taken
Hematologic Toxicity	

• Neutrophil count is < 1000 cells/ mm3 • Platelet count is < 75,000 cells/mm3	**Step 1:** Interrupt treatment (Carboplatin + Paclitaxel) until the toxicity has resolved to ≤ Grade 1 or pre-therapy baseline, up to 2 weeks (14 days). **Step 2:** Restart treatment with Carboplatin reduced by an AUC of 0.25 and Paclitaxel by 20%; monitor as clinically indicated.
• Grade 4 neutropenia (< 500 cells/mm3) lasting 7 days or more • Grade 3 or 4 neutropenia with an oral temperature of at least 38.5°C	**Step 1:** Interrupt treatment (Carboplatin + Paclitaxel) until resolved to ≤ Grade 1, up to 2 weeks (14 days). **Step 2:** Carboplatin reduced by an AUC 0.25 and paclitaxel by 20%. Monitor as clinically indicated.
Other Toxicities	
• Any Grade 2 or 3, if clinically significant **with the exception of mucositis or other toxicities deemed to be related to radiation (Grade 2 and 3 mucositis is expected with chemoRT)**	**Step 1:** Interrupt treatment (Carboplatin + Paclitaxel) up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1. **Step 2:** Carboplatin reduced by an AUC 0.25 and paclitaxel by 20%. Monitor as clinically indicated.
• Any recurrent Grade 2 or 3 after two (2) dose reductions, if clinically significant **with the exception of mucositis or other toxicities deemed to be related to radiation (see above)**	Discontinuation of adjuvant chemotherapy (Carboplatin + Paclitaxel) and follow-up per protocol.
• Any Grade 4 other than hematologic toxicities (see above)	Discontinuation of adjuvant chemotherapy (Carboplatin + Paclitaxel) and follow-up per protocol.

9.0 Study Calendar

			Definitive Therapy					Follow Up After Definitive Therapy (dated relative to end of definitive therapy)[13]						
	All Patients		Transoral Surgery Arm	Radiation Only Arm		Chemoradiation Arm		All Patients						
	Pre Therapy	Day 1		Pre-RT	Weekly During RT	Pre-ChemoRT	Weekly During ChemoRT	+ 1 month[A]	+ 3 month[B]	Every 3 months for months 3-12[C]	+ 12 month[D]	Every 3 months for months 13-36[E]	+ 24 month[F]	+36 month[F]
H&P (by Med Onc and Oto)[1]	X													
Tumor biopsy[2]	X													
Otolaryngology or Radiation Oncology Evaluation[12]	X							X		X		X		
Med Onc Evaluation[6]	X			X	X	X	X	X		X		X		
Radiation Oncology				X	X	X	X							
CBC with Diff	X			X	X	X	X							
CMP, Mg	X			X	X	X	X							
Pregnancy Test in women of childbearing potential	X					X								
Blood/plasma, oral rinses for correlative studies	X							X		X		X		

	All Patients		Transoral Surgery Arm	Radiation Alone Arm		Chemoradiation Arm		All Patients						
	Pre-Therapy	Day 1		Pre-RT	Weekly during RT	Pre ChemoRT	Weekly During ChemoRT	+ 1 month[A]	+ 3 month[B]	Every 3 months for months 3-12[C]	+ 12 month[D]	Every 3 months for months 13-36[E]	+ 24 month[F]	+36 month[F]
CT Neck and Chest[14]	X[9]													
PET/CT	X[9]								X[10]					
Chest Imaging[11]											X		X	X
Neck Dissection		X												
Primary site tumor biopsy[3, 7]														
Transoral Surgery			X											
Toxicity Evaluation[4]	X			X	X	X	X							
QOL Questionnaire[5]	X			X		X		X		X		X		
Financial & Work Survey	X								X		X		X	
Videofluoroscopy	X										X			
Audiogram[8]	X													
Dental Evaluation[8]				X		X								
Carboplatin (AUC=1)							X							

Paclitaxel (30 mg/m^2)							X							

[1] Initial evaluation by Otolaryngology (including fiber-optic nasal pharyngoscopy), and Medical Oncology
[2] Pre-enrollement tumor biopsy may be of primary lesion or a non-primary lesion
[3] If able to be obtained
[4] Toxicities will be evaluated using the CTCAE, version 4.03
[5] Quality of life instruments include UWQOL, FACT-HN: version 4, HN-QOL, V-RQOL, and neck impairment index
[6] Medical oncology will manage patient enrollment and data collection across all arms as to standardize specimen and data (including patient surveys) collection processes
[7] Biopsy of primary tumor can be obtained prior or after the neck dissection. Inability to obtain such a biopsy is not an exclusionary criteria
[8] At the discretion of the treating physician for patients
[9] Imaging studies obtained at outside institutions prior to consultation and available for digital review are acceptable. Comment regarding review of imaging for the presence/absence of matted nodes will be required in initial screening visit documentation. Decision to obtain additional imaging is to the discretion of the prescribing physician.
[10] Required in those patients who underwent definitive therapy with either radiation or chemoradiation
[11] CT Chest or Chest X Ray at clinical discretion of the prescribing physician
[12] Patients will be followed by both Radiation Oncology and Otolaryngology. They will alternate seeing the patient seeing the patient during the specified intervals so that as a result, each service sees the patient approximately once every 6 months during which a flexible laryngoscopy will be performed for surveillance (+/- 3 weeks).
[13] Patients off trial will be followed for survival, disease specific survival, and disease status through 3 years
[14] Diagnostic CT of the Neck and Chest will be required only if the PET/CT does not have diagnostic quality CT imaging or if PET is not within 42 day window
[A] =+/- 2 weeks
[B] =+/- 3 weeks
[C] = +/- 3 weeks
[D] = +/- 4 weeks
[E] = +/- 4 weeks
[F] = +/- 2 weeks

10.0 Response Assessment Criteria

10.1 Efficacy will be determined by imaging. Initial staging imaging will be obtained at enrollment (valid within 28 days of trial drug initiation), then routine imaging will be obtained at 3 months from completion of definitive therapy.

10.2 Decision to obtain further imaging will be left to the provider (i.e. if on clinical exam there are signs concerning for disease recurrence)

10.3 If there is clinical or radiologic evidence concerning for recurrent malignancy, confirmatory biopsy will be required before designating the patient to have recurrent disease

11.0 Criteria for Discontinuation of Treatment

11.1 Unacceptable adverse event(s).

11.2 Intercurrent illness, which prevents further administration of treatment.

11.3 Patient preference.

11.4 Progressive disease.

11.5 Life threatening or other unacceptable drug-related toxicity.

11.6 General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator(s).

12.0 Drug Information

12.1 Carboplatin

12.1.1 Chemistry: Carboplatin (CBDCA) is a hydrophilic platinum coordination compound and is an analog of cisplatin, producing intrastrand DNA cross-links.

12.1.2 Human Toxicology: Side effects of CBDCA include: myelosuppression, nausea, vomiting, abdominal pain, diarrhea, and constipation. Other toxicities include: allergic reactions (including hypersensitivity, i.e. rash, urticaria, erythema, pruritis, bronchospasm, and profound hypotension), peripheral neuropathy, paresthesias, loss of hair, hearing loss, visual disturbances, and change in taste. Serum creatinine elevations and blood urea elevations have occurred as well as abnormal liver function tests and decreased serum electrolyte values. Although rare, pain asthenia, cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in some patients. Cancer-associated hemolytic uremic syndrome has been reported rarely carboplatin may cause fetal harm; therefore, women of childbearing potential should be advised to avoid becoming pregnant. The renal effects of nephrotoxic compounds may be potentiated by carboplatin. Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or to other platinum-containing compounds or mannitol. This drug should not be used in patients with severe bone marrow depression or significant bleeding. The occurrence of acute

leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

12.1.3 Pharmaceutical Data

12.1.3.1 Kinetics: The differences in potencies of carboplatin as cisplatin are due to differences in equation rates. The initial half-life of carboplatin is 1.1-2.0 hours and the post-distributional half-life is 2.5-5.0 hours. Sixty-five percent of the dose is excreted into the urine within twelve hours. Carboplatin is not bound to plasma proteins.

12.1.3.2 Formulation: Carboplatin is supplied as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous injection. Each vial contains equal parts by weight of carboplatin and mannitol. Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, D5W, or normal saline injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

These dilutions all produce a carboplatin concentration of 10 mg/mL. Carboplatin can be further diluted to concentrations as low as 0.5 mg/mL with D5W or normal saline injection, USP.

12.1.3.3 Storage and Stability: Unopened vials of carboplatin for injection are stable for the life indicated on the package when stored at controlled room temperature (15-30°C), and protected from light. When reconstituted as directed, the solution of carboplatin exhibits no decomposition for eight hours at room temperature (25 oC). Like cisplatin, this drug should not be given through aluminum needles. Caution: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded eight hours after dilution.

12.1.3.4 Administration: Intravenous infusion.

12.1.4 Supplier: Carboplatin is commercially available and should be purchased by a third party.

12.2 Paclitaxel

12.1.1 Chemistry: Paclitaxel is a semi-synthetic antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization hence producing abnormal bundles of microtubules throughout the cell cycle. As a result, paclitaxel inhibits interphase and cellular function.

12.1.2 Human Toxicology: Side effects of paclitaxel include: hypersensitivity reaction, myelosuppression, alopecia, peripheral neuropathy, nausea/vomiting, mucositis, alkaline phosphatase elevation, abnormal EKG, myalgia/arthlagia, asthenia, and hypotension. The development of severe hypersensitivity reactions is rare and documented in 1% of patients overall.

12.1.3 Pharmaceutical Data

12.1.3.1 Kinetics: Following IV administration, plasma concentrations decline in a biphasic manner due initially to distribution and later due to slow efflux of the drug from the peripheral compartment. Pharmacokinetic studies have demonstrated extensive extravascular distribution and/or tissue binding of paclitaxel In addition, paclitaxel has been demonstrated to be highly protein bound (89-98% of infused sample). The drug is extensively non-renally cleared with 71% excreted via GI tract and 14% via renal clearance. It has been demonstrated to be metabolized primarily by CYP450 2C8 and to a lesser extent 3A4. As a result, the pharmacokinetics of paclitaxel may be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4

12.1.3.2 Formulation: Paclitaxel is a clear, colorless slightly yellow viscous solution intended for dilution prior to intravenous infusion. Each mL of sterile non-pyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor, and 49.7% dehydrated alcohol:

12.1.3.3 Storage and Stability: Unopened vials of paclitaxel for injection are stable for the life indicated on the package when stored at controlled room temperature (20-25ºC), and protected from light. Neither freezing nor refrigeration adversely affects the stability of the product. When reconstituted as directed, the solution of carboplatin exhibits no decomposition for up to 27 hours at room temperature (25 ºC).

12.1.3.4 Administration: Intravenous infusion.

12.1.4 Supplier: Paclitaxel is commercially available and should be purchased by a third party.

13.0 Radiation Therapy

13.1 Immobilization, imaging, and target definitions: All patients will undergo immobilization using a thermoplastic mask as described previously[31] or another device providing similar or better immobilization. Targets will be defined on the planning CT images with aid from pre-operative diagnostic CT and PET-CT. The targets will consist of the primary tumor (gross tumor volume, GTVs), as well as lymph node groups involved or at risk of metastases in the dissected neck (clinical target volumes, CTVs). The GTVs will be expanded to yield the corresponding CTVs according to clinical assessment in each case. All CTVs will be expanded uniformly by 0.3 cm to yield the corresponding planning target volumes (PTVs). Organs at risk (OARs) that will be defined and contoured for each case for IMRT

optimization will include the parotid and submandibular glands, lips, oral cavity (encompassing the oral surfaces of the lips, cheeks (buccinator muscle), hard and soft palate, tongue, base of tongue and floor of mouth), glottic larynx, pharyngeal constrictor muscles, upper esophagus, spinal cord, and mandible. Additional OARs may be defined in specific cases as clinically indicated.

13.2 Treatment planning: All targets will be treated in each treatment fraction. The planning objectives will be adequate target irradiation and achieving maximal sparing of OARs, as per the optimization goals described below. Adequate PTV coverage and relative dose homogeneity, however, will be constraints which will bear a higher weight in optimization and will usually override noninvolved tissue sparing goals, with the exception of the constraints on the spinal cord and non-involved lips, for which the highest priority will be assigned due to prohibitive risks of late and acute toxicity, respectively, for these two OARs. Adequate target coverage of the non-involved lymph node CTVs will be prioritized below the sparing constraints for the glottic larynx, inferior pharyngeal constrictor muscle, upper esophagus, and in some cases, the noninvolved contralateral salivary structures as per our routine clinical practice. Sparing of the remaining OARs will be prioritized below that of the CTVs.

13.3 Target doses:

13.3.1 PTV1 (Gross tumor): 70 Gy in 35 fractions
13.3.2 PTV2 (High risk subclinical targets): 59 Gy in 35 fractions
13.3.3 PTV3 (Low risk subclinical targets): 56 Gy in 35 fractions
13.3.4 PTV66 (Microscopically positive regions with either extracapsular extension or positive margins at neck dissection): 66 Gy in 35 fractions

13.4 Optimization goals:

13.4.1 The primary PTV dose will be 99% + 7% of the prescribed dose and to sub-clinical PTVs within +/- 5% of the prescribed dose. The maximal "hot spot" within a PTV will be <115% of the prescribed dose to that target delivered to a volume of at least 0.5 cc. The maximal dose outside the targets will be <105% of the prescribed dose delivered to at least 0.5 cc. volume.
13.4.2 The maximal dose to the spinal cord, expanded by 0.5 cm, will be < 50 Gy, to the non-expanded cord < 45 Gy, and where applicable, to the optic pathways < 50 Gy and to the brainstem <54 Gy.
13.4.3 Mean dose to each parotid gland will be < 24 Gy
13.4.4 Mean dose to each submandibular gland will be < 30 Gy
13.4.5 Mean dose to the non-involved oral cavity will be < 30 Gy
13.4.6 Mean dose to the glottic larynx will be < 20 Gy
13.4.7 Mean dose to the non-involved upper and middle pharyngeal constrictors will be < 50 Gy
13.4.8 Mean dose to the lower pharyngeal constrictors and esophagus will be < 20 Gy
13.4.9 Maximal dose to the mandible will be <70 Gy or < 105% of the prescribed dose delivered to a volume of at least 0.5 cc, whichever is lower.
13.4.10 Mean dose to the lips will be < 30 Gy
13.4.11 Maximum dose to the eyes, where applicable, will be < 40 Gy
13.4.12 Maximal dose to the brachial plexus, where applicable, will be < 65 Gy

13.4.13 Maximal dose to each cochlea will be < 40 Gy

13.5 The planning process: When target expansion to yield the PTV causes its extension beyond the skin contour, incorporation of zero dose (outside the tissue) should be avoided in the PTV dose calculations. This may be achieved by editing the PTV or by taking into account only the PTV residing within the external contour, in DVH calculations. All radiation therapy will be administered at the University of Michigan (Ann Arbor, MI).

13.6 Treatment Interruptions: It is expected that the entire treatment for definitive irradiation will be completed in approximately 7.5 weeks. Treatment interruptions due to symptomatic mucositis or skin reactions should be minimal. In the case of severe mucositis impairing oral intake, a gastric tube will be inserted and radiation will continue uninterrupted at the discretion of the treating physician. Weight will be recorded weekly in the Radiation Oncology Chart. If the patient's unintentional weight loss exceeds 10% of the initial weight or if the patient is malnourished before radiation, a feeding tube will be inserted.

14.0 Surgical Techniques

14.1 Neck Dissection – Neck dissection will be defined as the comprehensive removal of the cervical lymph nodes. The levels of neck dissection that will be removed are at the discretion of the treating physician, and will involve a minimum of levels II, III and IV. Level I and level V may be removed if involved clinically or radiographically, or at the discretion of the treating physician. For tumors at or approaching midline, bilateral neck dissection will be performed at the discretion of tumor board recommendations and the treating surgeon.

Neck dissection will be selective, sparing critical structures (spinal accessory nerve, internal jugular vein, sternocleidomastoid muscle) whenever possible and at the discretion of the treating surgeon. If the tumor involves these structures, they may be removed to extirpate the neck disease.

14.2 Transoral surgery – Transoral surgery will be used in patients with low risk pathologic factors (see schema 6.0). This will be performed using transoral robotic surgery, transoral laser microsurgery, or conventional transoral surgery, at the discretion of the treating physician. Standard of care surgical principles (see NCCN Principles of Surgery) will be followed. Intraoperative frozen section margins will be used at the discretion of the treating physician. All surgical resection margins must be adequately sampled and described in the surgical dictation and pathology report.

15.0 Informed Consent

Patients who meet the inclusion criteria will be approached for possible participation in this study. The nature of the investigation will be described to the patient including the risks and side effects of study treatments, alternative treatments, the potential benefit of the study to themselves and others, and the time commitment and frequency of patient visits and the clinical evaluations they will be required to undergo. The patient will then have the opportunity to ask questions. The patient will be given the appropriate informed consent form for consideration. Each patient will be allowed to read (or have read to them) the informed consent form and understand before discussing consent with the investigator. If consent to participate is granted, the patient's signature will be obtained on the informed consent form. The original consent form will be kept

in the patient's chart at the Clinical Trials Office. Copies of the informed consent will be provided to the patient, and will also be available to the principal investigator and the nurse coordinator.

16.0 Patient Registration

16.1 All patients will be registered with the University of Michigan Clinical Trials Office prior to initiating treatment.

17.0 Reporting Potentially Serious Adverse Events

17.1 Serious Adverse Events

17.1.1 **An adverse event** is any new, undesirable medical experience or change of an existing condition which occurs during or after treatment, whether or not considered product-related.

17.1.2 **A serious adverse event** is any untoward medical occurrence that suggests significant hazard or side effect that:

1. results in death.
2. is life-threatening (places the patient at immediate risk of death).
3. requires or prolongs inpatient hospitalization is disabling or incapacitating.
4. is a congenital anomaly/birth defect.

The definition of serious adverse event (experience) also includes important medical events. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

17.1.3 **Attribution:** Definitions of relationship to study are as follows:

UNRELATED: The AE is clearly ***NOT*** related to the intervention/investigational agent.

UNLIKELY: The AE *is* ***doubtfully related*** to the intervention/investigational agent.

POSSIBLY: The AE ***may be related*** to the intervention/investigational agent.

PROBABLY: The AE ***is likely related*** to the intervention/investigational agent.

DEFINITELY: The AE ***is clearly related*** to the intervention/investigational agent.

Adverse events attributable to the chemotherapy will be reported if the adverse events are at an intensity that is more severe than previously documented or considered significant by the investigator. The definition of "related" is that there is a reasonable possibility that the drug caused the adverse experience.

17.2 Definitions and reporting

If required on the adverse event case report forms, the investigator will use the following definitions of severity in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 to describe the maximum intensity of the

adverse event. If the event is serious, the CTCAE grade reported in the adverse event CRF must be consistent with the description of CTCAE grade included in the narrative section of the serious adverse event report.

GRADE	Clinical Description of Severity
0	no change from normal or reference range
1	mild adverse event
2	moderate adverse event
3	severe adverse event
4	life-threatening or disabling adverse event
5	death related to adverse event

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

- if it is unclear what study treatment includes, list all drug(s), other therapies, changes to existing therapy, diagnostic procedure, etc. that are specified by the protocol

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

Information about all serious adverse events will be collected and recorded on the FDA MedWatch 3500a form. To ensure patient safety each serious adverse event must also be reported within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Any serious adverse event occurring after the patient has provided informed consent, has started taking the study medication, and until 4 weeks after the patient has stopped study treatment discontinuation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

17.3 Instructions for rapid notification of serious adverse events

17.3.1 Reporting responsibility

The principal investigator has the obligation to report all serious adverse events to the FDA and IRB

17.3.2 Reporting procedures

The investigator must complete the FDA MedWatch 3500a form in English, assess the relationship to study treatment and send the initial completed MedWatch form within 24 hours. The original and the duplicate copies of the FDA MedWatch form and the fax confirmation sheet must be kept with the case report forms at the study site.

3. The Clinical Trials Office (CTO) staff will coordinate the reporting process between the Investigator and the IRBMED as well as other applicable reporting agencies (FDA, CTEP, NCCN). Copies of all related correspondence and reporting documents will be maintained in the regulatory file.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The MedWatch form, and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

Deaths or life-threatening adverse events will be reported to the University of Michigan Medical Institutional Review Board (IRBMED) in accordance with the reporting policy of the IRB.

All adverse events will be noted in the case report forms

17.3.3 Data and Safety Monitoring

This trial will be monitored in accordance with the NCI approved University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Plan.

The study specific Data and Safety Monitoring Committee (DSMC), consisting of the protocol investigators, data manager or designee, and other members of the study team involved with the conduct of the trial, will meet quarterly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study

participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness.

At the regular DSMC meetings, the protocol specific Data and Safety Monitoring Report form will be completed.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board (DSMB) on a quarterly basis for independent review.

18.0 Data Handling and Record Keeping

18.1 Case Report Forms / Electronic Data Record

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial.

A CRF is required and should be completed for each included subject. It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Subject source documents are the physician's subject records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, the investigator must prospectively document which items will be recorded in the source documents and for which items the CRF will stand as the source document.

18.2 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

19.0 Ethical considerations and administrative procedures

19.1 Ethics and good clinical practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.

2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

19.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). Any amendments to the protocol, other than administrative ones, must be approved by this committee.

19.3 Amendments to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes.

20.0 Biologic Correlatives

Hypothesis 1. *Recurrent genetic drivers and lost suppressors depend on specific co-dependent lesions and/or transcriptional programs to drive HPV+ HNSCC pathogenesis. Furthermore, pivotal genes in these co-dependent pathways serve as therapeutic targets to enhance standard therapy. Thus, developing biomarkers that predict response to standard therapy will help identify the patients that would most benefit from early advancement to precision medicine trials.*

Experimental design: We will perform integrative targeted sequencing of primary HPV+ tumor specimens to identify the distribution of lesions co-incident with commonly deregulated genes (e.g. *NOTCH1*, *EGFR*, *FGFR1/3*, *PIK3CA*, *CyclinD1* and *CDKN2A*) as well as the transcriptional programs deregulated in these tumors. We will utilize the knowledge gained from existing publicly available sequencing studies[15-17,32-36], which contain <100 HPV+ cases *that often lack integrated gene expression analysis and annotation of clinical response*, to perform targeted DNA and RNA sequencing in our cohort. We will also perform targeted RNA-Seq to assess the expression of key effectors from commonly deregulated pathways in publicly available HPV+ data, enabling the evaluation of co-dependent pathways between DNA and RNA. The co-incidence of events will be correlated with immunohistochemical stains for established HNSCC biomarkers and correlations established between molecular events and clinical data.

Head and neck cancer cell lines are highly valuable and sought after research tools. There is a dearth of tumor cell lines from HPV+ oropharyngeal cancers. Whenever sufficient fresh tissue is available from the excess surgical specimen not required for diagnosis, such tissue will be sent to the Head and Neck Oncology Research laboratory where it will be divided for cell line

establishment; frozen for later histologic studies and confirmation of protein expression of genes identified by genomics; and as a source of RNA for confirmation or testing of expression of mutant or rearranged gene products. If cell lines are successfully derived they will become the wholly owned intellectual property of the University of Michigan and can be used for research or shared with other investigators at non-profit research institutions, provided that those recipients use the cell lines only for basic research performed under their direct supervision. In some case the University of Michigan may license cell lines to corporate entities for specific research or development purposes for which the University will receive licensing fees and royalties that will be distributed according to University regulations.

1i. Preparation of HPV+ tissues for targeted DNA and RNA sequencing. To identify correlations between the most highly recurrent genomic and/or transcriptomic events (i.e. those that occur in >5% of patients) as well as with clinical response, retrospective FFPE tissues from surgically responsive and non-responsive HPV+ cases with long term follow up data will be assessed together with prospectively collected tissue samples from this trial. Together 190 HPV+ oropharynx HNSCC cases have been previously collected by the University of Michigan Head and Neck SPORE program[37], of which 20% did not respond to therapy[38]. Using chi-squared tests, by assessing 200 patients, we can achieve 80.7% statistical power at a significance level of 0.05 to detect a change of outcome rates between patients with/without an individual genomic event with a small to medium effect size of 0.2. If we use the Bonferroni correction for 50 genes, with 250 patients we can achieve a 93% statistical power at a significance level of 0.001 with a medium effect size of 0.3. Thus, we will aim for 250 patients to complete the 50 gene analysis and integrated pathway, but are adequately powered to discover individual events by accruing only an additional 10 tumors.

Collaborator Dr. McHugh is a board certified pathologist and will identify representative FFPE sections with >50% tumor content, he has extensive experience in tissue specimen evaluation for molecular analysis[39-51]. We will use macrodissection to enrich for tumor content as needed. At least 3x10um sections per case will be cut for simultaneous DNA/RNA extraction using the Qiagen Allprep FFPE DNA/RNA kit and protocols optimized by our group to isolate assayable DNA (median 1.5 ug) and RNA (median 5.3 ug). As little as 9x10um sections from a single needle biopsy core yield sufficient DNA and RNA for the studies proposed herein. DNA and RNA will be quantified using the Qubit fluorometer.

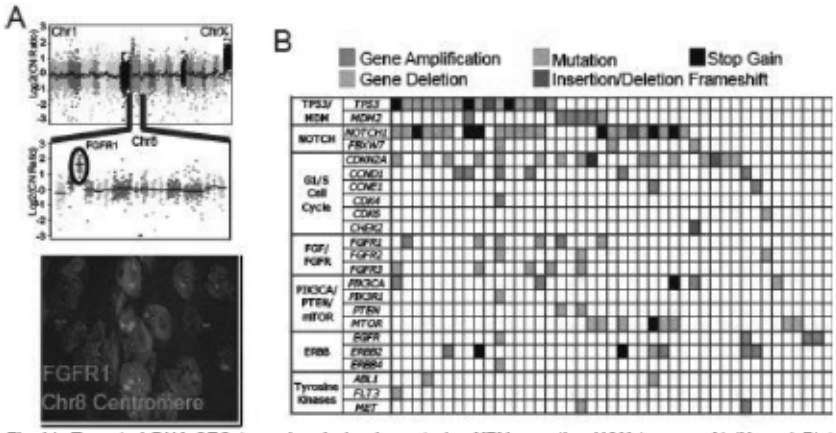


Fig 11: Targeted DNA-SEQ to molecularly characterize HPV negative H&N tumors. A) (Upper) Plot shows relative DNA copy number from AmpliSEQ analysis of an FFPE tumor sample. Top panel shows genes assessed across the genome. Chr1 shown on left and ChrX on the right. Bottom panel shows zoomed in Chr8 and *FGFR1* copy number increase. **(Below)** FISH was performed with *FGFR1* and Centromere8 probes to confirm amplification. A representative image is shown taken with a 40x objective lens. **B)** Plot shows relative aberration status from 42 FFPE isolated DNA samples from HNSCC tumors that were profiled using the Ampliseq method and the Oncomine Cancer panel (OCP). Alignment and variant calling were performed using standard plugins in the Torrent Server Suite (v3.6) and variants were filtered through a pipeline to remove low confidence calls, sequencing errors, germline variants and common polymorphisms [1]. Results were compared to known mutations in COSMIC, the Oncomine Powertools Database (containing pan-cancer TCGA data), and our internal sequencing database.

1ii. Targeted next generation sequencing (NGS). Targeted, amplicon based NGS will be performed as shown in our preliminary data to the left using Ion Torrent or Illumina based sequencing (as in Fig 11). Briefly, barcoded libraries will be generated from 40ng of DNA per sample using our HNSCC-gene enriched custom Ion AmpliSeq panel, and the Ion Ampliseq Library Kit 2.0 with barcode incorporation. Templates will be prepared using the PGM Template OT2 Kitv2 on the Ion One Touch2; all protocols will be performed according to the manufacturer's instructions. Sequencing of multiplexed templates will be performed on Ion 318 chips using the Ion PGM 200 Sequencing Kitv2, sequenced to an average depth >100x. We routinely generate between 400-500 million aligned bases per 318 chip, yielding ~300-500x coverage for ~4-6 Oncomine Cancer Panel prepared templates. Mutation analysis will be performed in Torrent Suite 3.6, with alignment by TMAP using default parameters, and variant calling using the Torrent Variant Caller plugin using default low-stringency somatic variant settings. Variants will be annotated using ANNOVAR[52]. Called variants will be filtered to prioritize likely candidate somatic drivers by removing the following variants: synonymous variants, those with frequencies >0.001 in ESP6500 or 1000 genomes, those with flow corrected read depths (FDP) <20, flow variant allele containing reads (FAO) <5 or variant allele fractions (FAO/FDP) <0.05. Copy number alterations will be identified as described[40,53] (24, 39) using normalized read counts per amplicon with GC content correction and comparison to distributions from multiple unrelated normal FFPE derived genomic DNA samples. Gene-level copy number estimates will be determined by taking the coverage-weighted mean of the per-probe ratios, with expected error determined by the probe-to-probe variance; genes with $|Z|>2.5$ with respect to both the normal pool and the internal error will be considered as gained or lost. Our team has established robust protocols for Ion Torrent sequencing, and has used the above methodology to characterize >600 tissue specimens. Alterations will be advanced for potential as HPV+ co-dependent drivers and correlated with RNA pathway alterations based on known roles in oncogenesis and H&N cancer, comparison to Oncomine (including TCGA and publicly available data) and COSMIC mutational data, and comparison to in house databases of driving lesions. Sanger sequencing, FISH, or qPCR will be performed to confirm prioritized alterations.

1iii. Targeted RNA-SEQ for molecular subtyping, gene fusion identification and pathway activity. Reverse transcription will be performed on 300ng of isolated RNA from each tissue sample using gene specific priming with subsequent targeted RNA-SEQ using FFPE optimized assays as in Fig12. Genes have been selected to assess critical HNSCC pathways including *NOTCH* signaling status (including both *NOTCH* induced/repressed genes), deregulated FGF/FGFR pathway genes, *EGFR*, known HNSCC cancer fusions (through 5' and 3' assays for *FGFR-TACC3*[54] and *EGFR-ADACM* (TCGA-CV-6941), R-spondin [55], potential therapeutic targets in other malignancies (ie. 5' and 3' assays for ALK and RET overexpression), and housekeeping genes. Additional genes and pathways may be advanced from other aims and probes will be designed to assess the expression of all viral genes from the HPV genome. Our team has extensive experience in RNA-SEQ, transcriptome evaluations and statistical analysis and will determine the frequencies of RNA signatures with DNA lesions as described[37-46,56-62].

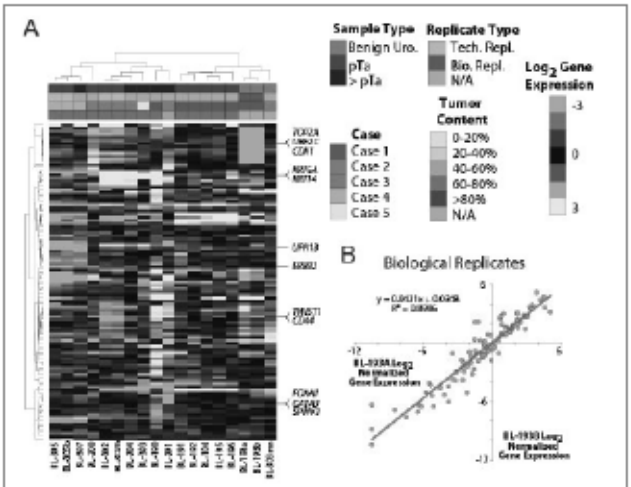


Fig 12. Example of targeted RNA-seq from FFPE isolated RNA. A) Reverse transcription and targeted multiplexed PCR (Ampliseq) was performed on 20ng FFPE isolated RNA per sample on a cohort of macrodissected benign urothelium, non-invasive urothelial carcinoma (pTa) and invasive urothelial carcinoma (>pTa). Technical and biological replicates are indicated, as well as unique components isolated from the same case. For each sample, the log_2 total reads for each target gene (n=103) was normalized to the average log_2 total reads for 8 housekeeping genes. Median centered normalized target gene expression and samples were clustered using centroid linkage clustering and visualized as a heatmap. **B)** Scatter plot of target gene expression (log2 normalizd gene expression) for two biological replicates of normal urothelium (BL193A and BL193B, macrodissected from separate blocks). (R^2=0.8986).

1iv. Determination of protein expression and validation of sequencing data. We will create a tissue microarray of excess FFPE tissue from samples sequenced for this Aim. Gene fusions and copy number alterations will be confirmed by fluorescence in situ hybridization (FISH) and critical targets advanced from sequencing studies will also be assessed by immunohistochemistry (IHC) if IHC grade antibodies are available. Staining and scoring will be completed as we described[63-65]. We will leverage this data by integrating it with the sequencing data generated here to identify correlations between copy number, mutation and expression as well as HPV status, E6 variant expression and integration with clinical outcome from the SPORE database[5,63-66] using statistical methods described above.

Pitfalls, alternative strategies and future directions. We do not anticipate significant obstacles as we have extensive experience in tissue examination, NGS and integrative statistical analysis of molecular data in cancer as well as modeling of disease[40,46,47,49,50,56,67]. Additionally, Dr. Brenner is involved in several protocols that are sequencing tissue specimens as part of clinical trials or protocols, including the MiOncoseq-SU2C program[54,68]. The cohort size is based on conservative statistical estimates as noted to reach independent correlative endpoints. Targeted sequencing has been proposed to enable a focused analysis of tumors with limited DNA/RNA yields. However, we have had success sequencing whole exomes from FFPE tissues from large quantities of DNA using multiple platforms and may implement these if the technology becomes robust enough during the course of the proposal for smaller quantities of DNA. Similarly, we are currently evaluating whole transcriptome analysis as an alternative to targeted RNA-SEQ from FFPE in samples with sufficient RNA yield. Overall, we expect that completion of this Aim will identify the co-incident frequency of commonly deregulated pathways on the DNA and RNA levels that will predict response to standard therapy. Importantly, we will create a molecularly characterized TMA to assess correlations between HPV+ mutation/rearrangement status and protein expression. Taken together,

this Aim will provide a wealth of data and resources for future studies and provide a comprehensive data set correlating genetic aberrations with clinical outcome.

Hypothesis 2: Recurrent cancer in HPV positive OPSCC can be detected in saliva and serum biospecimens collected at routine interval time points and will identify tumor recurrence earlier than clinical exam.

Correlative Justification

Patients enrolling in deintensification trials for HPV+ OPSCC are at risk for treatment failure, thus careful monitoring in the post-treatment period is of extreme importance. The measurement of serum and saliva circulating free (cf)DNA and antitumor antibodies as a biomarker for recurrence may be an important, noninvasive method to detect treatment failures. We have previously examined serum antitumor antibodies (E6 and E7) in a longitudinal sample of patients who were treated under UMCC 2002-0221. Our preliminary data indicate that patients who have decreased clearance of E6/E7 antibody from their baseline measurement are at risk for disease recurrence. In addition, other groups have identified HPV cfDNA in salivary samples in patients with HPV+OPSCC, suggesting this noninvasive biomarker as a way to measure disease recurrence as well. Finally, we have R01 funding to perform targeted next generation sequencing on the primary tumor specimens from all patients enrolling in this trial, which can be used to prioritize evaluable somatic mutations in cfDNA from both the blood and saliva of each patient for targeted sequencing studies (Hypoothesis 1). Therefore our goal is to collect longitudinal samples of saliva and serum as a part of our trial to determine if serum and saliva biomarkers can predict recurrence in HPV+ OPSCC. Our hypothesis is that *saliva and serum biospecimens collected at routine interval time points will identify tumor recurrence earlier than clinical exam.*

Sample Collection

We plan on collecting and banking serial serum and saliva samples until 36 months from diagnosis. These samples are obtained at baseline and every 3 months therapy (see Study Calendar, section 9.0). Samples will be banked for planned analysis in the Brenner lab.

Blood Samples

1i. Patients will be sent to the blood draw stations at baseline and every three months as part of their routine follow up appointments.

1i.1. Two heparinized green top 6 mL tubes and two Cell-Free DNA blood collection tubes (Streck) will be drawn at each time point. Sample tubes will be provided by Brenner Lab.

1i.2. We will extract measure cfDNA from serum samples using the QIAamp Circulating Nucleic Acid Kit according to manufacturer instructions, cfDNA will be sequenced according to standard protocol in the Brenner lab and we will use our previous technique with an ELISA assay to determine E6 and E7 antibody levels.

Saliva samples

2i. Salivary Samples will be collected via swish and spit method in clinic. This is a method which we have developed institutionally described as follows

2i.1. Patient will be given 10 mL of Scope mouthwash to swish around the oral cavity and also gargle for a total of 30 seconds. After 30 seconds, patients will be instructed to expectorate the fluid into a 50 mL centrifuge tube

2i.2. If patients are unable to use Scope due to a medical condition (ie unhealed postoperative wounds), a 3 mL saline solution will be given to patient to rinse and gargle.
After 30 seconds, they would expectorate this fluid into an Oragene preservative.
2i.3. The resultant solution from either collection method will be frozen within 2 hours of collectionfor future analyses. Current lab techniques have been developed as to isolate both DNA and RNA for detection of HPV and tumor DNA. Targeted sequencing of samples to detect HPV type, viral gene expression, and molecular alternations will be performed as above and correlated with tumor genetics and HPV variant status in the primary sample.
2i.4.Oral rinses will be performed in clinic under the supervision of the study coordinator.
-

Sample Transportation

- Whenever as specimen has been obtained (i.e. after a procedure, blood draw, oral rinse in clinic), the study coordinator will transport the sample directly to the Brenner laboratory.

21.0 Statistical Considerations

21.1. *General*

This is a prospective single arm phase II clinical trial to assess whether neck dissection-driven selection to minimize treatment modalities can reduce the negative impact of treatment on eating and swallowing quality of life of survivors at one-year relative to standard treatment. Patients with surgically resectable HPV+, T1-T3 and N0-N2b oropharyngeal cancer will undergo up front neck dissection to more accurately stage patients, and then treatment will be stratified based on adverse features found on pathologic examination. We hypothesize that this paradigm will improve quality of life post treatment because patients with adverse features in the neck that would require adjuvant radiation or chemoradiation will not undergo surgery to the primary and thus will only receive one (radiation alone) or two (chemoradiation) modalities to critical swallowing structures. Alternatively, patients who undergo neck dissection who have no adverse features have the potential to undergo single modality therapy to the primary site. Our hypothesis is that patients treated with this paradigm will experience less negative impact of treatment on eating and swallowing QOL compared to our historical cohort treated under UMCC 0221.

21.2 *Justification of the Design*

We hypothesize that the proposed paradigm will improve post treatment eating and swallowing quality of life as compared to our historical control. The mean (std) change score of our primary outcome, HNQOL eating domain score, in our historical control data was -13.0 (see background). We predict we will see a mean reduction smaller in magnitude in patients undergoing our proposed protocol. We will perform a propensity score adjusted (stratified) linear regression analysis to estimate the causal effect of our proposed treatment strategy on the mean change score at one year compared to our historical control data. A two-sided p-value less than 0.05 will be considered significant.

The inclusion criteria for this protocol is very specific and we plan to screen all OPSCC patients coming to UM for inclusion in this protocol. Therefore, we do not anticipate a shift in baseline characteristics of patients entering this new protocol as opposed to our historical control. Nonetheless, we will perform a propensity score adjusted analysis (for cohort membership) to minimize potential bias introduced in this single arm study.

A power analysis, assuming a type I error rate of 5%, was conducted based on two methods of analysis: (a) a two sample t-test of the change scores, and (b) an analysis of covariance (ANCOVA)

of the change (1 year post- pretreatment) after covariate adjustment for propensity score strata. Based on our historical data (see background section 1.0) With 90 evaluable patients, using a two sample t-test, a difference in mean eating domain change score from -13 to -3 would have 90% power. To achieve 80% power under this scenario 48 evaluable new patients are required.

A two sample t-test comparing the two cohorts would be appropriate only under the condition that there are no differences in the cohorts that confound the estimation of treatment effect. Sample size calculations under the t-test scenario serve as a minimum requirement, and we look to scenario (b) as the more logical approach to our final analysis.

For simplification, a power analysis was performed based on separating the data into two strata (s=1,s=2) based on a hypothetical propensity score distribution . The power of an ANCOVA analysis will be dependent on the extent to which mean change scores ($\widehat{\Delta_{s,p}}$) differ across the propensity score strata ($_s$), how they differ across the actual protocol groups ($_p$), the expected change score among new protocol participants ($\Delta_{(s,2)}$), as well as the magnitude of correlation (rho) expected between the propensity score strata and mean change score.

The tables below display the operating characteristics of an ANCOVA analysis for likely scenarios under different conditions based on our historical data. Table 1 displays differences in Δ by strata in the historical data that differ in magnitude and direction, assuming a common mean change score of -3 among the new protocol participants. Table 2 assumes a large difference in change score across propensity score strata but common magnitude of protocol effect considering two different magnitudes of hypothesized protocol effect (d).

Table 1: Power for ANCOVA analysis, varying strata differences

Strata differences	$\Delta_{s=1,p=1}$	$\Delta_{s=2,p=1}$	$\Delta_{(p=2)}$	ρ=0.1	ρ=0.5	ρ=0.8
small = 2	-13	-11	-3	0.85	0.93	0.99
large = 5	-13	-8	-3	0.7	0.82	0.99
small = -2	-13	-15	-3	0.96	0.99	0.99
large = -5	-13	-17	-3	0.98	0.99	>0.99

Table 2: Power for ANCOVA analysis, varying magnitude of protocol effect

d	$\Delta_{s-1,p-1}$	$\Delta_{s-2,p-1}$	Δ_{s-1p-2}	$\Delta_{s-2,p-2}$	ρ=0.1	ρ=0.5	ρ=0.8
10	-13	-8	-3	2	0.88	0.95	0.99
8	-13	-8	-5	0	0.76	0.86	0.99
10	-13	-17	-3	-7	0.91	0.97	0.99
8	-13	-17	-5	-9	0.76	0.86	0.99

Based on our historical cohort data estimates, small and large differences that might be identified in change scores, and a range of correlations between propensity score strata and outcome the tables above demonstrate that the power of the study to detect a difference in eating quality of life change at one year with 90 patients will be adequate under many likely scenarios.

21.3 *Stopping Rule*

Stopping Rule for Unacceptable Mortality:

Traditionally, we expect nearly 20% of patients treated for HPV + OPSCC to fail (disease specific death) within 3 years. This protocol will exclude a number of poor prognosis patients (HPV-, T4, N3, matted nodes), leading to an improvement in our expectation of success. Still, we expect that the failure rate among the eligible patients to be as high as 15%. If we observe strong evidence at any time during the trial that under the trial paradigm the proportion of failures exceeds 15%, we will stop accrual and evaluate whether to proceed.

Evidence of an unacceptable failure rate will be based on the proportion of treatment failures (disease-specific deaths) among accrued subjects no matter whether complete follow-up has been reached. Beginning after 20 patients are enrolled, the number of disease specific deaths will be monitored. If the lower bound of an exact binomial confidence interval for the # disease specific deaths/# treated, ever reaches above 15%, we plan to stop accrual and reassess treatment assignment strategy. This stopping rule will be assessed at regular intervals during accrual and at least every 10 enrolled patients. Table 1 and Figure 3 depict what we define as grounds for stopping due to unacceptable mortality at various points in accrual.

Stopping Rule for Neck Function

Currently there is no published data examining the effect of radiation or chemoradiation on shoulder function. The initial validation for the NDII was published by our group in 2002, and examined the impact of quality of life on neck dissection[69]. The paper examined a primary surgical cohort and did show that patients who underwent radiation after surgery had worse shoulder dysfunction. This primary surgical cohort differs from our cohort in three major ways: 1) the initial NDII looked at all subsites of the head and neck which have different metastatic patterns, 2) over half the cohort was T4 (which would have effective excluded them from our study) and 3)half the patients underwent a modified radical neck dissection. This last point is important in that we no longer standardly perform modified radical neck dissection, which is known to have significantly worse shoulder function. A modified radical neck dissection involves the skeletonization of the spinal accessory nerve in level 5 of the neck which is believed to be the cause of the shoulder dysfunction. This is not performed routinely in OPSCC as this disease does not metastasize to this nodal basin. We do know that patients who undergo physical therapy can have improvement in shoulder function, and this is standard to offer patients after neck dissection.

Unpublished data from our group examined the prevalence of shoulder dysfunction using the NDII after primary chemoradiation for advanced OPSCC. All patients treated from 2003-2010 at UM for advanced OPSCC under the treatment protocol UMCC.0221 were surveyed in this retrospective study. The mean interval since completion of treatment was over 5 years and ranged from 3 to 10 years (mean=62.7 months). Twenty-four out of 87 of these patients underwent post chemoradiation neck dissection (28%). While we do not believe this is a perfect comparison group for analysis of NDII and quality of life 1 year after treatment completion it can serve as a basis for monitoring whether shoulder function is unacceptably affected in our proposed protocol strategy. The mean NDII score for the cohort was 87.4 (SD 22.1, range 5-100). We will estimate the mean one year NDII score among participants after 1/3 of patients (30 patients) have completed one year follow-up. If the sample mean NDII is lower than 65.3 (one standard deviation below the mean from our historical data) we will stop accrual and reassess treatment assignment strategy.

21.4 *Accrual*

Approximately 10 eligible patients per year will be enrolled to this trial.. Assuming successful enrollment of nearly all of these patients, allowing an attrition rate of 10%, the enrollment to obtain 90 evaluable patients is expected to last approximately 10 years. Subjects will be considered evaluable for the primary endpoint after completion of protocol treatment according to the study schema stratification (transoral surgery, radiation alone or chemoradiation.) Patients who enroll but do not complete protocol treatment at UM will be replaced.

21.5 *Analysis Plan*

We do not anticipate that there will be meaningful differences in the distribution of pretreatment characteristics in patients entering this trial as opposed to our control data, however, we will perform a propensity score adjusted analysis to estimate the causal effect of our proposed treatment strategy on the mean domain score change compared to the historical control patient data.

Change in HNQOL domain scores 12 months after completion of treatment will be compared to historical change scores using standard parametric methods such as linear regression modeling. The analysis will be performed after propensity score adjustment for historical or new protocol membership. Additional multivariable modelling will be performed to control for potentional confounding factors such as disease subsite, age, smoking status and comorbidities. Repeated measures regression models will also be explored to characterize the longitudinal trajectory of QOL from pretreatment through the 6-, 12- and 24- month follow-up time periods.

Table 1: Unacceptable Failures during Accrual

Number Patients Accrued	Disease Specific Deaths within 3 years
20	7
30	9
40	11
50	13
60	15
70	17
80	19
90	21

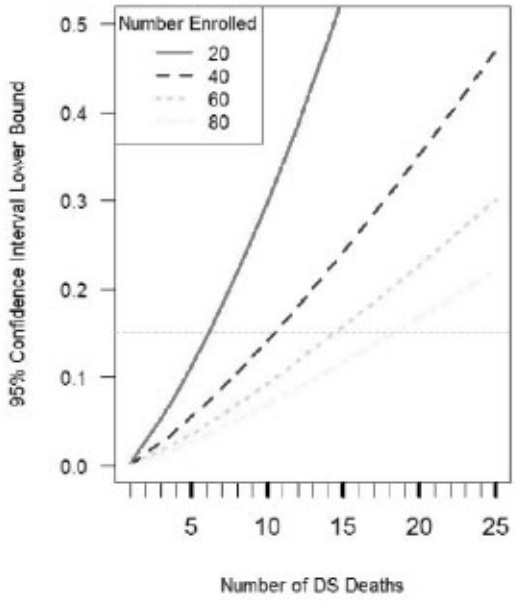


Figure 3: Unacceptable Failures during Accrual

21.4 *Analysis Plan*

Here we describe the analyses for each of the protocol objectives.

Primary Objectives

1. To determine whether treatment stratification by neck dissection to more accurately pathologically stage patients and minimize the number of treatment modalities in patients with low risk oropharyngeal squamous cell carcinoma can improve quality of life.

   Four QOL instruments will be administered: the University of Washington Quality of Life (UWQOL)[70], University of Michigan Head and Neck Quality of Life Instrument (HN-QOL)[71], the University of Michigan Voice Related Quality of Life Measure (V-RQOL)[72], and the FACT Head and Neck (version 4) (FACT H&N)[73]. Quality of life (QOL) assessments will be made prior to treatment (i.e. pre-neck dissection), pre-adjuvant or additional therapy (transoral surgery, radiation, or chemoradiation), and at 6 months, 12 months, and 24 months (+/- 4 months) after completion of all modalities.

   QOL measures 12 months after completion of treatment will be compared to historical data using standard parametric methods such as linear and logistic regression modeling, where appropriate. Unadjusted and adjusted models will be considered for potential confounding factors such as an individual baseline QOL, specific subsite, age, smoking status and comorbidities. Repeated measures regression models will also be explored to characterize the longitudinal trajectory of QOL from pretreatment through the 6-, 12- and 24- month follow-up time periods.

Secondary Objectives

2. To determine progression free survival, disease specific survival and overall survival outcomes

   Overall and disease specific survival times will be defined from date of neck dissection to death event. Progression free survival will be defined from date of completion of treatment to progression event. Death from any cause will be considered an event for overall survival (OS). Death from OPSCC will be considered an event for disease specific survival (DSS) where death from other causes will be censored at time of death. Persistent disease at completion of treatment, post-treatment recurrence or disease specific death will be defined events for progression free survival (PFS). Kaplan-Meier estimates (95% Confidence intervals) will be estimated for 1, 2, and 3 years of follow-up.

3. To determine the impact of neck dissection on shoulder function using the Neck Dissection Impairment Index.

   The neck dissection impairment index will be scored and summarized for all patients who receive neck dissection. Between group comparisons for treatment groups and baseline characteristics (age at diagnosis, gender) will be performed using Analysis of Variance (ANOVA).

4. To assess acute and late toxicities of each treatment modality (surgery, chemotherapy, radiation).

   The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 will be used to describe the maximum intensity of adverse events and attribution to treatment will be assigned according to the definitions in section 16.0. Adverse events and toxicities will be tabulated for all participants with particular attention to Grade 3-4 attributable to any treatment.

5. To evaluate serum and tissue biomarkers to predict treatment outcome

   We will perform targeted DNA and RNA sequencing to identify the distribution of lesions co-incident with commonly deregulated genes (e.g. NOTCH1, EGFR, FGFR1/3, PIK3CA, CyclinD1 and CDKN2A) as well as the transcriptional programs deregulated in these tumors. We will also perform targeted RNA-Seq to assess the expression of key effectors from commonly deregulated pathways in publicly available HPV+ data, enabling the evaluation of co-dependent pathways between DNA and RNA. The co-incidence of events will be correlated with parameters advanced from Dr. Brenner's ongoing work and correlations established between molecular events and clinical data. The data from this protocol will be included in a larger study in Dr. Brenner's lab which is powered appropriately. We also plan on collecting and banking serial plasma and saliva samples. Samples will be banked for future exploratory analyses in Dr. Brenner's laboratory as described in the biological correlatives section.

22.0 References

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23.0 Appendices

Appendix A: ECOG Performance Status Scale

DESCRIPTION	SCALE
Normal Activity	0
Symptoms of disease, able to carry out activities of daily living	1
Out of bed >50% of time; occasionally needs help	2
In bed >50% of time; needs nursing care	3
Bedridden; may need hospitalization	4

Appendix B

Highly Effective Methods of Contraception

1) Total abstinence or
2) Male or female sterilization or
3) Combination of any two of the following (a+b or a+c, or b+c):

a) Use of oral, injected or implanted hormonal methods of contraception

b) Placement of an intrauterine device (IUD) or intrauterine system (IUS)

c) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Appendix C
Functional Capacity

Objective Assessment

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

A. No objective evidence of cardiovascular disease.

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

B. Objective evidence of minimal cardiovascular disease.

Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

C. Objective evidence of moderately severe cardiovascular disease.

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

D. Objective evidence of severe cardiovascular disease.

Appendix D HUM00105447

Quality of Life Assessments (UWQOL, FACT-HN, HN-QOL, V-QOL, Neck Impairment Index), Financial & Work Survey

UWQOL

Study # _____
Intials _____
Date of Questionnaire _____
Week # _____

Each of the following items lists different numbered statements. Think about what each statement says, then place a circle around the one statement that most closely describes how you have been feeling during the past week, including today. Please circle only one statement for each item.

I. PAIN (General)

A. General

10 I have no pain.
20 There is mild pain not needing medication.
30 I have moderate pain--requires regular medication (codeine or non-narcotic).
40 I have severe pain controlled only by narcotics.
50 I have severe pain not controlled by narcotics.

B. Mouth

10 I have no pain in my mouth.
20 I have mild pain but it is not affecting my eating.
30 I have moderate pain which is affecting my eating.
40 I have severe pain and need medication in order to eat.
50 I have severe pain and cannot eat even with the medication.

C. Throat

10 I have no pain in my throat.
20 I have mild pain but it is not affecting my eating.
30 I have moderate pain which is affecting my eating.
40 I have severe pain and need medication in order to eat.
50 I have severe pain and cannot eat even with the medication.

II. DISFIGUREMENT

10 There is no change in my appearance.
20 The change in my appearance is minor.
30 My appearance bothers me but I remain active.
40 I feel significantly disfigured and limit my activities due to my appearance.
50 I cannot be with people due to my appearance.

III. ACTIVITY

10 I am as active as I have ever been.
20 There are times when I can't keep up with my old pace, but not often.
30 I am often tired and I have slowed down my activities although I still get out.
40 I don't go out because I don't have the strength.
50 I am usually in a bed or chair and don't leave home.
50 I am usually in a bed or chair and don't leave home.

IV. RECREATION/ENTERTAINMENT

10 There are no limitations to recreation at home and away from home.
20 There are a few things I can't do but I still get out and enjoy life.
30 There are many times when I wish I could get out more but I'm not up to it.
40 There are severe limitations to what I can do, mostly I stay home and watch T.V.
50 I can't do anything enjoyable.

V. EMPLOYMENT

10 I work full time.
20 I have a part time but permanent job.
30 I only have occasional employment.
40 I am unemployed.
50 I am retired (circle one below)
51 not related to cancer treatment
52 due to cancer treatment

VI. EATING

A. Chewing

10 I can chew as well as ever.
20 I have slight difficulty chewing solid foods.
30 I have moderate difficulty chewing solid foods.
40 I can only chew soft foods.
50 I cannot chew soft foods.

B. Swallowing

10 I swallow normally
20 I cannot swallow certain solid foods.
30 I can only swallow soft foods.
40 I can only swallow liquid foods.
50 I cannot swallow.

VII. SALIVA

A. Amount

10 I have a normal amount of saliva
20 I have a mild loss of saliva
30 I have a moderate loss of saliva.
40 I have a severe loss of saliva.
50 I have no saliva.

B. Consistency

10 My saliva has normal consistency.
20 My saliva is slightly thicker.
30 My saliva is moderately thicker.
40 My saliva is extremely thicker.
50 I have saliva that dries in my mouth and/or on my lips.

VIII. TASTE

10 I can taste food normally.
20 I can taste most food normally.
30 I can taste some foods normally.
40 I can taste few foods normally.
50 I cannot taste any foods normally.

IX. SPEECH

10 My speech is the same as always.
20 I have difficulty with saying some words, but can be understood over the phone.
30 I have moderate difficulty saying some words, and cannot use the phone.
40 Only family and/or friends can understand me.
50 I cannot be understood.

X. MUCUS OR PHLEGM

A. Amount

10 I have a normal amount of mucus.
20 I have a mild amount of mucus
30 I have a moderate amount of mucus.
40 I have a severe amount of mucus.
50 I have no mucus.

B. Consistency

10 My mucus has normal consistency
20 My mucus is slightly thicker
30 My mucus is moderately thicker
40 My mucus is extremely thicker
50 I have no mucus

Comments:

FACT-HN

FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

HN-QOL

INSTRUCTIONS: This survey is designed to assess how much you are bothered by your Head and Neck condition and/or treatment. Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

1. As a result of your head and neck condition or treatment, over the past FOUR WEEKS how much have you been BOTHERED by your…

		Not at all	Slightly	Moderately	A lot	Extremely
A.	Ability to talk to other people	☐	☐	☐	☐	☐
B.	Ability to talk on the phone	☐	☐	☐	☐	☐

2. As a result of your head and neck condition or treatment, over the past FOUR WEEKS how much have you been BOTHERED by problems with…

		Not at all	Slightly	Moderately	A lot	Extremely
A.	Volume of your voice	☐	☐	☐	☐	☐
B.	Clarity of your voice	☐	☐	☐	☐	☐
C.	Difficulty opening your mouth	☐	☐	☐	☐	☐
D.	Dryness in your mouth while eating	☐	☐	☐	☐	☐
E.	Chewing food (for example, pain, difficulty opening or closing your mouth, moving food in your mouth, or teeth or denture problems)	☐	☐	☐	☐	☐
F.	Swallowing liquids	☐	☐	☐	☐	☐
G.	Swallowing soft foods and/or solids	☐	☐	☐	☐	☐
H.	Your ability to taste food (For example, loss of taste, and/or loss of appetite due to poor taste)	☐	☐	☐	☐	☐

I. Pain, burning, and/or discomfort in your mouth, jaw, or throat	☐	☐	☐	☐	☐
J. Shoulder or neck pain	☐	☐	☐	☐	☐

3. Over the past FOUR WEEKS, how often did you take pain medication?...

Never	Rarely	Sometimes	Frequently	Always
☐	☐	☐	☐	☐

4. Over the past FOUR WEEKS how much have you been bothered by…

	Not at all	Slightly	Moderately	A lot	Extremely
A. Concerns or worries about your appearance related to your head and neck condition or treatment	☐	☐	☐	☐	☐
B. Emotional problems related to your head and neck condition or treatment	☐	☐	☐	☐	☐
C. Embarrassment about your symptoms	☐	☐	☐	☐	☐
D. Frustration about your condition	☐	☐	☐	☐	☐
E. Financial worries due to medical problems	☐	☐	☐	☐	☐
F. Worries that your condition will get worse	☐	☐	☐	☐	☐
G. Physical problems related to your head and neck condition	☐	☐	☐	☐	☐

5. Were you working (employed) prior to being diagnosed with cancer? Yes ☐ No ☐ **If no, go to question 6**

5A. If yes, did your doctor declare you unable to work due to your head and neck condition or treatment? Yes ☐ No ☐

6. Have there been other problems related to your head and neck condition that were not mentioned? If so, please write them in the space below and tell us how much this problem has bothered you. (For instance, if your treatment included surgical transfer of tissue from a donor site to the head and neck, does the donor site bother you)

	Not at all	Slightly	Moderately	A lot	Extremely
A. _____	☐	☐	☐	☐	☐
B. _____	☐	☐	☐	☐	☐
C. _____	☐	☐	☐	☐	☐

7. For the past FOUR WEEKS, please rate your OVERALL amount of disturbance or BOTHER as a result of your head and neck cancer condition?	☐	☐	☐	☐	☐
8. Overall how satisfied are you with your Head and Neck cancer care at this Hospital?	☐	☐	☐	☐	☐

9. Overall how would you rate your response to treatment?

Poor	Fair	Good	Very Good	Excellent
☐	☐	☐	☐	☐

10. Approximately how long did it take you to answer this questionnaire? _____Minutes

	Not at all	Slightly	Moderately	A lot	Extremely
11. How difficult was it to complete this questionnaire?	☐	☐	☐	☐	☐

V-RQOL

VOICE - RELATED QUALITY OF LIFE (V-RQOL) MEASURE
UNIVERSITY OF MICHIGAN

NAME:_____ DATE:_____

We are trying to learn more about how a voice problem can interfere with your day to day activities. On this paper, you will find a list of possible voice-related problems. Please answer all questions based upon what **your** voice has been like over the past **two weeks**. There are no "right" or "wrong" answers.

Considering both how severe the problem is when you get it, and how frequently it happens, please rate each item below on how "bad" it is (that is, the **amount** of each problem that you have). Use the following scale for rating the **amount** of the problem:

1 = None, not a problem
2 = A small amount
3 = A moderate (medium) amount
4 = A lot
5 = Problem is as "bad as it can be"

Because of my voice,	**How much of a problem is this?**
1. I have trouble speaking loudly or being heard in noisy situations.	1 2 3 4 5
2. I run out of air and need to take frequent breaths when talking.	1 2 3 4 5
3. I sometimes do not know what will come out when I begin speaking.	1 2 3 4 5
4. I am sometimes anxious or frustrated (because of my voice).	1 2 3 4 5
5. I sometimes get depressed (because of my voice).	1 2 3 4 5
6. I have trouble using the telephone (because of my voice).	1 2 3 4 5
7. I have trouble doing my job or practicing my profession (because of my voice).	1 2 3 4 5
8. I avoid going out socially (because of my voice).	1 2 3 4 5
9. I have to repeat myself to be understood.	1 2 3 4 5
10. I have become less outgoing (because of my voice).	1 2 3 4 5

Neck Impairment Index

Head & Neck Cancer Shoulder and Neck Assessment

INSTRUCTIONS: Many patients with head and neck cancer receive radiation treatment, surgery, or both to their neck as part of the overall care of their cancer. This survey is designed to evaluate how much your neck and/or shoulder currently affect you as a result of the treatment you received in your neck during the overall management of your cancer. Please answer every question. Mark the **ONE** box that best applies to you.

As a result of the cancer **TREATMENT OF YOUR NECK**, how much have you been bothered in the following over the past **4 WEEKS**:

1. Are you bothered by neck or shoulder **pain or discomfort?**

Not at all	A little bit	A moderate amount	Quite a bit	A lot
❑	❑	❑	❑	❑

2. Are you bothered by shoulder **stiffness**?

Not at all	A little bit	A moderate amount	Quite a bit	A lot
❑	❑	❑	❑	❑

3. Are you bothered by difficulty with **self-care** activities because of your neck or shoulder (for example: combing hair, dressing, bathing)?

Not at all	A little bit	A moderate amount	Quite a bit	A lot
❑	❑	❑	❑	❑

As a result of the cancer **TREATMENT OF YOUR NECK**, how much have you been limited in the following over the past **4 WEEKS**:

4. Have you been limited in your ability to **lift light** objects because of your shoulder or neck?

Not at all	A little bit	A moderate amount	Quite a bit	A lot
❑	❑	❑	❑	❑

5. Have you been limited in your ability to **lift heavy** objects because of your shoulder or neck?

Not at all ❑ A little bit ❑ A moderate amount ❑ Quite a bit ❑ A lot ❑

6. Have you been limited in your ability to **reach above** for objects because of your shoulder or neck (for example- from shelves, tables, or counters)?

Not at all ❑ A little bit ❑ A moderate amount ❑ Quite a bit ❑ A lot ❑

As a result of the cancer **TREATMENT OF YOUR NECK**, how much have you been affected by the following over the past **4 WEEKS**?

7. Are you bothered by your **overall activity level** because of your shoulder or neck?

Not at all ❑ A little bit ❑ A moderate amount ❑ Quite a bit ❑ A lot ❑

8. Has the treatment of your neck affected your participation in **social activities**?

Not at all ❑ A little bit ❑ A moderate amount ❑ Quite a bit ❑ A lot ❑

As a result of the cancer **TREATMENT FOR YOUR NECK**, how much have you been limited in the following activities over the past **4 WEEKS**:

9. Have you been limited in your ability to do **leisure or recreational** activities because of your neck or shoulder?

Not at all ❑ A little bit ❑ A moderate amount ❑ Quite a bit ❑ A lot ❑

10. Have you been limited in your ability to do **work** (including **work** at home) because of your neck or shoulder?

Not at all ❑ A little bit ❑ A moderate amount ❑ Quite a bit ❑ A lot ❑

With the following items, please indicate how **TRUE** the statements have been over the past **4 WEEKS**.

11. My **leisure and recreational** activities are important to me:

Definitely True ❑ Mostly True ❑ Don't Know ❑ Mostly False ❑ Definitely False ❑

12. My **work** (including **work in home)** is important to me:

Definitely True ❑ Mostly True ❑ Don't Know ❑ Mostly False ❑ Definitely False ❑

Please complete each question below by checking the appropriate box. The following questions will provide information relating to the treatment you received in your neck as a part of your overall cancer treatment.

13. Which **side of your neck** did you receive surgery as part of your overall cancer treatment?

Left ❑ Right ❑ Both ❑ Not Sure ❑

14. If you received treatment on both sides of your neck, which side of your neck bothers you the most?

Left ❑ Right ❑ The Same ❑ Not Sure ❑

15. How much physical activity or exercise did you do involving your shoulder after your neck treatment?

None at all ❑ A little bit ❑ A moderate amount ❑ Quite a bit ❑ A lot ❑

Please complete each question below by filling in the appropriate numbers. The following items will provide information relating to the change of your body mass index (BMI) during the course of your head and neck cancer treatment:

16. How much did you weigh before your neck surgery? _____ pounds

17. How much do you weigh today? _____ pounds

18. How tall are you? _____ feet _____ inches

19a. As a result of the cancer treatment for your head and neck, have you received any **physical therapy**? (if no, go to question #20)

Yes **No**

19b. How **long after** your neck dissection did you **start** physical therapy for your neck (circle one)?

Less Than One Month **One Month** **More Than One Month**

19c. Who administered your physical therapy (**circle one**)?

Therapist **Family Member** **Friend**

19d. Did your **insurance** cover the cost of your physical therapy? **yes** **no** (**circle one**)

If **yes**, for how long (i.e. for how many sessions) did your insurance cover your physical therapy?_____

19e. How **long** did you undergo **physical therapy (weeks or months)**? _____

19f. How **often** did you undergo **physical therapy (days per week)**? _____

19g. What **kind** of **physical therapy** did you receive?
(**Circle all that apply**)

ACTIVE? (You moving your own body part)

PASSIVE? (Your therapist moving your body part)

TENS (Transepithelial Neural Stimulation)?

ALTERNATIVE MEDICINE (I.E. – ACUPUNCTURE, HERBAL MEDICINE, ETC.)?

19h. Did **you think** physical therapy helped? (**circle one**)

Not at all A little bit A moderate amount Quite a bit A lot

20a. As a result of your shoulder, do you take any **pain medication** (**circle one**)?

Yes No

20b. If yes, what **kind** of **pain medication** (i.e. Trentol, Vitamin E, etc.) do you take?

_____

How **often**? _____

21. What was your employment prior to your head and neck surgery neck dissection? What is it now? Were these changes (if there were any) due to your shoulder condition? If "**yes**," please include the changes in your response below.

22. Did you participate in many recreational activities prior to your head and neck surgery neck dissection? Do you participate in the same recreational activities now? Were these changes (if there were any) due to your shoulder condition? If "**yes**", please include the changes in your response below.

23. (For interviewer) What is the patient's **body mass index**?

-Height:_____

-Weight:_____

24. Where did you receive radiation therapy (i.e. U of M Hospital, another hospital)?

_____

Financial and Work Survey:

Last Name: First Name:
Date of Birth:
Date of visit/Date form completed:_

We hope to gain knowledge about your cancer treatment and health care costs:

1. Are the financial costs of cancer treatment higher or lower than you expected?

   ☐ Lower than expected ☐ As expected ☐ Higher than expected

2. How concerned are you about paying for your cancer treatment

   ☐ Not worried ☐ A little worried ☐ Somewhat worried ☐ Worried ☐ Very worried

3. Have you delated the start of a cancer treatment due to costs (for example, wait more than 7 days for insurance approval)?

   ☐ Cost or insurance approval have not delayed my cancer treatment
   ☐ I've experienced 1 delay due to costs or insurance approval
   ☐ I've experienced more than 1 delay due to costs or insurance approval

Have you done the following since your head and neck cancer diagnosis?

4. Decreased your basic spending on things like food and clothing:

   ☐ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

5. Used savings to pay for cancer care:

   ☐ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

6. Delay the filling of prescribed medication due to cost:

   Cancer Supportive Medications (anti-nausea, antibiotics, steroids, oral rinses)

   ☐ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

   Pain Medications

   ☐ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

   Nutritional Supplements (e.g. Boost, Ensure, etc.)

   ☐ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

Have you done the following since your head and neck cancer diagnosis? (continued)

7. Fill only part of prescribed medication due to cost:

   Cancer Supportive Medications (anti-nausea, antibiotics, steroids, oral rinses)

□ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

Pain Medications

□ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

Nutritional Supplements (e.g. Boost, Ensure, etc.)

□ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

8. Stop taking a medication due to cost:

Cancer Supportive Medications (anti-nausea, antibiotics, steroids, oral rinses)

□ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

Pain Medications

□ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

Nutritional Supplements (e.g. Boost, Ensure, etc.)

□ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

9. Borrow money to pay for medication:

□ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

10. Refuse recommended tests due to costs:

□ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

11. Skip a clinic visit (oncology or other) to save on costs:

□ Never ☐ Once ☐ Rarely ☐ Often ☐ Always

12. Overall, to what degree of financial burden have cancer treatment costs been on you or your family?

- □ Not a financial burden at all
- □ Minor financial burden
- □ Moderate financial burden
- □ Significant financial burden
- □ Catastrophic financial burden

Now we hope to gain knowledge about how your cancer has affected your work and family life:

13. When you were diagnosed with head and neck cancer, were you working for pay?

☐ Yes ☐ No **(If NO, please go to question 15)**

14. In total, approximately how much work have you missed because of you head and neck cancer or its treatment
    - ☐ Less than a month
    - ☐ Between 1 month and 3 months
    - ☐ Between 3 months and 6 months
    - ☐ Between 6 months and 1 year
    - ☐ I stopped working altogether

15. When you were being treated for head and neck cancer, where any of the following <u>available</u> to you through your work? Indicate all that apply:

▪ Health insurance:	☐Yes	☐ No	☐ I don't know
▪ Paid sick leave:	☐Yes	☐ No	☐ I don't know
▪ Extended sick leave:	☐Yes	☐ No	☐ I don't know
▪ Unpaid time off:	☐Yes	☐ No	☐ I don't know
▪ Disability benefits:	☐Yes	☐ No	☐ I don't know
▪ Flexible work schedule:	☐Yes	☐ No	☐ I don't know
▪ Other (please explain):			

16. Have you continued to work for pay while going through head and neck cancer treatment?

☐Yes ☐ No

17. As a result of your head and neck cancer or its treatment did you have any of the following experiences? **Indicate/select all that apply**

▪ I arranged to work fewer hours:	☐Yes	☐ No
▪ I changed jobs:	☐Yes	☐ No
▪ I used sick leave:	☐Yes	☐ No
▪ I used unpaid time off:	☐Yes	☐ No
▪ I quit my job:	☐Yes	☐ No
▪ I lost my job:	☐Yes	☐ No
▪ I had trouble doing my job well:	☐Yes	☐ No
▪ I kept my job mainly to keep my health insurance:	☐Yes	☐ No
▪ Other (please explain):		

18. Are you working for pay <u>now</u>?

☐ Yes ☐ No **(If NO, Please go to question 20)**

19. What is the reason you are not working for pay now?

- ☐ Quit my job because of the diagnosis of head and neck cancer and/or treatment
- ☐ Lost my job because of the diagnosis of head and neck cancer and/or treatment
- ☐ Retired because of head and neck cancer and/or treatment
- ☐ Quit my job for reasons unrelated to head and neck cancer diagnosis and/or treatment
- ☐ Lost my job for reasons unrelated to head and neck cancer diagnosis and/or treatment
- ☐ Retired from my job for reasons unrelated to head & neck cancer diagnosis and/or treatment
- ☐ Other (please explain): _____

20. In the last 12 months, has there been a period of at least 3 months when you were without health insurance.

☐ Yes ☐ No

Please continue to final page →

	COST (COmprehensive Score for financial Toxicity) Patient –Reported Outcome Measure	Not at all	A little bit	Some-what	Quite a bit	Very much
1	I know that I have enough money in savings, retirement, or assets to cover the costs of my treatment.	0	1	2	3	4
2	My out-of-pocket medical expenses are more than I thought they would be.	0	1	2	3	4
3	I worry about the financial problems I will have in the future as a result of my illness or treatment.	0	1	2	3	4
4	I feel I have no choice about the amount of money I spend on care.	0	1	2	3	4
5	I am frustrated that I cannot work or contribute as much as I usually do.	0	1	2	3	4
6	I am satisfied with my current financial situation.	0	1	2	3	4
7	I am able to meet my monthly expenses.	0	1	2	3	4
8	I feel financially stressed.	0	1	2	3	4
9	I am concerned about keeping my job and income, including work at home.	0	1	2	3	4
10	My cancer or treatment has reduced my satisfaction with my present financial situation.	0	1	2	3	4
11	I feel in control of my financial situation.	0	1	2	3	4

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title UMCC 2015.126: Phase II Treatment Stratification Trial Using Neck Dissection-Driven Selection to Improve Quality of Life for Low Risk Patients with HPV+ Oropharyngeal Squamous Cell Cancer

1.2 Company or agency sponsoring the study: University of Michigan

1.3 Names, degrees, and affiliations of the researchers conducting the study:
Principal Investigator:
Francis Worden, MD University of Michigan/Internal Medicine-Hematology/Oncology

2. PURPOSE OF THIS STUDY

2.1 Study purpose:
You are being invited to join in a clinical research study because you have been diagnosed with HPV+ squamous cell carcinoma of the throat (oropharynx) that has spread to the lymph nodes in your neck.

The study is being conducted to minimize the number of treatment methods (surgery, radiation, chemotherapy) being used to treat patients with human papilloma virus (HPV) positive oropharyngeal squamous cell cancer (OPSCC) in order in improve quality of life. We plan to perform a surgical biopsy of the lymph nodes in the neck (neck dissection) at diagnosis to more accurately stage patients. Further treatment will be determined based on the results of the neck dissection. This treatment approach looks to minimize the number of treatment methods used. Our theory is that patients treated with this protocol will utilize fewer treatment methods and will have a better quality of life as compared to our patients treated with radiation plus or minus chemotherapy.

Before you agree to join in this study, you need to know the risks and benefits so you can make an informed decision. This is known as "informed consent". This consent form tells you about the study that you may wish to join. Please read the information carefully and discuss it with anyone you want. This may include a friend or a relative. If you have questions please ask the study doctor or study staff to answer them. Once you know about the study and the tests that will be done, you will be asked to sign this form to join the study.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and

you will not lose any benefits to which you are otherwise entitled. If you decide not to join the study or decide to discontinue at a later time, the study doctor will tell you about other treatments.

3.1 Who can take part in this study?
This is a clinical research study. You are being asked to participate in this study because you are at least 18 years of age and have been diagnosed with metastatic head and neck squamous cell carcinoma. If you agree to join in this study, you will receive standard of care treatment based on the results of your neck dissection.

3.2 How many people (subjects) are expected to take part in this study?
Approximately 100 people will be enrolled from the University of Michigan.

4. INFORMATION ABOUT STUDY PARTICIPATION

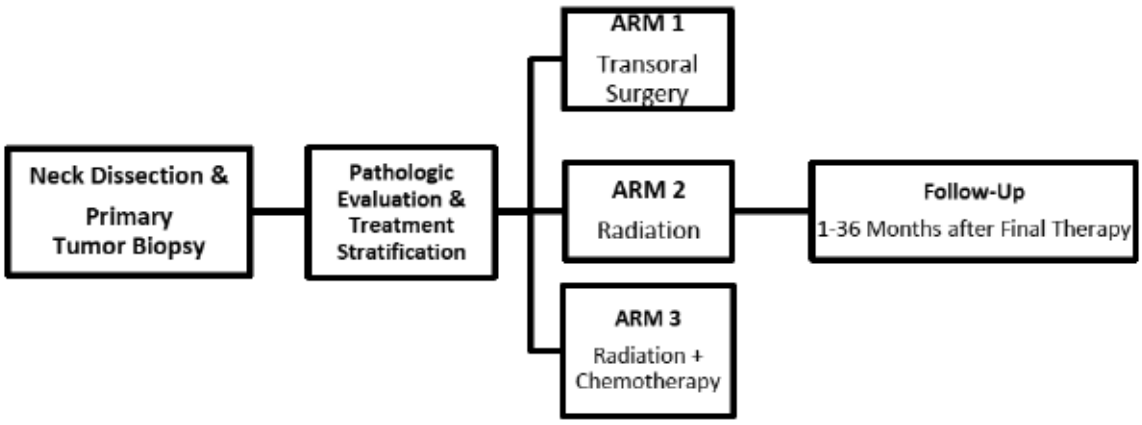
4.1 What will happen to me in this study?
If you agree to participate, sign this consent, and are found to be eligible for the study, you will be "enrolled". After enrollment, you will have a neck dissection procedure and biopsy of the primary tumor. The results will be reviewed and based on the results, you will be placed into one of three treatment groups:

1) Transoral surgery: subjects with 0-1 lymph nodes involved with cancer that measure less than six centimeters will undergo transoral surgery of the primary site.

2) Radiation only: subjects with 2 or more lymph nodes involved with cancer, or the presence of tumor involving small blood vessels/nerves (perineural/perivascular extension) will undergo radiation therapy.

3) Chemoradiation (Chemotherapy + Radiation therapy): subjects with cancer extending out of lymph nodes (extracapsular extension) in any number of lymph nodes or inability to surgically remove all of the primary tumor by transoral surgery (positive margins) will undergo chemoradiation.

Study Schema



Radiation (subjects in Radiation and Chemoradiation arms)
You will have radiation therapy five days a week (Monday-Friday) until the total dose of radiation prescribed by your doctor is reached.

Before beginning your radiation therapy, you will undergo routine radiation therapy simulation and a CT scan for treatment planning purposes. Radiation will be planned and delivered using advanced techniques aiming at encompassing adequately the cancer while sparing the major glands that produce saliva.

Chemotherapy (subjects in the Chemoradiation arm)
The chemotherapy drugs, carboplatin and paclitaxel, will be given through a needle in your vein (intravenously) once per week for as long as you receive radiation therapy. Carboplatin and paclitaxel will be administered every Monday before you start your radiation therapy. The dose of carboplatin and paclitaxel will be delivered by a pump through an intravenous catheter that goes into a vein in your arm. Before the pump delivers any drug, it will deliver several standard medications to decrease the unpleasant side effects. The infusion will take about 1-3 hours to complete.

Carboplatin and paclitaxel are drugs commonly used to treat head and neck cancer.

Subject Responsibilities
You must be willing to:

- Provide accurate and complete information about your medical history and your present condition.
- Follow the study procedures and keep all scheduled appointments. Inform the study team in advance if you have a problem with keeping an appointment.
- Tell the study team about any other medications (including herbal over-the-counter medications) you are taking and medical treatments you receive before and during the study. You may not take certain medications or receive certain medical treatments without the permission of the study team during the study or for up to 6 months after the last dose of study medication.
- Tell your study doctor about any new side effect, injury, or symptom you experience.
- Tell your study doctor of any changes in current medical conditions. This information must be reported to your study doctor between study visits by using the contact numbers at the end of this consent form.
- You will be asked not to donate blood while you are taking part in this study and for 3 months following the last dose of the study regimen.
- You must not take part in any other studies involving an investigational product while you are taking part in this study.
- Upon study completion or early withdrawal, it is important for you to speak with your study doctor to arrange follow-up care.
- You agree to be regularly contacted by the site until the end of the study.

Before starting the study (Screening)
After signing this consent form, you will return to the University of Michigan to undergo the remaining "screening tests." Screening tests will help your study doctor determine if you continue to be eligible for the study.
Your study doctor will ask you about your health and your medical history including your cancer history. You will be asked about any medications you have been taking or are currently taking, including all prescription and non-prescription medicines. It is important that you tell your study doctor about any medications you are taking including over-the-counter medications, vitamins, herbal medications and alternative medicines. You will be instructed to inform your study doctor at any time during your study participation if you begin to take any medication(s), including over-the-counter and/or herbal medicines. Drugs can interact with each other.

You will have the following tests and assessments performed within 28 days of your neck dissection:

- Demographic information will be collected.
- Complete physical exam including your height and weight.
- Blood pressure, heart rate, and temperature (Vital signs).
- What type of daily activities you can do (Performance status evaluation).
- You mayhave a heart tracing of the electrical activity of your heart (electrocardiogram [ECG]).

- Blood samples will be taken (approximately 1 teaspoon) for laboratory testing including blood counts (hematology), and sugar, fats, minerals, and enzymes (chemistry).
- If you are female of childbearing potential, your blood (½ teaspoon) or urine will be tested to see if you are pregnant.
- Urine sample will be collected for routine laboratory testing including protein, blood, sugar, and fat.
- You will complete the Head and Neck Quality of Life questionnaires and the Financial & Work Survey
- You will swallow a small quantity of barium or barium-coated food, such as a cookie, while a series of x-rays are taken of the throat – a video swallow study (Videofluoroscopy).
- A type of hearing test, if your doctor thinks you should have this test (Audiogram).
- A computed tomography (CT) will be done to measure your disease.
- A fresh biopsy of your tumor will be performed. Leftover tissue from your biopsy will be stored at a tissue repository at the University of Michigan.
- Research blood/plasma (2 ½ teaspoons) and saliva samples for future research studies will be collected.

The results of these tests will be evaluated before you can receive a study regimen. It is possible that after these tests are reviewed, you will not be able to take part in this research study. There may be other reasons why you cannot participate. Your study doctor will discuss these and other treatment options with you.

During the study (Definitive Therapy)
Once the results of your neck dissection and primary tumor biopsy are reviewed, you will be enrolled into one of three therapy groups. The tests are procedures that will be done for each therapy group are listed below.

1) Transoral Surgery Arm:
   - You will have surgery through the mouth (transoral) to completely remove the primary tumor

2) Radiation Only Arm:
   - You will have the following tests and procedures before you begin your radiation regimen
     - Physical exam including vital signs
     - Blood samples will be taken (approximately 1 teaspoon) for laboratory testing including hematology (blood cell counts), and chemistry (sugar, fats, minerals, and enzymes).
     - You will complete the Head & Neck Quality of Life questionnaires
     -
   - The following procedures will be performed weekly during your radiation therapy
     - Physical exam including vital signs
     - Blood samples will be taken (approximately 1 teaspoon) for laboratory testing including hematology (blood cell counts), and chemistry (sugar, fats, minerals, and enzymes).
   - The following procedures will be performed daily (Monday-Friday) during your radiation regimen
     - Radiation therapy sessions

3) Chemoradiation Arm:
   - You will have the following tests and procedures before you begin your chemoradiation regimen
     - Physical exam including vital signs
     - Blood samples will be taken (approximately 1 teaspoon) for laboratory testing including hematology (blood cell counts), and chemistry (sugar, fats, minerals, and enzymes).
     - You will complete the Head & Neck Quality of Life questionnaires
   - The following procedures will be performed weekly during your chemoradiation therapy
     - Physical exam including vital signs

  - Blood samples will be taken (approximately 1 teaspoon) for laboratory testing including hematology (blood cell counts), and chemistry (sugar, fats, minerals, and enzymes).
  - You will receive the chemotherapy drugs carboplatin and paclitaxel via an intravenous (IV) injection
- The following procedures will be performed daily (Monday-Friday) during your chemoradiation regimen
  - Radiation therapy sessions

Follow-up after Definitive Therapy (all subjects)
You will have the following tests and procedures:

- One month after your final therapy
  - Complete physical exam, including vital signs
  - Blood/plasma/saliva samples taken for research studies (3 tablespoons)
  - Head & Neck Quality of Life questionnaires
- 3 months after your final therapy
  - PET/CT scan
  - Financial & Work Survey
- Every 3 months for months 3-12
  - Complete physical exam, including vital signs
  - Blood/plasma/saliva studies for research studies (3 tablespoons)
  - Head & Neck Quality of Life questionnaires
- 12 months after your final therapy
  - CT of the chest or Chest x-ray, if your study doctor thinks you should have one
  - Videofluoroscopy
  - Financial & Work Survey
- Every 3 months for months 13-36
  - Complete physical exam, including vital signs
  - Blood/plasma/saliva studies for research studies (3 tablespoons)
  - Head & Neck Quality of Life questionnaires
- 24 months after your final therapy
  - CT of the chest or Chest x-ray, if your study doctor thinks you should have one
  - Financial & Work Survey
- 36 months after your final therapy
  - CT of the chest or Chest x-ray, if your study doctor thinks you should have one

<u>Blood/Plasma and Saliva samples for Research</u>
Blood and saliva samples will be collected at screening and then every 3 months while you are in the study. Approximately 12 mL (2 ½ teaspoons) of blood will be drawn at each time point. Saliva samples will be collected using a "swish and spit" method. You will be given a solution of mouthwash or saline to swish in your mouth for 30 seconds and then spit into a large tube.

Genetic testing will be performed on your blood and saliva samples to see if the biomarkers or proteins present in these samples can predict whether tumors such as yours will come back after treatment. You will not receive the results of these tests. The results are not expected to provide any information that will affect your treatment.

All of your blood and saliva samples collected for research in this study will be stored and tested at a lab at the University of Michigan. The samples will not have your name on them but will be labeled with a barcode label that links your sample to a coded lab ID number. The scientists testing your samples will not know your identity.

Your samples will be stored indefinitely at the University of Michigan. They will not be shared with anyone outside the University of Michigan.

Banking your samples for genetic and future testing is a mandatory part of this research study. If you do not want your samples used for this testing, you will not be able to participate in this study. If you do decide to take part in this study, you can change your mind at any time about storing your samples for this research. Tell your study doctor or the study staff that you no longer want your samples used for research and your samples will be destroyed. You will no longer be able to continue participation in this research study. The results of any testing using your samples that has already been performed or is in progress will be used in order to maintain the integrity of the research.

Optional Tumor Tissue for Research

Head and neck cancer cell lines that are found in tumor tissue are very valuable research tools. Many tumor cell lines can be found in HPV+ oropharyngeal cancers; which is the cancer that this study is exploring.

There is a separate, optional research process that will allow the University of Michigan to store and use your leftover fresh tumor tissue (from the excess surgical specimen) for this research. This will be explained to you in a separate consent and your decision to participate or not participate in that process will not affect your participation in this study.

4.2 How much of my time will be needed to take part in this study?

If you join the study, the number of clinic visits you have will depend on which therapy arm of the study you are in and your response to the treatment.

Transoral surgery:

- Screening: Your screening visit can last up to 8 hours but all of the procedures do not have to be done on the same day.
- Definitive Therapy: You will have one visit for your surgical procedure.
- Post-operative care: You are typically in the hospital 1-7 days after your surgery for close monitoring and care. We will monitor your surgical site for bleeding, and your blood counts if necessary.
- Follow-up: After your surgical procedure, you will return to the clinic for 17 follow-up visits. Each Follow-up visit should take about 2-3 hours.

Radiation Therapy:

- Screening: Your screening visit can last up to 8 hours but all of the procedures do not have to be done on the same day.
- Definitive Therapy: You will come to the clinic five times a week (Monday thru Friday) for about 7 weeks for radiation treatments. Each session of radiation therapy will last about 10-20 minutes. At your first visit, you will complete the Quality of Life questionnaires before you receive radiation. It should take about 45 minutes to 1 hour to complete the questionnaires. In addition, you will be seen in clinic once a week while being treated with radiation, each visit will last 1-2 hours.

- Follow-up: After your radiation therapy sessions have completed, you will return to the clinic for 17 follow-up visits. Each follow-up visit should take about 2-3 hours.

Chemoradiation Therapy:

- Screening: Your screening visit can last up to 8 hours but all of the procedures do not have to be done on the same day.
- Definitive Therapy: You will receive chemotherapy once a week (Monday) for chemotherapy followed by a clinic visit and radiation treatment. The infusion of the chemo drugs will take about 1-3 hours and your radiation therapy will take about 10-20 minutes. You should expect to be in clinic Mondays for about 4 hours. At your first visit, you will complete the Quality of Life questionnaires before you receive your first infusion of chemo drugs. It should take about 45 minutes to 1 hour to complete the questionnaires. You will come to the clinic four times a week (Tuesday thru Friday) for radiation therapy. Each session of radiation therapy will last about 10-20 minutes. You will be treated with chemoradiation for a total of 7 weeks.
- Follow-up: After your chemoradiation therapy session are completed, you will return to the clinic for 17 follow-up visits. Each Follow-up visit should take about 3-4 hours.

4.3 When will my participation in the study be over?

The total length of time that you will be in the study will depend on the type of treatment you receive and how your cancer responds to the treatment. After your treatment period has ended, you will have follow-up visits every 3 months for 36 months (3 years).

4.4 What will happen with my information and/or biospecimens used in this study?

Your biospecimens and collected information will be shared with the University of Michigan Head & Neck Oncology team. With appropriate permissions, your samples and collected information may also be shared with other researchers, here, around the world, and with companies. Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

Risks are possible side effects of study medicine, undergoing tests and procedures, such as imaging scans, biopsies, and blood or tumor sample collection.

Risks of radiation

Side effects and possible complications of radiation can vary, depending on where the cancer is, how large it is, and how much radiation you receive.

<u>Very Likely (25% or greater incidence)</u>

- Sores in the mouth and/or throat which can be painful and make it very difficult to chew and or swallow foods
- Mouth dryness or changes in taste and/or smell that may be permanent
- Thick saliva
- Hoarseness
- Tanning or redness and/or irritation of the skin in the head and neck area being treated with radiation
- Ear pain and/or pressure
- Fatigue

- Weight loss
- Permanent hair loss in the area treated with radiation (face, chin, neck)
- Loss of teeth, or cavities in the teeth, if strict dental care is not followed and/or hypersensitivity of teeth

Less Likely, But Serious (less than 25% incidence)

- Decrease in function of the thyroid gland that may require you to take thyroid replacement medicine to prevent you from feeling tired or having a low energy level
- Serious damage to the spinal cord, nerves in the neck, jawbone, voice box, skin, or other parts of the head and neck that may require a major operation to correct and, rarely, can even be life threatening
- Temporary pain or scarring around nerves in the shoulder that could cause numbness and/or weakness
- Breathing problems
- Difficulty with swallowing and eating for which you might need a long term or permanent feeding tube; possibility of inhaling food and/or liquids into the lungs – which could also result in pneumonia.
- Serious ear infections and/or hearing loss
- Damage to the spinal cord leading to permanent weakness and/or symptoms like a "stroke". Stroke has been reported to be slightly higher after head and neck radiation, compared with the general population, due to the possibility of increased formation of plaque in the carotid artery (causing blockage).

All of these side effects may be a result of standard radiation treatment, as well as radiation according to this study. Your physicians do not know whether the chance of complications arising from participation in this study is different from the chance of complications arising from standard radiation. You will be followed on a weekly basis for symptom management and supportive care.

Risks of chemotherapy drugs (for subjects in chemoradiation arm)
Carboplatin and paclitaxel have not been approved by the FDA for head and neck cancer.

Carboplatin
The most common side effects of carboplatin include (10% or greater incidence):

- Low blood counts.
  - Decreased number of white blood cells may increase your risk of infection.
  - Decreased number of red blood cells may increase your risk of anemia which may cause fatigue.
  - Decreased number of platelets may increase your risk of bleeding.
- Nausea / vomiting
- Allergic reactions such as rash, hives, redness, and itching
- Nervous system complications (neurologic)
  - Damage to the peripheral nerves (peripheral neuropathy) with early symptoms of tingling or numbness in the feet or fingers.
  - Hearing loss
- Blood laboratory results indicating a decrease in kidney function.
- Abnormal liver enzyme blood levels. This may indicate inflammation or damage of the cells of the liver.
- Side effects affecting the heart and blood vessels (cardiovascular) include:
  - Shortness of breath
  - Chest pain
  - Heart failure
  - Stroke
  - Blood clots
- Abdominal pain

- Weakness
- Mouth and lip sores and sore throat (mucositis)
- Low blood pressure
- Diarrhea
- Constipation
- Difficulty breathing
- Hair loss
- Temporary worsening of eyesight or changes to your vision.
- Taste changes
- Reaction at the injection site, such as redness or swelling

Rare (less than 1% incidence) side effects include:

- Severe allergic reaction (anaphylaxis)

Paclitaxel

The most common side effects of paclitaxel (10% or greater incidence)include:

- Allergic reactions such as rash, hives, redness, and itching
- Low blood counts.
    - Decreased number of white blood cells may increase your risk of infection.
    - Decreased number of red blood cells may increase your risk of anemia which may cause fatigue.
    - Decreased number of platelets may increase your risk of bleeding
- Hair loss
- Tingling, numbness, and/or pain in your hands and feet (peripheral neuropathy). This is not usually severe and improves or resolves when you stop therapy, but sometimes there is some permanent numbness.
- Joint and muscle pain
- Nausea/ vomiting
- Diarrhea
- Sore mouth and tongue (mucositis)
- Fever or infection
- Increase in liver function blood tests
- Abnormal EKG
- Weakness
- Fatigue
- Low blood pressure
- Swelling of hands or feet
- Reaction at the injection site, such as redness or swelling

Rare (1% or less incidence):

- Severe allergic reactions

Risks from study procedures

Some of the study procedures may have possible side effects, risks and discomforts. You may experience none, some or all. During the study you will have to have blood taken, get CT scans or have a piece of your cancer removed for testing. These are standard and routine procedures and your study doctor will be able to explain these to you in detail and provide you with any risks and/or side effects associated with these.

Risk of biopsy

The possible risks associated with removal of a piece of your cancer (a biopsy) depend on the part of the body where the biopsy will be performed. You may experience pain from the biopsy and you may have bruising, soreness or scarring at the biopsy site. Rarely, a patient who has had a biopsy may experience infection and/or internal bleeding and depending on the location of the biopsy, 'punctured lung' and/or 'collapsed lung' (due to an abnormal collection of air or gas in the space that separates the lung from the chest).

Risks of Venipuncture/Intravenous Needle Insertion:
The collection of a blood sample may cause some discomfort. Obtaining blood may sometimes cause pain/discomfort at the site where the blood is drawn, bruising, bleeding, occasional light-headedness and, rarely, infection or fainting.

Risks of Computed Tomography (CT) Scan with Contrast Dye:
The risks associated with a computed tomography (CT) scan are very rare. Exposure to radiation due to receiving CT scans may increase your risk of developing cancer. You will be exposed to a contrast dye (iodine). The risks associated with administration of the contrast dye are a warm or burning sensation in the area that the intravenous line is placed while the dye is being administered. You may experience a flushing or warmth throughout your body that lasts a few seconds. You may experience an allergic reaction to the iodine. The allergic reaction may include rash or hives. Rare reports of anaphylactic shock, a serious potentially life-threatening allergic reaction resulting in extremely low blood pressure, loss of consciousness, coma and possibly death have been documented. You will be monitored closely for these allergic reactions and will be treated immediately should one occur. If you are allergic to iodine, notify your doctor. The contrast substance injected during the CT scan may cause pain, burning feeling, sweating and rarely a serious allergic reaction that can be serious - if you know you're allergic to iodine; you must inform your doctor immediately. The contrast agent used in the CT scan may cause kidney damage, especially if you're diabetic, dehydrated and if you're older. In addition your thyroid function may be affected. Please inform your doctor if this is the case. CT imaging uses ionizing radiation, which increases your risk to cancer. Everyone is exposed to naturally occurring ionizing radiation every day. The amount of radiation exposure from 1 CT scan is approximately comparable to 1-3 years of natural background radiation.

Risks of Neck Dissection:
A neck dissection is the removal of lymph nodes in the neck where cancer can spread. There are small risks associated with neck dissection. These include scarring of the skin on the neck, pain in the shoulder, neck infection, or bleeding after the neck dissection requiring another operation to control the bleeding. There are small risks to the nerves that control facial movement, elevation of the shoulder, movement of the breathing muscle (diaphragm) speaking and swallowing. There is a very small risk of stroke.

Risks of transoral surgery:
The risks of transoral surgery are low. The tumor in the throat is removed through the mouth, so there is a chance of injury to the dental structures, tongue, palate and lips. Special padding is used to protect these structures. To access the tumor for removal, we also use a retractor on the tongue which can cause temporary numbness. After surgery, there is pain in the throat which is controlled with pain medication. There is a small chance of permanent pain associated with the surgery. There is small risk of bleeding after surgery, which is approximately 5 %. This bleeding can be life threatening, as bleeding can go down in the lungs since the surgery is performed in the mouth. This would require another surgery to stop the bleeding.

Risks of Core Needle Biopsy:
You may experience pain from this procedure that could also include bruising, soreness or scarring at the biopsy site. Rarely, a patient may experience infection and/or internal bleeding and depending on the location of the biopsy, 'punctured lung' and/or 'collapsed lung' (due to an abnormal collection of air or gas in the space that

separates the lung from the chest). The biopsy procedure is usually performed while the patient is under local anesthesia (for example lidocaine), meaning the tumor site is numbed. Side effects from the local anesthesia are rare but may include convulsions or seizures, breathing problems, chest pain, rapid heart rate, irregular heartbeat, dizziness, bluish lips and fingernails, drowsiness, headache, itching, nausea and/or vomiting, raised red swellings on the skin, lips, tongue, or in the throat, restlessness, unusual tiredness or weakness, back pain, difficulty in opening the mouth, inability to hold bowel movement and/or urine, loss of sexual function, temporary paralysis (loss of function) of legs, persistent or prolonged numbness or tingling ("pins and needles" sensations) of lips and mouth, and shivering.

Imaging equipment may be used to guide the needle to the desired site. This may involve ultrasound or x-ray. If x-ray is used, a subject will be exposed to a small dose of radiation. In addition, a patient may be injected with a contrast dye (for example iodine). This may cause some side effects including hives, itching, lightheadedness, nausea and a metallic taste in the mouth. Rarely, the iodine may result in a severe allergic reaction, including shock, very low blood pressure and cardiac arrest.

Videofluroscopy/ X-ray:
Some people may have an allergic reaction to the barium. Some people gag while drinking the barium fluid. In rare cases, a person may choke and inhale (aspirate) some of the liquid into the lungs. Barium can cause a little constipation but this can be avoided by drinking plenty of fluid for the rest of the day after your procedure. Your stools may be paler than usual for the next few days - this is nothing to be alarmed about. It is just the barium passing through your system.

All x-ray procedures involve some exposure to radiation and so pose a degree of risk. Everyone is exposed to natural background radiation from the environment throughout their lives. One in 3 people will develop cancer at some point in their lives due to many various causes including environmental radiation. Radiation from a medical procedure involving x-rays can add very slightly to this risk. Special care is taken during x-ray examinations to use the lowest radiation dose possible while producing the best images for evaluation. The added risk of cancer due to this radiation is extremely small.

ECG:
You may also have an ECG which is a painless test that looks at the electrical activity of your heart by putting small sticky patches on your chest, arms and legs. These patches have thin wires that connect to a machine which will read and print a report. The test takes about 5-10 minutes. Some areas, where the patches will be placed, may need to be shaved. After the test, there may be a small amount of irritation where the patches were attached.

Reproductive risks
Women who are pregnant or nursing a child cannot participate in this trial. You must confirm, to the best of your knowledge, that you are not now pregnant, and that you do not intend to become pregnant during the trial.
The risks to an unborn human fetus or a nursing child from the medications you are required to take in this study are not presently known. If you suspect that you have become pregnant during the trial, you must notify the study doctor immediately. You will not be able to participate in the trial if you are pregnant, become pregnant or are breastfeeding.

Women
If there is ANY chance that you can get pregnant, you must either agree to not have vaginal intercourse or you must use TWO types of birth control (one from each list below) AT THE SAME TIME. These birth control methods must be used from the time of enrollment, while receiving your study regimen including during temporary breaks

from therapy, and for at least 3 months after your cancer regimen has finished. The following methods are considered acceptable birth control methods:

Primary forms
- tubal sterilization (tubes tied)
- partner's vasectomy
- intrauterine device
- hormonal contraceptives - (includes transdermal patch, injectables, implantables)

Secondary forms
- male latex condom with or without spermicide
- diaphragm with spermicide
- cervical cap with spermicide
- vaginal sponge (contains spermicide)

Any birth control method can fail. The reports of birth control failing are more frequent for female patients who use only a single form of birth control. Using two forms of birth control at the same time greatly reduces the chances of pregnancy.

Men
Men must agree to either abstain from sexual activities that could result in pregnancy or use an acceptable form of birth control while taking part in the study and for 3 months after your last study regimen dose. Acceptable forms of birth control are male latex condom (with or without spermicide) or vasectomy. In addition, men should not donate sperm or semen while taking part in the study and for 3 months after the last study regimen dose. In case you father a child while in this study you will be asked to give information to the study doctor regarding the mother's pregnancy. Consent from your partner will be needed to allow your study doctor to medically follow this pregnancy until delivery to monitor the mother`s and child`s safety.

Genetic Information Nondiscrimination Act (GINA):
The federal Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums
- Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups, however these groups have policies in place that provide similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service
- Federal employees receiving care through the Federal Employees Health Benefits Plans

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about

any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors.

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You will receive medical care during the study. You may receive no direct benefit from being in this study. Information from this study may help you and/or other people with cancer in the future. Your condition may get better, it may get worse, or it may stay the same. You do not have to participate in this study to receive treatment for your condition.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, we may learn new things during the study that you may need to know. We can also learn about things that might make you want to stop participating in the study. If so, you will be notified about any new information. You can then decide if you want to continue the study regimen or any other study related activities. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?
Alternative treatments may include the use of surgery, radiation, or chemoradiation. You may be eligible for another research study. Your study doctor can discuss the potential benefit and risks of these alternative treatment methods with you.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
Please inform your doctor or study staff if you decide to interrupt or stop taking the study regimen. You will be asked to return to the study site as soon as possible to check how you are feeling. You should bring your study treatment to the clinic. Also, the study doctor may choose to discontinue your study regimen.
You may be asked to continue with study visits after stopping study regimen so that the end of treatment procedures can be performed.
If you cannot or do not want to continue to attend study visits while off study regimen, your study doctor or study staff may ask if they can contact you by telephone until the end of the study to check on how you are feeling. You may decline contact by telephone if you so choose.

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
If you choose to stop taking the study drug(s), please tell the study doctor/staff so this can be done safely.

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. The study doctor may remove you from this study for any reason without your consent. Examples why you may be taken out of the study are:

- Staying in the study would be harmful.
- You need treatment not allowed in this study.
- You fail to follow instructions.

- You become pregnant.
- The study is cancelled.
- You are not responding to the study regimen.
- It is not in your best interest to continue in the study.

If you should decide to leave the study you should tell the Study doctor or study staff. They will make sure that proper procedures are followed and a final visit is made for your safety.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
The study will pay for research-related items or services that are provided only because you are in the study. This includes research testing on your tumor, blood and saliva samples. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- University of Michigan Cancer Center Clinic Visits
- Biopsies and surgical procedures
- Medications you may be given while you are in the study, including carboplatin and paclitaxel
- Health care given during the study as part of your regular care. CT scans, X-rays, and blood tests are part of the standard medical care for your disease.
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You will not be paid for your participation in this study.

8.3 Who could profit or financially benefit from the study results?
It is not expected that anyone will benefit financially from this research study. However, research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
For purposes of this study, University of Michigan and the study team will use medical information collected or created as part of the study, such as medical records and test results, that identifies you by name or in another way. Research records will be kept in a separate research file that does not include names, registration numbers, or other information that is likely to allow someone other than the researchers to link the information to you. Your consent to participate in the study means you agree that University of Michigan and the study team may obtain your medical information that they request for study purposes from your physicians and your other health care providers. You are also agreeing that University of Michigan and the study team may use and share this information with the parties described below. In addition, you agree that, during the study, you may not have access to some of your medical information obtained or created as part of this study. You will be allowed to access this information once the study is finished.

For the web-based surveys, you will receive an email invitation inviting you to take the survey on-line at the Qualtrics site. You also have the option to take the surveys in clinic using a UMHS tablet. An additional password may be given to you in order for them to access to the site. There are systems in place that prevent the survey from being taken by the same user more than once. No identifying information is linked to your survey data. There are security precautions in place to protect against unauthorized access, but there is a small risk of unauthorized access. Information regarding Qualtrics security and privacy statements can be found at http://www.qualtrics.com/security-statement and http://www.qualtrics.com/privacy-statement. As an extra security measure it is recommended that you close your internet browser after completing the survey.

The tablets in clinic will be protected with two-factor authentication (Duo) and staff will need to log into the tablet with their secure UMHS password. Duo mobile privacy information can be found at https://help.duo.com/s/article/4683?language=en_US, along with privacy notice at https://duo.com/legal/privacy-notice-service.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?
Unless required by law, University of Michigan and the study team will share this medical information only with the Study Team and other professionals involved in the Study, the US Food and Drug Administration (FDA), governmental agencies in other countries where the study drug may be considered for approval, and the Institutional Review Board. If the results of this study are published or presented in a meeting, you will not be named and nobody will be able to tell that you were in the study from the publication or presentation. The purpose for using and sharing this information with these parties is to perform the study and to ensure the accuracy of the study data. Not all of the parties who will have access to your medical information as part of the study are prohibited by federal law from further sharing it, so the information, once received by them, may no longer be protected by federal law.

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- HIV/AIDS status
- Sexually transmitted disease or other communicable disease status
- Health plan/health insurance records
- All records relating to your cancer, the treatment you have received, and your response to the treatment

- Billing information
- Demographic information
- Personal information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

9.3 What happens to information about me after the study is over or if I cancel my permission?
As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after the study is over. Also, the study sponsor may still use or disclose information about you that was shared with the study sponsor before you cancelled your authorization, if allowed under state law.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?
Your authorization will not expire unless you cancel it.

You have the right to cancel this consent at any time by giving written notice to the study doctor listed in section 10 below. If you cancel this consent, then University of Michigan and the study team will no longer use or disclose your medical information, unless it is necessary to do so to preserve the scientific integrity of the study. However, cancelling this consent will not affect previous uses and disclosures and your medical information would not be removed from the study records.

If you fail to give your consent by signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any treatment provided as part of the study. Unless and until you do cancel the consent, it will remain valid and effective.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?
Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

[redacted]

You may also express a concern about a study by contacting the Institutional Review Board listed below.
University of Michigan Medical School Institutional Review Board (IRBMED)

[redacted]

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- A copy of this signed and dated "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Date of Birth (mm/dd/yy): _____

ID Number: _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

PERSONAL CENSUS FORM

UMCC #: 2015.126

Name _____ Date _____

The National Cancer Institute requires that The University of Michigan Comprehensive Cancer Center report race and ethnicity information about people who participate in clinical research to ensure that all populations are offered the opportunity to participate.

☐ Check here if you do not wish to provide some or all of the information below.

1. What race do you consider yourself to be? (Please select *one or more*)

☐ American Indian/Alaska Native[a]
☐ Asian[b]
☐ Black or African American[c]
☐ Native Hawaiian or Other Pacific Islander[d]
☐ White[e]
☐ More than one race[f]

2. Do you consider yourself to be Hispanic[g]? ☐ Yes ☐ No

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[a] American Indian or Alaska Native- A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

[b] Asian- A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

[c] Black or African American- A person having origins in any of the black racial groups of Africa. (Terms such as "Haitian" or "Negro" are sometimes used in addition to "Black" or "African American.")

[d] Native Hawaiian or Other Pacific Islander- A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

[e] White- A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

[f] More than one race- (It is preferred that this be selected in addition to the selection of the specific races listed above, but this may also be solely selected.)

[g] Hispanic or Latino- A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" is sometimes used in addition to "Hispanic" or "Latino."